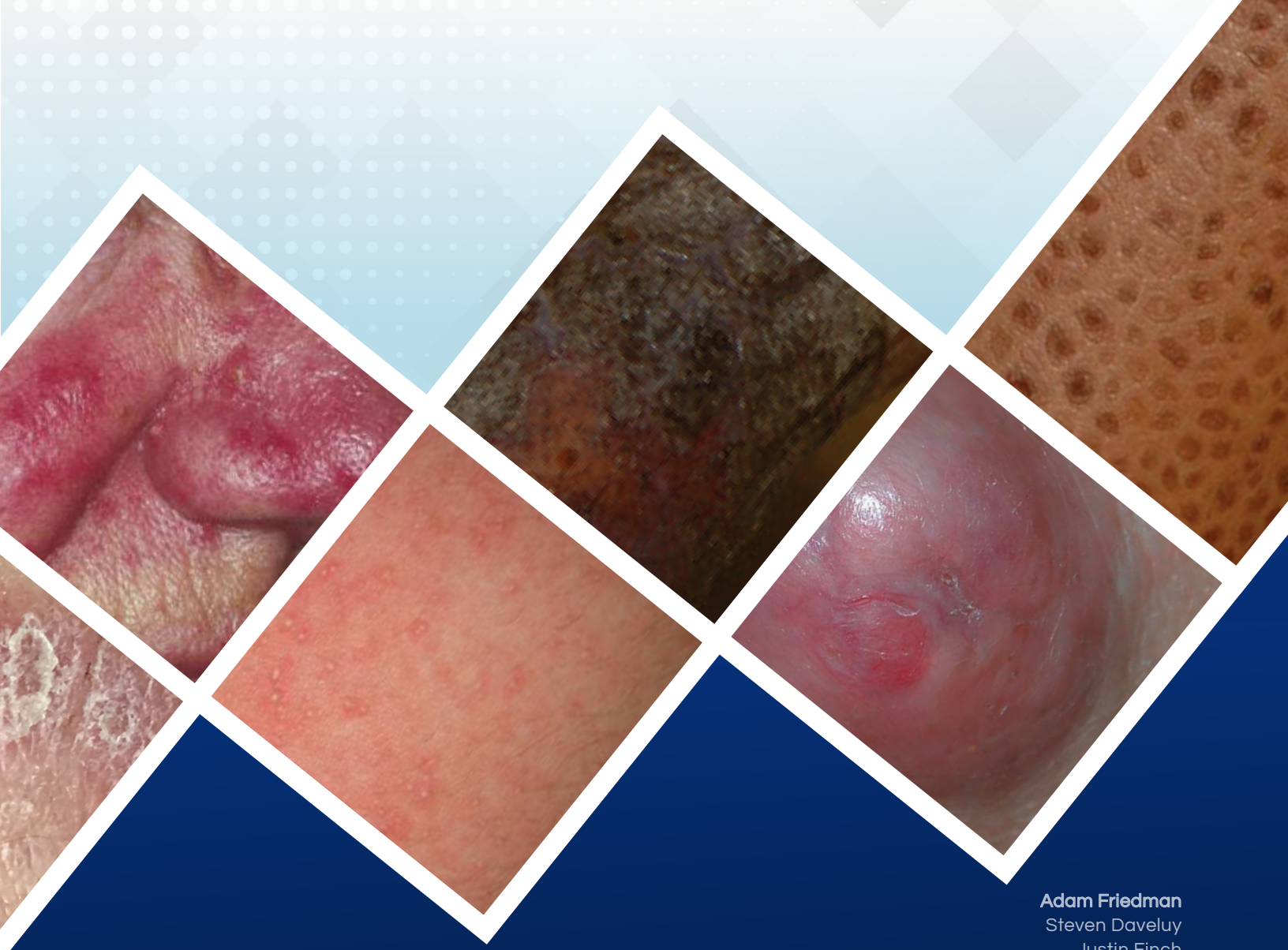

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Derm In-Review
2024 Study Guide

THE

Derm In-Review

STUDY GUIDE | 2024

Companion to the Derm In-Review
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ISBN: 978-1-7332033-8-8

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Dear soon to be colleagues,

It's clear that this decade's theme is crisis—if a decade could land in a Snickers commercial, the 2020s would be the breakout star. Up might be down, but at least one thing can be consistent: WE HAVE YOUR BACK.

Derm In-Review is down to provide high yield, evolving, and updated exam prep materials made for you, by your peers, to ensure you don't have to stress about this stepping stone in your career, even if you are worrying about the dumpster fire around you.

An incredibly diverse array of academic leaders and resident/freshly minted dermatologists (aka the DIR advisory council) are itching to better the already BEST and most comprehensive Board review. Like the stratum corneum, we adapt the environment and protect the viable cells of the dermatology community from test tackling tachyphylaxis.

So, what should you look forward to in this new edition of the Derm In-Review Study Guide? Well, the 2024 edition welcomes some important additions, such as a new Deputy Editor—the one and only Dr. Steven Daveluy, who will no doubt raise the bullae roof on this joint! We are also bringing back the historic *JAAD CME* review, in addition to color coding for the Basic vs Core exams, numerous new kodies, and the latest and greatest in our therapeutic armamentarium.

It is always smart to remember that the study guide should be partnered with all the goodies housed by the online study system including the constantly growing question bank, which can be found at DermatologyInReview.com. Also utilize the photo publication ***The Full Spectrum of Dermatology: A Diverse and Inclusive Atlas*** and become accustomed to its adjoining online gallery. Together these tools are sigma (not sure what that means, but the kids keep saying it)—they provide the most effective and relevant information and methods to prepare you for your exams.

We would like to thank UCB and Incyte, our sponsors, for their support of this program for the 2024-2025 academic year. We are grateful for their commitment to education. Just remember, you've got this. You have traveled far to get here, you deserve it, and you will succeed. Go get it!

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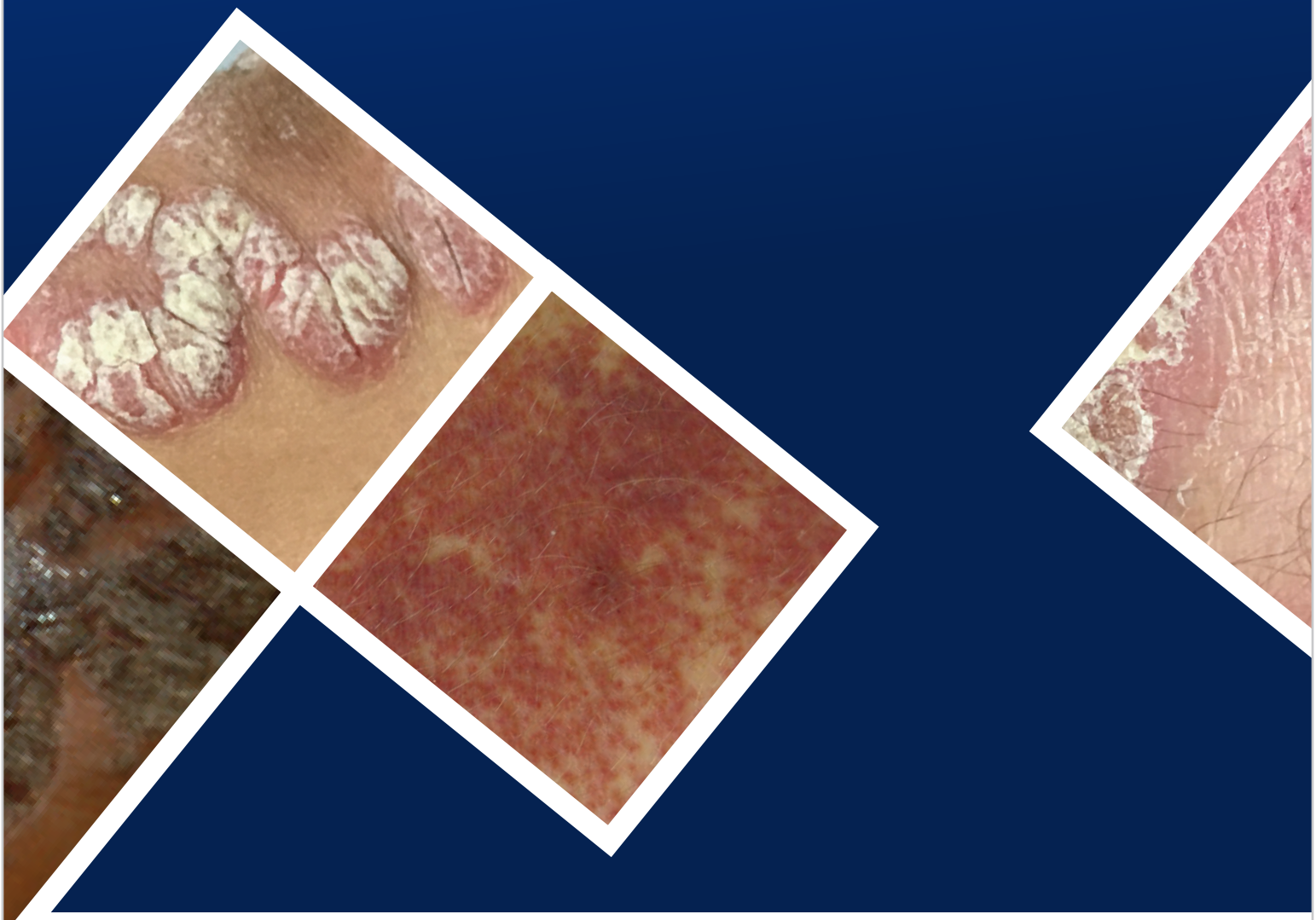

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Certain words or phrases have been bolded to highlight pertinent or key information.

Tip Boxes highlight exam-relevant information for quick study.

TIP

Disease Associations

BPAg1/BPAg2-NC16A	Bullous pemphigoid
BPAg2	Lichen planus pemphigoides
Portion of BPAg2	Linear IgA disease
BPAg2-NC16A	Pemphigoid gestationis

Helpful mnemonic memory cues are displayed in **mnemonic boxes** throughout the chapters.

MNEMONIC

SCALP

Skin
Connective tissue
Aponeurosis (galea)
Loose connective tissue
Periosteum

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Chapter 1

BASIC SCIENCE

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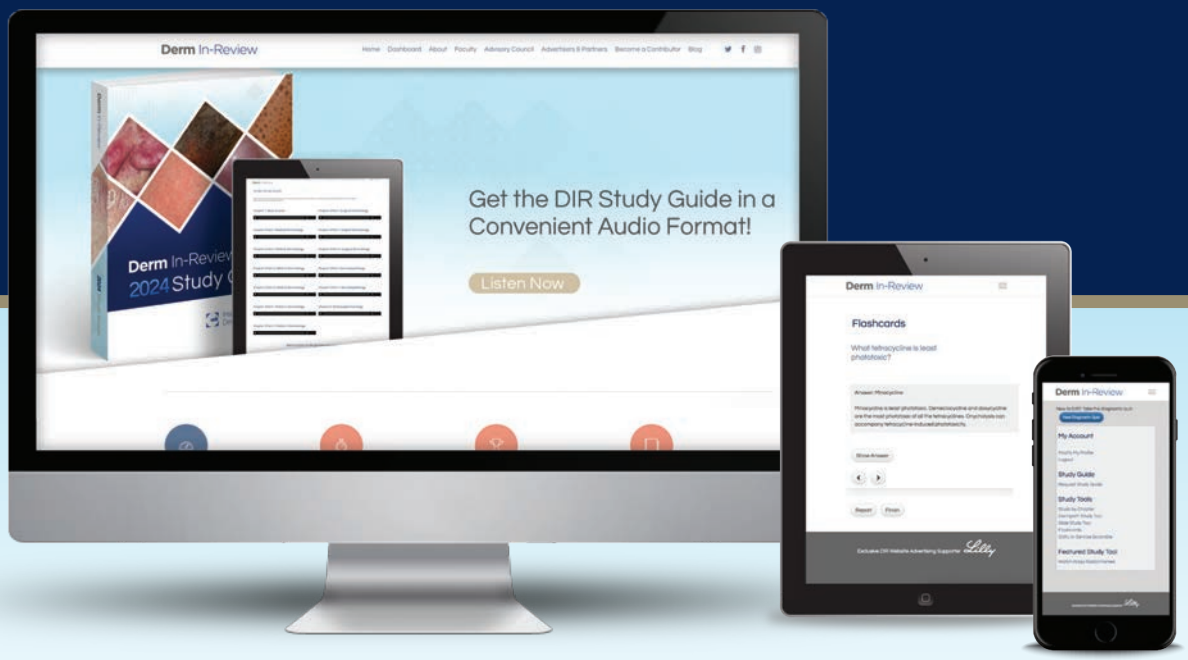

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1.1 Basic Science

EPIDERMIS

Epidermis

- Consists of the following cells:
  - Keratinocytes: 80%
  - Melanocytes: Located in the basal layer
  - Langerhans cells: Suprabasal, 2-8% of total epidermal cell population
  - Merkel cells: Located in the basal layer

Keratinocytes

- **Ectodermal derivation during the first few weeks of embryonic development**
- 90% of total epidermal population
- Express 54 functional keratins (37 epithelial and 17 hair keratins): 40-70 kDa
  - Bind to each other in the rod region
- Acidic keratins: Keratin 9 (K9)-K20, chromosome 17
- Basic keratins: K1-K8, chromosome 12
- Intermediate filaments (see also Section 2.3 Bullous and Vesicular Dermatoses)
  - Type I = acidic keratins 9-20, chromosome 17
  - Type II = basic keratins 1-8, chromosome 12
  - Type III = vimentin, glial fibrillary acidic protein (GFAP), desmin, peripherin
  - Type IV = neurofilaments
  - Type V = nuclear lamins
  - Type VI = nestin
- Keratinocytes are able to release, respond to, and produce tumor necrosis factor (TNF)-α. Causes increased differentiation

TIP

Acidic and basic keratins are coexpressed in order to form filamentous structure: "Obligate heteropolymers"

TABLE 1.1.1 INTERMEDIATE FILAMENTS

Type I	Type II	Type III	Type IV	Type V	Type VI	Others (Unclassified)
Keratins 9-20	Keratins 1-8	Vimentin	NF-L, NF-H,	Lamin A/C	Nestin	Filensin
20 (acidic)	8 (basic)	Desmin	NF-M	Lamin B1		Phakinin
		GFAP	α-Internexin	Lamin B2		
		Peripherin	Syncoilin			
			Synemin			

GFAP = glial fibrillary acidic protein; NF-L, NF-H, NF-M = neurofilament light, heavy, and medium polypeptides, respectively.

TABLE 1.1.2 KERATIN EXPRESSION PATTERNS

Type II	Type I	Location	Hereditary Disease Association
K1	—	Suprabasal keratinocytes	Ichthyosis hystrix of Curth-Macklin Diffuse nonepidermolytic PPK (Unna-Thost)
K1	K10	Suprabasal keratinocytes	Bullous congenital ichthyosiform erythroderma, EHK (corrugated scale)
K1	K9	Palmoplantar suprabasilar keratinocytes	Epidermolytic PPK, diffuse nonepidermolytic PPK
K2e	K10	Upper spinous and granular layers	Ichthyosis bullosa of Siemens (milder EHK)
K3	K12	Cornea	Meesmann's corneal dystrophy
K4	K13	Mucosal epithelium	White sponge nevus (Cannon): Buccal

TABLE 1.1.2 KERATIN EXPRESSION PATTERNS CONTINUED

Type II	Type I	Location	Hereditary Disease Association
K5	K14	Basal keratinocytes	Epidermolysis bullosa simplex 1. Dowling-Meara (head or tail of central rod domain) 2. Koebner (segment 1a or 2b of rod domain) 3. Weber-Cockayne (nonhelical parts)
K5	K15	Mucosal basal layer	
K6a	K16	Outer root sheath, hyperproliferative keratinocytes	Pachyonychia congenita type I (Jadassohn-Lewandowsky), focal nonepidermolytic PPK
K6b	K17	Nail bed	Pachyonychia congenita type II, steatocystoma multiplex (Jackson-Lawler)
K8	K18	Simple epithelium	Cryptogenic cirrhosis
hHb1	—	Hair follicle	Monilethrix
hHb6	—		
—	K19	Bulge cells and simple epithelium	Paget's; CK7, CK20 are other markers
—	K20	Basal layer of epidermis	Merkel cell carcinoma
K1	K16		Nonepidermolytic PPK
—	K17		Steatocystoma multiplex
K5	—		EBS mottled pigmentation (nonhelical V_1 domain)
—	K14		EBS (autosomal recessive)
—	K14		Naegeli-Franceschetti-Jadassohn syndrome dermatopathia pigmentosa reticularis

CK = cytokeratin; EBS = epidermolysis bullosa simplex; EHK = epidermolytic hyperkeratosis; PPK = palmoplantar keratoderma.

Stratum Germinativum (Basale)

- Basal cells contain ornithine decarboxylase (marker of proliferative activity); stimulated by trauma, UV, epidermal growth factor (EGF), estrogens, β-agonists, tumor promoters; Inhibited by retinoids
- The basal layer
- K5 and K14 expressed: Defective in epidermolysis bullosa simplex
- K19 found in basal cells at transitional boundaries between different types of epithelia
- Microfilaments (actin, myosin, and α-actinin) assist in upward movement of cells as they differentiate

TIP

Keratin filaments in basal cells insert into desmosomes and hemidesmosomes

- Integrins regulate adhesion and initiation of differentiation
- **Once a basal cell leaves the basal layer in humans, normal transit time to stratum corneum is at least 14 days, and transit through stratum corneum to desquamation requires 14 days, leading to 28 days total**
- Stem cells give rise to transit-amplifying cells, which allow for maintenance of tissue

Stratum Spinosum

- Cells have rounder nucleus, more flattened appearance
- **Cells contain lamellar granules (L is for lipids)**
- Lamellar granules contain ceramides
- K5/K14 still present, but not made de novo in this layer
- New synthesis of K1/K10: Keratinization-specific keratins, characteristic of epidermis, markers of terminal differentiation
- **In psoriasis, actinic keratoses, and wound healing, suprabasilar keratinocytes downregulate K1/K10 and make K6/K16 (the mRNAs for K6/K16** are always present but only translated during proliferation)
- Hyperproliferative state markers: K6, K16, Ki-67
- Desmosomes form "spines": Calcium-dependent structures that promote adhesion
- Desmosomal plaque: Six polypeptides, plakoglobin, desmoplakins I and II, keratocalmin, desmoyokin, and band 6 protein (see Table 1.1.3 for listing of desmosomal proteins and associated diseases)

TABLE 1.1.3 DESMOSOMAL PROTEINS

Protein	Location	Disease Association(s)
Plakoglobin	Plaque	Naxos syndrome
Desmoplakin I/II	Plaque	Carvajal syndrome
Keratocalmin	Plaque	None described to date
Desmoyokin	Plaque	None described to date
Band 6 protein	Plaque	Ectodermal dysplasia/skin fragility syndrome
Plakophilin	Plaque	Ectodermal dysplasia/skin fragility syndrome
Envoplakin	Plaque	Paraneoplastic pemphigus (210-kDa antigen)
Desmocalmin	Plaque	None described to date
Desmoglein I	Transmembrane	AD Striate PPK/pemphigus foliaceus
Desmoglein III	Transmembrane	Pemphigus vulgaris
Desmocollin I	Transmembrane	Subcorneal pustular dermatosis
Desmocollin III	Transmembrane	None described to date

AD = autosomal dominant; PPK = palmoplantar keratoderma.

- **Transmembrane cadherins provide adhesive properties; contain desmogleins I and III; intracellular domains link with intermediate filament cytoskeleton**
- Gap junctions are more abundant in stratum spinosum compared with stratum basale
  - Communication between cells
  - More differentiated keratinocytes have more abundant gap junctions (few in basal cell layer)

TIP

Diseases Related to Gap Junction Proteins

Connexin 26	Vohwinkel's syndrome, keratitis-ichthyosis-deafness (KID) syndrome, palmoplantar keratoderma (PPK) with deafness
Connexins 30.3 and 31	Erythrokeratodermia variabilis
Connexin 30	Hidrotic ectodermal dysplasia

TIP

Lamellar granules deliver lipid precursors into the intercellular space:

- Glycoproteins
- Glycolipids
- Phospholipids
- Free sterols
- Glucosylceramides

- Lamellar granules: A type of membrane-bound intracellular structure, 0.2-0.3 μm in diameter; a lysosome with secretory function. They are lamellated bodies found intracellularly in upper-level keratinocytes. **Ceramide is the major lipid for barrier function of the skin**
  - First appear in stratum spinosum, but primary activity in stratum corneum
  - Discharge their contents into the extracellular space at the junction of the granular and horny layers, establishing a barrier to water loss, and with filaggrin, mediate stratum corneum adhesion
  - Deliver lipid precursors into intercellular space: Glycoproteins, glycolipids, phospholipids, free sterols, and glucosylceramides (predominant lipid of stratum corneum)

- Commonly used synonym is "Odland bodies"
- **Flegel's disease: Decreased lamellar granules**
- **Harlequin ichthyosis: Lamellar granules uniformly abnormal or absent. Defect in *ABCA12* at 2q34 (also defective in lamellar ichthyosis type II)**
- **X-linked ichthyosis: Steroid sulfatase missing in lamellar granules.** Increased levels of the β fraction of cholesterol sulfate can be identified by serum lipoprotein electrophoresis
- Prenatal diagnosis can be accomplished by measurement of decreased estrogen levels and the presence of nonhydrolyzed sulfated steroids in maternal urine. Characteristic brown scale is known as "dirty brown scale"

Stratum Granulosum (Components)

- Keratohyalin granules contain profilaggrin (F granules) and loricrin (L granules contain loricrin at periphery and help form cornified cell envelope) + keratin intermediate filament (KIF)
- K1 modified to K2, and K10 to K11 by proteolysis and phosphorylation
- Lamellar granules originate in Golgi
- Cornified cell envelope (CE): Proteins synthesized in spinous/granular layers
  - Durable, protein/lipid polymer formed within differentiating keratinocytes
  - Eventually exists outside of cornified cells
  - Components include:
    - Envoplakin
      - Homologous to desmoplakin. May link the CE to desmosomes and to keratin filaments
    - Involucrin
      - Cross-linked by transglutaminase in granular layer to an insoluble cell boundary
    - Loricrin
      - Located in upper spinous layer and throughout the stratum granulosum
      - 75% of CE's mass (major protein component of CE)
      - Vohwinkel syndrome variant associated with defect in loricrin
      - Filament aggregating activity
- **Filaggrin: Histidine rich; filament-aggregating activity; defect causes ichthyosis vulgaris**
  - Profilaggrin converted to monomeric filaggrin subunits when granular layer is transformed to cornified layer; a calcium-dependent process
  - Thought to promote aggregation and disulfide bonding of keratin filaments in cornified cell (like a glue)
  - **Degraded into urocanic acid and pyrrolidone carboxylic acid; both hydrate stratum corneum and block UV radiation**
  - Stored in kit granule
- Transglutaminase (TG): 3 versions that function in cross-linking the CE (calcium-dependent process). Forms γ-glutamyl-lysine isodipeptide bonds in the CE, most prominently with involucrin
  - **TG-1 (type K)**: Keratinocyte transglutaminase, membrane associated, **defect causes lamellar ichthyosis type I** (*TGM1* gene) and nonbullous congenital ichthyosiform erythroderma (*T9M1* + *ALOX12B* + *ALOXE3*)
  - **TG-2** (type C): Fetal epidermis and basal layer of adult epidermis, soluble
  - **TG-3**: When present in hair follicles and differentiated epidermal cells, soluble. When present in sublamina densa, can be antigen for dermatitis herpetiformis; 77 kDa

TIP

Basal layer: K5, K14—keratin filaments
Spinous layer: K1, K10—lamellar granules (K6, K16 in psoriasis)
Granular layer: K2, K11—keratohyalin granules

- There is programmed destruction of the granular cell: Loss of nucleus, yet retention of keratin filaments and filaggrin matrix
  - Destruction involves apoptosis, called transition cells ("T" cells)
  - Terminal differentiation is initiated by increase in calcium gradient in suprabasal epidermis

Stratum Corneum (SC)

- Transition from stratum granulosum accompanied by loss of 45-86% in dry weight
- **Provides mechanical protection**, barrier to water loss, and barrier preventing permeation of environmental soluble substances
- **Consists of keratin in filaggrin-rich matrix**
- **Normal SC cells have no nuclei**; nuclei may persist in incompletely keratinized cells (parakeratosis)
- "Bricks and mortar": Corneocytes (bricks) and extracellular lipid matrix (from loricrin)/lamellar lipid barrier (mortar)

Epidermal Differentiation

- **Triggered by calcium**
- Ends in CE
- Steps
  1. Cross-linking of envoplakin, periplakin, along cell membrane
  2. Lamellar granule 6 extrusion into extracellular space
  3. Loricrin cross-links envelope
  4. Keratin and filaggrin cross-link

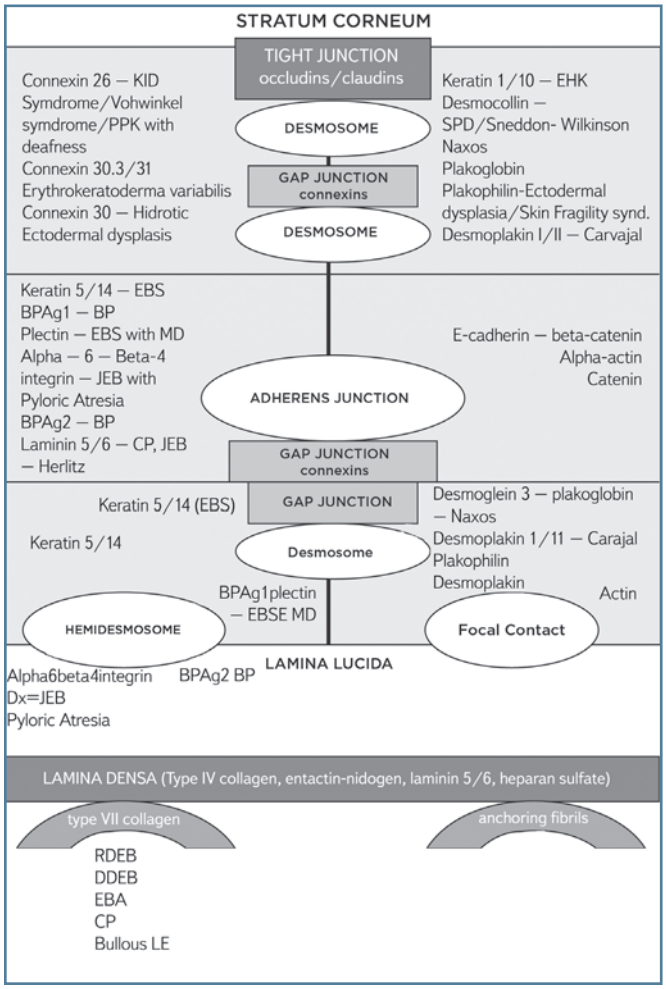

Figure 1.1.1 Skin adhesion molecules with corresponding diseases.

TABLE 1.1.4 EPIDERMOLYSIS BULLOSA

Condition	Defect
EBS	K5, K14, plectin
EBS: Herpetiformis (Dowling-Meara)	K5, K14 (head or tail of central rod domain)
EBS: Weber-Cockayne (palms/soles)	K5, K14 (nonhelical parts)
EBS: Koebner	K5, K14 (segment 1a or 2b of rod domain)
EBS: Muscular dystrophy	Plectin
JEB: Lethal, Herlitz	Laminin 5 (*LAMB3* gene)
JEB: Pyloric atresia	$\alpha_6\beta_4$-Integrin
Dominant DEB (Cockayne-Touraine, hyperplastic, albopapuloid Pasini): Atrophic white scars	Collagen VII (*Col7A1*)
RDEB: Hallopeau-Siemens	Collagen VII (*Col7A1*)
Bart's syndrome	Collagen VII
EB acquisita	Collagen VII
EBS: Mottled pigmentation	K5 (nonhelical V_1 domain)
EBS: AR	K14

AR = autosomal recessive; DEB = dystrophic epidermolysis bullosa; EB = epidermolysis bullosa; EBS = epidermolysis bullosa simplex; JEB = junctional epidermolysis bullosa; RDEB = recessive dystrophic epidermolysis bullosa.

Basement Membrane Zone

- See Figure 1.1.2
- Site of interaction between epidermis and dermis
- Three layers
  1. Lamina lucida
  2. Lamina densa
  3. Sublamina densa
- Hemidesmosomal adhesion complex
  1. Hemidesmosomal plaque
  2. Anchoring filaments
  3. Anchoring fibrils
- Know the electron microscopy picture of the basement membrane zone

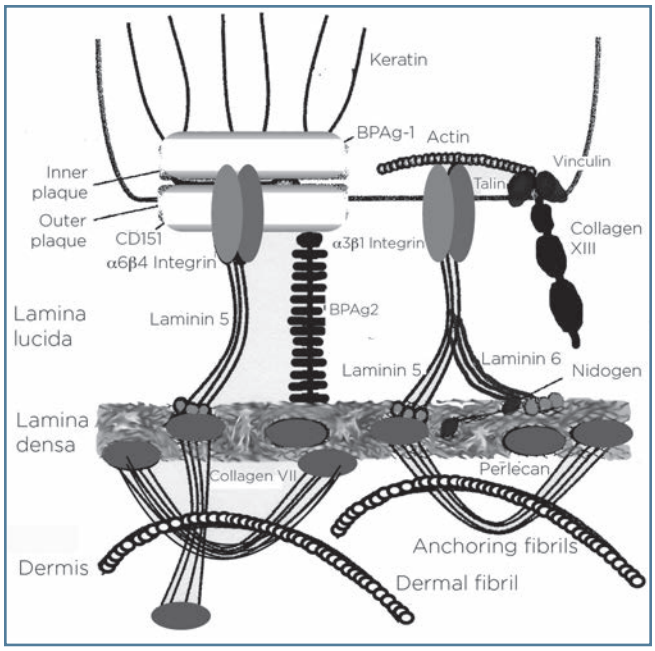

Figure 1.1.2 Dermal-epidermal junction components.

TABLE 1.1.5 KERATINOCYTE INTEGRIN RECEPTORS

Integrin	Ligand
β_1 Family	
$\alpha_1\beta_1$	Fibrillar collagen, laminin
$\alpha_2\beta_1$	Fibrillar collagen, laminin
$\alpha_3\beta_1$	Fibronectin, laminin 5, denatured collagen
$\alpha_5\beta_1$	Fibronectin
$\alpha_6\beta_1$	Laminin
β_4 Family	
$\alpha_6\beta_4$	Laminin 5
α_v Family	
$\alpha_v\beta_1$	Fibronectin, vitronectin
$\alpha_v\beta_3$	Vitronectin, fibronectin, fibrinogen, denatured collagen
$\alpha_v\beta_5$	Vitronectin
$\alpha_v\beta_6$	Fibronectin, tenascin

Lamina Lucida

- Hemidesmosome
  - Attachment complex for basal keratinocytes and extracellular matrix
  - Electron-dense domain on the ventral surface of basal keratinocytes: Bridge cytoskeleton and cutaneous basement membrane
  - Proteins
    - **BPAg1: 230-kDa protein (desmoplakin), noncollagenous glycoprotein**
      - **Intracellular at attachment plaque**
      - **Member of the plakin family and homologous to desmoplakin**
      - **Attaches intermediate filaments (keratins) to hemidesmosomal plaque**
      - **Belongs to the gene family that includes desmoplakin I**
    - **BPAg2: 180-kDa protein (collagen XVII)**
      - **Transmembrane protein**
      - **Interacts with BPAg1, β_4-integrin, and plectin intracellularly**
      - **Its NC16A domain (target of autoantibodies in bullous pemphigoid) interacts with α_6-integrin extracellularly**
      - **Also interacts with laminin 5 extracellularly**
      - Two forms: Full-length transmembrane and soluble 120-kDa ectodomain that is shed from cell surface
  - Integrins: Transmembrane proteins
    - **$\alpha_6\beta_4$-Integrin found at sites where keratin intermediate filaments attach**
    - Expression limited to basal layer of epidermis
    - Coordinates linkage between intermediate filaments and extracellular matrix of the basement membrane

TIP

Disease Associations

BPAg1/BPAg2-NC16A	Bullous pemphigoid
BPAg2	Lichen planus pemphigoides
Portion of BPAg2	Linear IgA disease
BPAg2-NC16A	Pemphigoid gestationis
BPAg2, C-terminal domain	Cicatricial pemphigoid

- β_4-Integrin membrane-proximal domain interacts with plectin, and its distal domain interacts with BP180; absence of β_4 prevents hemidesmosomal assembly
- Extracellular α_6 domain binds laminin 5
- **Defect in β_4 seen in cicatricial pemphigoid with ocular involvement only**
- **Defects in $\alpha_6\beta_4$ result in junctional epidermolysis bullosa (JEB) with pyloric atresia**

- Plectin: Member of the plakin family
  - Links intermediate filaments to the plasma membrane and cross-links various hemidesmosomal proteins
  - **Mutations result in epidermolysis bullosa simplex with muscular dystrophy**

Anchoring Filaments

- **Laminin 5 (also called laminin 332) and BP180 are major components**
- Trimeric proteins (composed of three classes of polypeptides) intersect to form a cross-like structure that can bind to other cell membrane and extracellular matrix molecules
  - Span from plasma membrane of basal keratinocytes to lamina densa
  - Two major roles:
    1. Structural network in basement membrane to which other proteins attach
    2. Signaling
  - Molecules that interact with other proteins (such as integrins) to transmit morphogenetic information to the cell's interior
  - Laminin 5/332 (major component of anchoring filaments; also called epiligrin)
  - Laminin 6 isoforms are found in the dermoepidermal junction (DEJ) of human skin and mucous membranes
- Uncein
  - Also known as antigen of 19-DEJ-1 monoclonal antibody; 19DEJ1-Ag
  - Associated with anchoring filaments
- Fibronectin
  - Central function in wound healing
  - Secreted by myofibroblasts; stimulated by EGF and thrombin
  - Allows fibroblasts to adhere to extracellular matrix (ECM), provides "scaffolding" for collagen fibrils and assists in wound contraction
- Nidogen
  - Also called entactin
  - Dumbbell-shaped
  - Binds to laminin 1

Lamina Densa

- Type IV collagen
  - Functions in structural support and confers flexibility to basement membrane
  - Highly cross-linked, forms a lattice
  - Primary component of anchoring plaques
- Heparan sulfate proteoglycan
  - Negatively charged, thus is a permeability barrier

Sublamina Densa

- Type VII collagen
  - **Targeted auto-antigen in epidermolysis bullosa acquisita and bullous lupus erythematosus**
  - **Mutated in dystrophic epidermolysis bullosa**
  - Primary constituent of anchoring fibrils
  - Homotrimeric protein

Anchoring Plaques

- Composed of type IV collagen
- Point of attachment for anchoring fibrils composed of type VII collagen (from "above") and collagens I and III from the dermis "below"

Melanocytes

- Pigment-producing cell derived from neural crest, projects cellular processes that interact with other cells
- Found in multiple tissues: **Epidermis, hair matrix, retinal pigment epithelium, ear (stria vascularis), leptomeninges, mucous membranes, ciliary body, choroid, iris, and enteric ganglion cells**

Skin Melanocytes

- In skin, localized to basal layer of epidermis
- **Melanin production (melanogenesis) occurs in specialized organelles called melanosomes**
- **Melanosomes, via dendritic-like processes, contact keratinocytes (epidermal melanin unit = approximately 36 keratinocytes in contact with one melanocyte) and transfer melanosomes to keratinocytes**

- Keratinocytes can produce both growth and inhibitor factors for melanocytes
  - Growth: Basic fibroblast growth factor (bFGF) and transforming growth factor (TGF)-α
  - Inhibitory: Interleukin (IL)-1, IL-6, TGF-β
- Be able to recognize a melanocyte on electron microscopy

Melanin Synthesis

- **Occurs in melanosomes; similar to lysosomes; pH-regulated organelles; tyrosinase (TYR), the rate-limiting step, is pH sensitive**
- **Two types of melanosomes: Eumelanosomes (make eumelanin) and pheomelanosomes (make pheomelanin)**. In humans most melanosomes switch from making one melanin to another
- Stages of melanosomes
  - Stage 1: Spherical
  - Stage 2: Ellipsoid
  - Stage 3: Matrix is melanized
  - Stage 4: Melanization is complete
- Elliptical melanosomes synthesize brown or black eumelanin; have longitudinally oriented, concentric lamellae. Critical enzymes include tyrosinase-related protein 1 (TYRP1) and TYRP2 (also called dopachrome tautomerase [DCT]). Hormones that drive pigmentation such as MSH induce gene expression of TYR, TYRP1, and TYRP2
- Spheroid melanosomes produce yellow or red pheomelanin; have microvesicular internal structure
- Melanin transfer involves the active phagocytosis of the dendritic tips of melanocytes by keratinocytes and hair cortex cells
- Melanin is distributed preferentially to more basally located keratinocytes
- Defects in melanin production (melanocyte number unchanged)
- **Oculocutaneous albinism (OCA)**
  - Defect in melanin synthesis due to loss of:
    - **Tyrosinase (OCA1) (melanosomes arrest in stage I or II)**
    - **P-gene (OCA2)**
    - ***TYRP1* gene (OCA3)**
- Individuals with darker skin tone have:
  - A greater production of melanosomes in the melanocytes
  - Individual melanosomes with a higher degree of melanization
  - Larger melanosomes
  - Higher degree of dispersion of melanosomes in the keratinocytes
  - A slower rate of melanosome degradation
  - **No difference in total melanocyte number**

Hair Melanocytes

- **Melanin unit exists in proximal anagen bulb: One melanocyte paired with five keratinocytes**
- Follicular melanogenesis coupled to hair growth cycle: Melanocyte proliferation occurs during early period of anagen
- Hair follicle contains melanocyte precursors that can repopulate the interfollicular epidermis
- Graying caused by gradual decline in the number of follicular melanocytes; influenced by both age and genes
- ***MC1R* gene mutations associated with red hair. Increased risk of melanoma and skin cancer**

Merkel Cells

- Mechanoreceptors at sites of high tactile sensitivity
- Located at the basal level of the epidermis
- Keratinocytic deformation induces secretion of chemokines by Merkel cells
- Location: Hair-bearing skin and glabrous skin of the digits and lips, oral cavity, and outer root sheath (ORS) of hair follicle
- **Cytokeratin 20 (CK20) is a specific and reliable marker of Merkel cells and presents as perinuclear dots**
- Make synaptic connection with neurons (the Merkel cell-neurite complex); neurochemical transmission occurs between an activated Merkel cell and its neuron

Langerhans Cells

- **Bone-derived, $CD34^+$, antigen-processing and -presenting cells of monocyte/macrophage lineage**
- Migrate from bone marrow in embryonic development and continue to repopulate epidermis during lifetime
- **Positive for CD207 (langerin), S100, and CD1a, and have Birbeck granules in cytoplasm.** Positive for CD45, ATPase (1st marker to develop), Fc receptor, C3, actin, and vimentin
- **Kidney-shaped nucleus, Birbeck granules seen on EM**
- Found in the skin and other epithelial tissues: Oral mucosa, esophagus, vagina
- Also found in lymph nodes and dermis

- Two stages in the Langerhans life cycle
  1. **In epidermis, ingest and process antigens; weak stimulators of T cells**
  2. **Activated Langerhans cells that have contacted antigen and can strongly stimulate naïve T cells**
- Once a Langerhans cell encounters and processes a given antigen, it "matures" and migrates to a local lymph node, where it then presents the antigen to a naïve (or resting) T cell, which activates that T cell
- **Langerhans cells are central to the pathogenic processes of atopic dermatitis, psoriasis, allergic contact dermatitis, and infections such as leishmaniasis**
- **Functionally impaired by ultraviolet radiation**
- Located in all layers of epidermis, but mostly in suprabasal layer
- Adhere to cells by E-cadherin
- Produce IL-1

TIP

Langerhans Cells

- The most important cells for recognition, uptake, and processing of antigens in the skin and presenting these antigens to naïve T cells
- Characteristic finding on electron microscopy: Birbeck granules—tennis racket–shaped bodies in the cell. Be able to identify an electron microscopy image of a Langerhans cell
- Disease processes involving Langerhans cells
  - Letterer-Siwe disease
  - Hand-Schüller-Christian disease
  - Eosinophilic granuloma
  - Hashimoto-Pritzker disease
  - Can be infected with HIV

TIP

CD1a stain also positive in leishmaniasis

Stem Cells

- Lineage-specific cells that can multiply and differentiate to mediate epidermal renewal/turnover
- Keratinocyte stem cells: Express markers such as Delta 1, MCSP, α_6- and β_1-integrins, LRIG1; low levels of CD71
- Melanocyte stem cells: Express markers such as ax3, TYRP1, TYRP2; negative for KIT, tyrosinase
- Hair follicle stem cells: Express markers such as SOX9, keratin 15, α_6- and β_1-integrins, CD200, PHLDA1, follistatin, frizzled homolog 1, LGR5; low levels of CD24, CD34, CD71, CD146
- Merkel cell stem cells: Express markers such as α_6-integrin, keratin 17, ATOH1, CD200, GLI1, SOX2

DERMIS

Dermis

- Collagen, elastic fibers, matrix (extracellular matrix and ground substance made up of proteoglycans and gelatin), cells (fibroblasts, monocytes, phagocytes, mast cells, dermal dendrocytes, glomus cells)

Collagen

- **Primary dermal component: Comprises** 75% of dry weight of skin
- Provides tensile strength and elasticity
- **Adult dermis: Types I, III, and V; type I accounts for 85% of collagen;** type III accounts for 10%; type V accounts for 5%
- **Lysyl hydroxylase and proline hydroxylase cross-link collagen (desmosine residues); vitamin C is a required cofactor (copper and vitamin B_6 also) for function of enzyme; vitamin C deficiency = scurvy**
- Types I and III are major interstitial fiber–forming collagens

TIP

Composed of three chains that vary according to collagen type. All have Gly-X-Y amino acid motif that repeats, where X and Y are proline and hydroxyproline

TABLE 1.1.6 TYPES OF COLLAGEN, TISSUE DISTRIBUTION, AND DISEASE ASSOCIATION

Type	Tissue Distribution	Disease Association
I (85%)	Mature skin, bone, tendon (except bone marrow and cartilage)	*COL1A1/2*: Ehlers-Danlos syndrome (EDS), arthrochalasia type; and osteogenesis imperfecta
II	Cartilage, vitreous	Relapsing polychondritis
III (10%)	Fetal skin, blood vessels, intestines	Wound repair, *COL3A1*—EDS vascular type
IV	Basement membranes	Alport syndrome and Goodpasture syndrome
V (5%)	Ubiquitous	*COL5A1/2*: EDS classical type
VI	Aorta, placenta	Congenital muscular dystrophy without skin findings
VII	Anchoring fibrils, amnion	Dystrophic epidermolysis bullosa (EB), bullous lupus, cicatricial pemphigoid
VIII	Cornea: Descemet's membrane	Corneal dystrophy
IX	Cartilage	No associated skin disease
X	Cartilage	No associated skin disease
XI	Cartilage	No associated skin disease. Stickler and Marshall syndromes (ophthalmic disease)
XII	Cartilage and fibroblasts	No associated skin disease
XIII	Fibroblasts	No associated skin disease
XIV	Skin, placenta, tendon, cartilage, muscle	No associated skin disease
XV	Placenta	No associated skin disease
XVI	Placenta	No associated skin disease
XVII	Anchoring filaments	Junctional EB, generalized atrophic benign EB, bullous pemphigoid
XVIII	Liver, kidney, placenta	
XIX	Breast, colon, kidney, liver, placenta, prostate, skeletal muscle, skin, and spleen	Rhabdomyosarcoma

Collagen Diseases

- Ehlers-Danlos syndromes
  - **Excessive flexibility and fragility of the skin with a tendency toward easy scar formation ("fish-mouth" scars)**
  - Calcification of the skin that produces pseudotumors
  - See Chapter 3 Pediatric Dermatology for description of types
- Random associated diseases
  - **Osteogenesis imperfecta: Abnormal type I collagen**
  - **Homocystinuria: Abnormal cross-linking of collagen because of mutated cystathionine synthase**
  - **Tenascin-X: Autosomal recessive type EDS similar to classic type. Associated with collagen fibrillogenesis**

Elastic Fibers

- 4% of dry weight of the skin
- Forms complex meshwork extending from lamina densa of the DEJ through the dermis and into the hypodermis
- Returns skin to normal configuration after being stretched
- Elastic fibers: 90% elastin, wrapped by fibrillin microfibrils (**mutated in Marfan's**)
- **Desmosine and isodesmosine are amino acids found in elastic fibers**
- Cross-linking of fibrillin requires lysyl oxidase (copper-dependent process)
- **Oxytalan fibers: Contain no elastin; run perpendicular from DEJ within superficial papillary dermis**
- **Elaunin fibers: Have less elastin and more fibrillin; run parallel in thin bands within the reticular dermis**
- Elastic fibers turn over slowly in the skin and are damaged by ultraviolet radiation

Elastin Diseases

- Cutis laxa
  - **Fibulin 5 gene defect**
  - Decreased desmosine and lysyl oxidase
  - Fragmentation and loss of elastic fibers
- Marfan's syndrome
  - **Decreased fibrillin I**
  - Fragmentation of elastic fibers, especially aortic
- Congenital contractural arachnodactyly
  - **Mutation in fibrillin 2**
- Pseudoxanthoma elasticum
  - MDRP (multiple drug—resistant protein)
  - ***ABCC6* gene defect** (adenosine triphosphate binding cassette subfamily C member 6)
  - Increased glycosaminoglycans on elastic fibers
  - Calcium deposition
  - Accumulation of fragmented and calcified elastic fibers
- Buschke-Ollendorff syndrome
  - ***LEMD3* (also called *MAN1*) gene defect**
  - Increased desmosine
  - Increased amount of thickened elastic fibers
- Anetoderma
  - **Decreased desmosine**
  - Loss and fragmentation of elastic fibers

Dermal Matrix Components

- Proteoglycans and glycosaminoglycans → ground substance that surrounds the fibrous constituents of the dermis; 0.2% of dry weight of the dermis
- Proteoglycans consist of a "core protein" with a glycosaminoglycan such as hyaluronic acid binding to the core protein; other glycosaminoglycans include dermatan sulfate, heparan sulfate, and chondroitin sulfate
- **Can bind up to 1,000 times their volume and regulate the water-binding capability of the dermis**
  - Utilized in dermal fillers
- Mucopolysaccharidoses represent genetic storage diseases resulting from abnormal lysosomal function and subsequent accumulation of these substances → for example, **Hurler's (α-L-iduronidase) and Hunter's (iduronate sulfatase)**. See Chapter 3 Pediatric Dermatology for more detail on these conditions

Papillary Dermis

- Young or healthy skin: Small-diameter collagen fibrils and oxytalan elastic fibers
- Aging or actinically damaged skin: Mature elastic fibers that are large and dense
- High density of fibroblast cells that proliferate rapidly
- Solar elastosis represents degenerated collagen in dermis

Reticular Dermis

- Large-diameter collagen fibers with mature, branching elastic fibers
- Elastic and collagen bundles progressively increase in size as they move toward the hypodermis

Cells of the Dermis

- Fibroblasts
  - **Derived from mesenchyme**
  - **Produce extracellular matrix framework**
  - Synthesize soluble mediators that regulate signaling between the dermis and epidermis
  - **During wound healing they produce fibroplasia and control wound contraction (myofibroblasts)**
- Mononuclear phagocytic cells
  - Monocytes, macrophages, and dermal dendrocytes from bone marrow
  - All phagocytic skin macrophages express CD11c, CD6; CR4 (CD11c) = α_2-integrin that binds C3b, leading to stimulation of phagocytosis

- Macrophage functions
  - **Phagocytic and tumoricidal**
  - **Processing and presenting antigens to naïve T cells**
  - **Microbicidal through production and release of lysozyme, peroxide, and superoxide**
  - Secretory (cytokines, growth factors, etc.)
  - **Involved in coagulation, atherogenesis, wound healing, and tissue remodeling**
  - CD11a = LFA (binds to ICAM)
  - CD11b = Mac-1 on phagocytes binds to LCAM

Mast Cells

- Greatest density in the papillary dermis, in sheaths of the appendages, and around blood vessels and nerves of the subpapillary plexus
- **Diseases: Mastocytosis, solitary mastocytoma, diffuse erythrodermic mastocytosis, telangiectasia macularis eruptiva perstans (TMEP), urticaria pigmentosa**
- **Derived from bone marrow $CD34^+$ stem cells**
- **Proliferation depends on the c-Kit receptor and its ligand stem-cell factor (SCF). Mutations in c-Kit (CD117) may result in mastocytosis or piebaldism**
- Stain cells for CD34, c-Kit, SCF or with Giemsa, Toluidine, Leder stain (naphthol chloroacetate esterase)
- **Many inflammatory mediators, such as histamine, heparin, tryptase, chymase, carboxypeptidase, neutrophil chemotactic factor, and eosinophilic chemotactic factor of anaphylaxis, are produced and stored in preformed secretory granules. Also produce IL-8 (strong neutrophil chemotactic factor) and prostaglandin D_2 (PGD_2)**
- **Cells release without storing: Growth factors (platelet-activating factor), cytokines, and leukotrienes including prostaglandin D_2**
- Secretory granule release induced by a variety of stimuli
- The release or degranulation process is identical regardless of stimulus
- Degranulation leads to vascular smooth muscle contraction, increased vascular permeability, tissue edema, and the recruitment of inflammatory cells
- **Responsible for immediate-type hypersensitivity reactions and participate in chronic inflammatory conditions**
- Histologically: Round or oval nucleus and dark-staining granules

TABLE 1.1.7 MAST CELLS

Mast Cell Type	Mediator	Location
T type	Tryptase only	Bowel and respiratory mucosa
TC type	Tryptase and chymase	Skin, gastrointestinal tract, submucosa
C type	Chymase only	Skin, lymph nodes

Dermal Dendrocytes

- Subset of antigen-presenting cells that function in the afferent limb of the immune response
- Derived from bone marrow
- Found in papillary dermis and upper reticular dermis
- Highly phagocytic, same as melanophages in the dermis that contain ingested pigment
- Likely the cell of origin in benign proliferative tumors such as dermatofibromas or fibroxanthomas

Glomus Cells

- Derived from **Suquet-Hoyer** canals
- Vascular smooth muscle cells
- Allow for the rapid shunting of blood from the arterioles to venules by bypassing capillaries; found primarily in palms and soles
- Disease processes include glomus tumor and glomangioma

ANTIGENS IMPLICATED IN AUTOIMMUNE DISEASES

See Chapter 2 Medical Dermatology for more information.

Paraneoplastic Pemphigus

- Plectin (500 kDa)
- Desmoplakin I (250 kDa), desmoplakin II (210 kDa)
- BPAg1 (230 kDa)
- Envoplakin (210 kDa)
- Periplakin (190 kDa)
- Unknown antigen (170 kDa)
- Desmoglein (Dsg) 1 and 3 (160 and 130 kDa, respectively)

Pemphigus Vulgaris

- Desmoglein 3 (130 kDa), coprecipitates with plakoglobin (85 kDa)

Pemphigus Foliaceus

- Desmoglein 1 (160 kDa)

Linear IgA Disease

- 97-kDa fragment that is similar to extracellular portion of BPAg2 (180 kDa) (collagen XVII)

Subcorneal Pustular Dermatosis (IgA Pemphigus, Sneddon-Wilkinson Disease)

- Desmocollin I (115 and 105 kDa)

Intraepidermal Neutrophilic IgA Dermatosis

- Desmoglein 3

Pemphigoid Gestationis

- BPAg2 (180 kDa)

Cicatricial Pemphigoid (CP, Mucous Membrane)

- BPAg2 (180 kDa), C-terminal domain
- Laminin 5: Anti-epiligrin CP
- Laminin 6
- α_4-Integrin: Ocular CP
- Type VII collagen

The Plakin Family

- Envoplakin (210 kDa)
- Periplakin (190 kDa)
- Desmoplakin (250 kDa)
- BPAg1 (230 kDa)
- Plectin (500 kDa)

TABLE 1.1.8 BLISTERING DISEASES

Antigen	Inherited	Autoimmune
K5, K14	EBS Dowling-Meara	
Plectin	EBS-MD	PNP
BPAg2	Generally atrophic benign EB	EB, CP, BP, PG
$\alpha_6\beta_4$-Integrin	JEB = gastric atresia	α_4-Integrin ocular CP
Laminin V	JEB	CP with increased risk of cancer (anti-Lam332 autoantibodies, previously termed anti-laminin 5 or anti-epiligrin MMP)
Collagen VII	DEB collagenous domain	EBA noncollagenous domain Bullous LE collagenous domain

BP = bullous pemphigoid; CP = cicatricial pemphigoid; DEB = dystrophic epidermolysis bullosa; EB = epidermolysis bullosa; EBA = epidermolysis bullosa acquisita ; EBS = epidermolysis bullosa simplex; PG = pemphigoid gestationis; JEB = junctional epidermolysis bullosa; LE = lupus erythematosus; MD = muscular dystrophy; MMP = mucous membrane pemphigoid; PNP = paraneoplastic pemphigus.

IMMUNOFLUORESCENCE PATTERNS

Direct Immunofluorescence

- **Intercellular space (ICS) deposition**
  - Majority show IgG → all types of pemphigus, except IgA pemphigus
  - Similar pattern seen in pemphigus vegetans (PV), pemphigus foliaceus (PF), and their variants
  - Complement C3 may be seen in ICS, too
  - **IgA → IgA pemphigus, target protein is desmocollin I** (115 kDa)
  - Positive predictive value of direct immunofluorescence (DIF) in diagnosis of pemphigus is 100%; the negative predictive value is 85%
- Intercellular space and basement membrane zone (BMZ) combination
  - **Paraneoplastic pemphigus → antibodies to BMZ proteins and desmosomal proteins**
  - **Drug-induced pemphigus → antibodies to desmoglein 1 (2/3 of patients) and desmoglein 3 (1/3 of patients)**

- BMZ deposition alone
  - **IgG and/or C3 at BMZ → bullous pemphigoid, mucosal pemphigoid, pemphigoid gestationis, epidermolysis bullosa acquisita (EBA), and bullous systemic lupus erythematosus (SLE)**
  - C3 much higher intensity than IgG favors pemphigoid group of diseases
  - IgG much higher intensity than C3 favors EBA and bullous SLE
  - Differentiation between bullous pemphigoid (BP) and pemphigoid gestationis (PG) is not possible using either histology or IF
  - Multiple deposits at the BMZ favor bullous SLE and EBA over the pemphigoid group
  - Useful for differentiating between bullous SLE and EBA based on underlying diagnosis of SLE by clinical and serologic criteria
  - **Linear deposition of IgA at BMZ → linear IgA bullous dermatosis or chronic bullous disease of childhood**
- DIF using salt-split specimens
  - 1 molar NaCl splits BMZ at lower lamina lucida
  - Differentiates BP from EBA: **Pemphigoid deposits seen at epidermal side of split; EBA and bullous SLE show deposits at dermal side**
  - Anti-epiligrin pemphigoid → dermal staining
- Mucosal disease
  - Seen with mucosal pemphigoid, EBA, cicatricial pemphigoid, and linear IgA disease
  - Mucosal lichen planus (LP) shows cytoid bodies with thick band of fibrinogen
  - IgG and C3 deposit in mucosal pemphigoid and anti-epiligrin disease
- Blood vessel deposition
  - Porphyria cutanea tarda (PCT), pseudoporphyria, and erythropoietic protoporphyria (EPP) → homogeneous deposits of multiple immunoreactants within superficial dermal blood vessel walls, in addition to BMZ deposition
  - IgG and IgA most common
- Papillary dermal deposition
  - **Dermatitis herpetiformis → IgA and C3 in papillary dermis and along the BMZ**
  - **Dermatitis herpetiformis (DH): IgA deposition in 100% of patients when biopsy taken from normal-appearing perilesional skin**

Indirect Immunofluorescence

- IgG anti-intracellular antibodies
  - Pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, and drug-induced pemphigus
  - Patients with burns, penicillin drug eruptions, skin grafts, bullous pemphigoid, and mucosal pemphigoid
  - **Paraneoplastic pemphigus: Rat bladder epithelium (75% sensitive, 83% specific); stains desmosomes**
- IgA anti-intracellular antibodies
  - IgA pemphigus (50% of patients)
- IgG anti-BMZ antibodies
  - 75% of patients with BP
  - 50% of patients with EBA
- IgA anti-BMZ antibodies
  - Adult and childhood forms of linear IgA disease
- Dermatitis herpetiformis
  - **Anti-endomysial, anti-reticular, and anti-gliadin antibodies**
  - Not diagnostic
- **Bullous pemphigoid vs EBA: Indirect immunofluorescence (IIF)**
  - **Salt-split skin: EBA shows dermal staining (collagen VII)**
  - **Pemphigoid disorders show epidermal and dermal staining**
- **Herpes gestationis factor** (Pemphigoid gestationis)
  - Amplified IIF procedure
  - Positive in 50% of patients with HG

Connective Tissue Diseases

TABLE 1.1.9 DIRECT IMMUNOFLUORESCENCE PATTERN IN CONNECTIVE TISSUE DISEASES

Disease	Direct Immunofluorescence Pattern/Useful Info
DLE	• Immune deposits along the DEJ → IgG and IgM • Cytoid bodies → degenerated basal keratinocytes dropped into the papillary dermis → IgM and IgA • Patterns: Shaggy, granular, linear • Biopsy the oldest, untreated lesion on non-sun-exposed skin
SCLE	• Immune deposits along the DEJ and basal keratinocytes → IgG and IgM • Cytoid bodies → IgM and IgA • Granular fluorescence throughout the cytoplasm and nucleus of basal keratinocytes (unique to SCLE) → reflects binding to Ro and La antigens
Mixed connective tissue disease	• Deposits within epidermal cell nuclei (IgG) • Rarely along the DEJ
Scleroderma, morphea, and neonatal LE	• DIF of no value
Erythema multiforme	• DIF shows immunoglobulin within superficial vessel walls, DEJ, and cytoid bodies
Dermatomyositis	• Pattern similar to LE, but intensity of fluorescence pattern is usually lower in DM
Vasculitis	• Deposition of C3 within superficial blood vessel walls • In HSP, IgA is the primary immunoglobulin (75% of patients)
Lichen planus	• DIF positive in vast majority • Deposition within cytoid bodies in superficial dermis → IgM and fibrinogen • DEJ deposition is granular
SLE	• Serology more reliable than DIF • DEJ deposition → lupus band test, lesional and nonlesional skin • Cytoid bodies → IgM and IgA • Immune deposits may be located in superficial dermal blood vessel walls similar to vasculitis • Epidermal keratinocyte nuclei staining, seen in patients with antibodies to U1RNP

DEJ = dermoepidermal junction; DIF = direct immunofluorescence; DLE = discoid lupus erythematosus; DM = dermatomyositis; HSP = Henoch-Schönlein purpura; LE = lupus erythematosus; SCLE = subacute cutaneous lupus erythematosus; SLE = systemic lupus erythematosus.

HAIR FOLLICLE BIOLOGY

Embryology

- **First primordial hair follicles form at 9 weeks gestation** on eyebrows, upper lip, and chin
- Remaining follicles develop at 4 to 5 months in a cephalad to caudal direction
- New follicles cannot develop in adult skin
- **Ectodermal origin except hair papilla, which derives from mesoderm**

Follicular Morphogenesis

- Induced by exchange of signals between epithelial and mesenchymal cells
- Pregerm stage: Focal crowding of epidermal basal nuclei matched by a cluster of mesenchymal cells beneath the basement membrane
- Crowding of basal keratinocytes causes a slight bud on underside of epidermis—termed the follicle germ or primitive hair germ

- Follicle peg: The hair germ grows obliquely downward and forward into the mesenchyme in the shape of a solid column of epithelial cells
- Tip of the epithelial cord becomes matrix portion of the bulb
- Outgrowths of cells from the outer root sheath give rise to the presumptive sebaceous gland (uppermost) and the bulge (lowermost)—the insertion site of the arrector pili muscle
- Dermal papilla: Deepest portion of the bulbous hair peg that forms an invagination surrounding the bulk of the underlying mesenchymal cells
- Matrix keratinocytes: Above the basement membrane overlying the dermal papilla—give rise to hair shaft and inner root sheath; melanocytes responsible for the pigmentation of the hair dispersed among these matrix cells
- Outer root sheath: Most peripheral epithelial cells of the follicle; most likely not formed from matrix cells

TIP

Inside to outside: Cuticle — inner root sheath (IRS) — Huxley/Henle — outer root sheath (ORS) — glassy/vitreous

Hair Follicle Organization

- Outer root sheath (trichilemmal keratin): Most peripheral of cellular components
- Inner root sheath: Three compartments, stains red because of citrulline
  1. **Henle's layer: Keratinizes first**
  2. **Huxley's layer**
  3. **Cuticle**
- Hair shaft: Three compartments
  1. **Cuticle**
  2. **Cortex: Forms bulk of hair;** no keratohyalin granules
  3. **Medulla: Central**
- **Critical line of Auber: Widest diameter of the bulb; bulk of mitotic activity that gives rise to the hair and the inner root sheath occurs below this level**

The Hair Cycle

- Anagen
  - **84%, 3-4 years**
  - Follicle traverses entire epidermis
  - **Matrix keratinocytes in the bulb region proliferate rapidly; these cells are pluripotent cells capable of differentiating into cuticle, cortex, and medulla of hair shaft**
  - Divided into six substages (I to VI): the first five called collectively proanagen—defined by progressively higher levels of new hair tip position within the follicle; the 6th stage, metanagen, defined by emergence of hair shaft above the skin surface
  - **End of anagen: Apoptosis**
  - Duration of anagen phase by hair location
    - **Scalp: Lasts 2-6 years**
    - **Leg: 19-26 weeks**
    - **Arm: 6-12 weeks**
    - **Mustache: 4-14 weeks**
- Anagen effluvium
  - Frequently seen following administration of cancer chemotherapeutic agents
  - **Stimulus induces the abrupt cessation of mitotic activity in rapidly dividing hair matrix cells;** hair shaft thins and then breaks at skin surface
  - Occurs within days to weeks of the stimulus
  - **Entirely reversible with cessation of drug therapy**
  - Causes
    - Antimetabolites
    - Alkylating agents
    - Mitotic inhibitors
    - Thallium
    - Boron
    - Examples: Doxorubicin, the nitrosoureas, and cyclophosphamide
- Catagen
  - 2%, club ends, lasts 3 weeks
  - Scalp hairs show gradual thinning and lightening of the pigment at the base of the hair shaft
  - Melanocytes in the matrix cease producing melanin and undergo apoptosis
  - Involution of lower two-thirds of hair follicle by keratinocyte apoptosis
  - Matrix keratinocytes abruptly cease proliferating and undergo terminal differentiation
  - At end of catagen, the follicular papilla comes to rest at the bottom of the permanent portion of the hair follicle

TIP

Early and Excessive Loss of Club Hairs from the Normal Resting Follicles in the Scalp

- Physical stress such as: Surgery, anemia, traction, or systemic illness
- Psychological stress
- Endocrine causes such as: Hypo- or hyperthyroidism or peri-/postmenopausal states
- Nutritional deficiencies: Biotin, iron, protein (kwashiorkor), zinc, essential fatty acid or calorie deficiency (marasmus or starvation diets)
- Hypervitaminosis A
- Parturition
- Fever
- Drugs

- Telogen
  - ~14%, duration is 3 months
  - **Hair has club-shaped proximal end, and is typically shed from the follicle**
  - **The inner root sheath is totally absent from the telogen follicle**
  - Hair growth occurs in a "wave pattern" in humans in utero, with the first telogen phase entered near the time of birth with shedding 2 to 3 months later
  - Mosaic growth present by end of first postnatal year
- Molecules important for transition from anagen to telogen
  - **FGF5:** Mutation leads to angora phenotype; hair is 30-50% longer than normal
  - Hairless: Mutation causes atrichia
  - **Vitamin D receptor:** Mutation causes atrichia
- Molecules important for transition of telogen to anagen
  - **Sonic hedgehog (SHH)**
  - **Patched (receptor for SHH)**
  - **β-Catenin**
- Molecules controlling the size of the follicle
  - SHH, β-catenin, noggin, bone morphogenetic protein (BMP), FGFs, TGF-β, laminin 10
- Telogen effluvium
  - These factors push the follicle from anagen to catagen and telogen
  - If there is no disease, and no inflammation
    - Drugs are implicated
      - Amphetamines
      - Aminosalicylic acid
      - Angiotensin-converting enzyme inhibitors
      - Anticoagulants
      - β-Blockers
      - Bromocriptine
      - Carbamazepine
      - Cimetidine
      - Danazol
      - Etretinate
      - Interferon
      - Lithium
      - L-Dopa
      - Oral contraceptives
      - Valproic acid
    - Clinical presentation
      - Diffuse loss
      - Only rarely involves greater than 50% of the scalp
      - **Pull test abnormal: Pull 40 hairs and more than 6 pulled out is abnormal (only 10-15% in telogen); ensure patient hasn't shampooed that day**
      - **Total number of hairs on scalp: 100,000 with 100-150 normally lost on a daily basis; telogen effluvium results in 150-400 lost per day**
      - In many, no specific cause identified
      - Most cases improve spontaneously within a few months and hair regrows. Takes 6-12 months for hair density to return to normal
    - Therapy
      - No specific therapy
    - General hair factoids
      - At any one time, **85% of human scalp hair in anagen, 14% in telogen, 1% in catagen**
      - Glassy membrane can be seen as the hair follicle resorbs in catagen (remnants of basement membrane)
      - **Hairs grow 0.4 mm per day**
      - Hair follicles in scalp: 100,000 in brown/black hair, with 10% more in blondes, and 10% less in redheads

Structure of Hair

- Nonliving biologic fibers
- Cortex contains the bulk of the hair keratins
- Keratins are intermediate filaments in which 400-500 amino acid residues of individual chains are arranged in sequences containing heptad repeats paired together to form coiled coils
- Other hair proteins include the keratin-associated proteins (KAPs):
  1. High sulfur, protein rich in cysteine
  2. High glycine/tyrosine-containing proteins
- **Disulfide bonding contributes to the physical properties of the fiber. These bonds are broken during hair styling and reformed when the desired change is accomplished**
- **Cuticle maintains the integrity of the fiber. If damaged by physical or chemical means, the fiber is more likely to break—trichoptilosis ("split ends")**

Hair Pigmentation

- **Hair color determined by melanocytes and hair is pigmented only when it grows.** The melanocytic activity of follicular melanocytes is coupled to anagen stage
- Hair color: Melanocytes deposit melanosomes in keratinocytes of the matrix close to papilla
- Melanin formation absent through telogen and catagen
- Eumelanin is the pigment of brown/black hairs and pheomelanin is the pigment in red/blond hairs
- Intensity of color is proportional to the amount of pigment, and absence of pigment produces white hair; markedly reduced pigment produces gray hair

Types of Hair

- Lanugo: Soft, fine hair that covers much of the fetus and is usually shed before birth
- Vellus scalp hair: Lengths less than 1 cm
- Indeterminate scalp: Approximately 1 cm
- Terminal scalp: Longer than 1 cm
- Eyelash and eyebrow hairs are considered terminal

Bulge-Activation Hypothesis

- The follicular epithelial stem cells located in the bulge region of the outer root sheath undergo transient proliferation during early anagen, producing the transient amplifying (TA) cells. TA cells rapidly proliferate, migrate downward, and eventually become matrix keratinocytes. Because TA cells have a limited proliferative capacity, they exhaust their proliferative reserve and undergo terminal differentiation (catagen)
- Hair follicle stem cells express markers such as SOX9, keratin 15, α_6- and β_1-integrins, CD200, PHLDA1, follistatin, frizzled homolog 1, LGR5; low levels of CD24, CD34, CD71, CD146)
- Though bulge-derived stem cells mainly differentiate into hair, they have the potential to transdifferentiate into epidermal stem cells in the setting of injury or wound healing

Defects of Hair Shaft

- **Monilethrix: Mutated hair keratin hHb6; alternating thick and thin areas, beaded hair**
- **Netherton's syndrome: Trichorrhexis invaginatum (bamboo hair); mutation in serine-protease inhibitor**
- **Pili annulati: Banded hair**
- **Menkes disease: Twisted hair (pili torti); deficiency in copper transporter**
- **Uncombable hair syndrome: Triangle-shaped hair**
- **Hereditary mucoepithelial dysplasia: Red gums, keratosis pilaris (KP), episodic hair loss**
- **Naxos syndrome: Mutation in plakoglobin; wooly hair hyperkeratosis of palms and soles, cardiac arrhythmia**

SEBACEOUS GLANDS

- Enlarge at puberty in response to increased androgens
- Often consists of several lobules that empty into a sebaceous duct
- **Holocrine secretion**
- **Usually found in association with hair structures,** but there is no relationship between the size of the sebaceous gland and the size of the associated hair
- Under androgenic hormonal control, not neural control
- Free sebaceous glands not associated with hairs are found in specific locations
  - **Montgomery's areolar tubercles:** Nipple and areola
  - **Fordyce's condition:** Free sebaceous glands on vermillion border of the lips and on the buccal mucosa
  - **Meibomian glands:** Located deep on the eyelids, usually embedded in tarsal plate. Modified sebaceous glands. Forms the most exterior (lipid) layer of the tear film preventing evaporation. Inflammation = chalazion. Empties to mucosa
  - **Glands of Zeis:** Located on superficial eyelid margin. Also contribute to exterior tear film layer. Inflammation = hordeolum. Empties to skin
  - **Tyson's glands:** Free sebaceous glands located on the genitalia

- **Found everywhere on the skin except the palms, soles, and prepuce**
- Sebaceous gland stem cells (express markers such as blimp1)
- Rate of sebum production is 1 mg/10 cm^2
- Plays a thermoregulatory role
- Human sebum differs from other lipids by the **presence of wax esters**

TABLE 1.1.10 SEBUM AND EPIDERMAL COMPONENTS

Component	Sebum (%)	Epidermis (%)
Glycerides	57.5	65
Wax esters	26	0
Squalene	12	0
Cholesterol esters	3	15
Cholesterol	1.5	20

ECCRINE GLANDS

- Long thin duct open to skin
- **Thermoregulatory**
- Postganglionic sympathetic fibers
- Composed of three segments: The intraepidermal duct (acrosyringium), the intradermal duct, and the secretory portion
- Basal coil exists either in the lower portion of the dermis or at the border of the dermis and the subcutaneous fat
- S100, carcinoembryonic antigen (CEA), keratin positive
- Present everywhere on the skin, but absent in modified skin that lacks cutaneous appendages: **Vermillion border of the lips, nail beds, labia minora, glans penis, clitoris, external auditory canal**
- **Highest density on palms and soles**
- Sweat formed in two steps: Secretion of primary fluid, isotonic NaCl; then reabsorption of NaCl by the duct. Sweating rate is most important determinant of NaCl concentration in final sweat fluid. Other components of sweat include lactate, urea, ammonia, amino acids, proteins, and proteases
- **One of the few fetal structures that does not develop craniocaudally** (develops first on palms and soles in the 4th month, on the body in the 5th month). Fully formed at birth but matures and becomes fully functional postnatally
- Eccrine gland stem cells (express markers such as keratins 15, 18, and 19)

APOCRINE GLANDS

- Innervated by **sympathetic fibers**
- Develop from mantle of hair follicle. First seen week 24 on scalp
- Tubular glands that demonstrate **decapitation secretion; part of cell pinched off during secretory process**
- Like eccrine glands, composed of three segments: Intraepidermal duct, intradermal duct, and secretory portion
- Duct of apocrine gland usually leads to a pilosebaceous follicle above entrance of the sebaceous duct
- **Apocrine glands found in axillae, anogenital region, external ear canal (ceruminous glands), in the eyelids (Moll's glands), in the breast (mammary glands), and periumbilical region**
- Function begins at puberty. Unclear role; possible olfactory communication
- Secretion in response to emotive stimuli mediated by the limbic system—through action of epinephrine/norepinephrine. Denervation does not abolish this response, though apocrine sweating requires intact nerve supply. During sleep, the glands are inactive, which supports the idea of emotional control
- Initial secretion is odorless. The odor is derived from C_6-C_{11} acids; the most abundant is 3-methyl-2-hexenoic acid
- Glands stain positive for keratin, S100, CEA, lysozyme
- Diseases:
  - **Fox-Fordyce disease: Occlusion of apocrine ducts**
  - **Chromhidrosis: Pigmented sweat due to lipofuscin context**
  - **Bromhidrosis: Abnormal body odor by apocrine gland secretion**

NAILS

- The nail unit is made of several components: The proximal and lateral nail folds, the nail matrix, the nail bed, the hyponychium, and the nail plate itself
- **Development and maintenance of the nail unit require pathways such as Wnt signaling, which has recently been shown to potentially induce digit regeneration in the presence of nail stem cells**
- **The nail plate is produced by the nail matrix**
- Nail keratins comprise about 80% of the dry weight of the nail plate, and they are divided between "soft" and "hard" (sulfur rich, cross-linked)

Inherited Diseases of the Nails

- Pachyonychia congenita:
  - Type I (Jadassohn-Lewandowsky syndrome): Mutations in *KRT16* → focal PPK, distinctively thickened hyperkeratotic fingernails and toenails (all 20), with onycholysis and frequent staphylococcal or candidal paronychial infection, pincer nails, follicular hyperkeratosis of elbows and knees, oral leukokeratosis, palmar and plantar keratoderma with hyperhidrosis
  - Type II (Jackson-Lawler) syndrome: Involves mutations in *KRT17* and clinically resembles the type I syndrome with the additional findings of both natal teeth and steatocystoma multiplex; less severe palmoplantar keratoderma with milder or absent oral lesions
  - Type III (Schafer-Brunauer) syndrome: Features all the findings of the type I disease associated with leukokeratosis of the corneas, involves mutations in *KRT6A*
  - Type IV, pachyonychia congenita tarda: Keratin 16 and 17 mutations, applies to a late onset of the disease during the second or third decade of life and involves mutations in *KRT6B*
- Nail-patella syndrome: Autosomal dominant (AD), mutations in *LMX1B*; triangular lunulae, micronychia with hemonychia and longitudinal splitting, anonychia, palmoplantar hyperhidrosis, absent or hypoplastic patella, bilateral posterior iliac horns, radial head subluxation, thickened scapula, scoliosis, glomerulonephritis, Lester iris (hyperpigmentation of the pupillary margin of the iris)
- Dermatopathia pigmentosa reticularis (DPR): AD, mutation in keratin 14 gene. Triad of cutaneous reticulate hyperpigmentation, noncicatricial alopecia, onychodystrophy. Keratin 14 mutation is shared with Naegeli-Franceschetti-Jadassohn syndrome. Shared clinical features in both are adermatoglyphia, palmoplantar keratoderma, and hypohidrosis. However, alopecia is only seen in DPR and dental abnormalities are seen in only in Naegeli-Franceschetti-Jadassohn syndrome
- Hair-nail ectodermal dysplasia (keratin 85 mutation): Consists of nail fragility and alopecia

NERVES AND RECEPTORS OF THE SKIN

- Sensory nerve fibers may exist alone (free nerve endings) or in conjunction with specialized receptors of touch, pain, temperature, itch, and mechanical stimuli
- Receptors are especially dense in hairless areas
- **Innervation sweat glands (cholinergic for eccrine; adrenergic for apocrine. Innervation vascular smooth muscle (adrenergic → vasoconstriction). Innervation hair follicles (adrenergic → contracting)**
- Innervation of the skin is derived from the musculocutaneous branches of the spinal nerves
- Sensory nerves are roughly distributed in dermatomes, but overlap occurs
- Itch is transmitted via afferent fibers of the Aδ and C-polymodal nociceptor class
- Adrenergic innervation controls vasoconstriction, apocrine secretion, and contraction of arrector pili muscles
- **Eccrine sweating is under the control of cholinergic nerves**
- **Sebaceous glands are not under neuronal control, and only respond to chemical stimuli such as hormones**
- **Sympathetic nerve fibers (eccrine gland [acetylcholine]), vascular smooth muscle, arrector pili, apocrine and sebaceous glands (respond to chemical stimuli [hormones])**
- Adrenergic receptors in the sympathetic nervous system play a key role in modulating the cutaneous vasculature, and individual receptor subtypes vary in tissue distribution and function
- Activation of α1- and α2-adrenergic postsynaptic receptors results in vasoconstriction that may improve persistent erythema associated with rosacea

Free Nerve Endings

- Most widespread and important type
- Penicillate fibers found subepidermally in hair-bearing skin: detect touch, pain, temperature, and itch; function in fine discrimination in the nonhairy, ridged areas of skin
- Papillary nerve endings are found at the orifice of the hair follicle and are particularly sensitive to cold
- Free nerve endings also penetrate the epidermis to contact Merkel cells

Corpuscular Receptors

- Contain a capsule and inner core, and contain both neural and nonneural constituents
- **Meissner's corpuscle: Ovoid, elongated mechanoreceptor located in the dermal papillae of digital skin; detect touch and light pressure**
- **Pacinian (Vater-Pacini) corpuscle: Exists in deep dermis and within subcutis in weight-bearing sites of the body; functions as an adapting mechanoreceptor that responds to vibrational stimuli; perineural capsule**
- Krause end bulbs: Mucocutaneous receptors found on glans penis, clitoris, labia minora, perianal area, and vermillion border of the lips

1.2 Immunodermatology

THE INNATE IMMUNE SYSTEM (OVERVIEW)

It is helpful to divide the immune system into two complementary branches based on the plasticity of their responses. **The innate immune system is often ascribed nonspecific receptors, but it is more accurate and useful to understand that it uses predetermined receptors that specifically recognize nonself pathogens but not self-antigens.** In contrast, the adaptive immune system (see section below) relies on gene rearrangement to produce receptors specific for individual antigens, and these receptors may potentially bind both nonself and self-antigens.

The immune system is composed of both cellular and noncellular components. Keratinocytes and mucosal epithelia provide a physical barrier against pathogens and can also secrete cytokines such as TNF and IL-1. Soluble factors such as antimicrobial peptides, cathelicidins, complement, cytokines, and antibodies assist the cellular components (leukocytes). Leukocytes are subdivided by function into granulocytes (neutrophils, eosinophils, mast cells, basophils), lymphocytes (B cells, T cells, natural killer cells), and monocytes (called histiocytes in tissue; Langerhans cells in the epidermis).

Secreted Proteins of the Innate Immune System

- Rapid response, **"first line of defense," low specificity**
- Lack of memory: Repeated exposure does not change the response
- Provides **initial inflammatory signals that recruit lymphocytes** (adaptive immunity)
- **Lack of innate inflammatory signal may induce tolerance by adaptive immunity**
- Receptors
  - **No gene rearrangement, limited antigen recognition repertoire**
  - **Germline-encoded, distinguish nonself from self**
  - **Pattern recognition receptors include Toll-like receptors (TLRs) and nucleotide oligomerization domain (NOD) receptors; these receptors recognize PAMPs (pathogen-associated molecular patterns)**
  - TLR family has 13 members. Highest expression levels are found in monocytes, dendritic cells, and B cells
  - **TLR7 binds imiquimod, also expressed on melanocytes, native ligand is ssRNA**
  - TLR7 activation results in pleiotropic responses, including **antigen-presenting cell (APC) activation and cytokine production (IL-12, interferon [IFN]-γ, TNF-α)**
  - **TLR2 may be activated in inflammatory acne**
  - **TLR2 and TLR9 polymorphisms associated with atopic dermatitis**

TIP

TLR7 binds imiquimod; native ligand is ssRNA

TIP

Decreased expression of antimicrobial peptides in atopics vs psoriatics may explain increased cutaneous infection in the former

TIP

Innate Immunity Cytokines
Cytokines: Particularly TNF-α, IL-1, IL-10, IL-12, IFN-α, IFN-γ

- Noncellular components
  - There is a deficiency of HBD-2 and LL 37 in lesions from patients with atopic dermatitis compared to those with psoriasis
  - **Antimicrobial peptides: Defensins and cathelicidins are produced by phagocytes and keratinocytes and directly kill bacteria, fungi, and viruses**
  - ***DEFB4* encodes β-defensin 2, which is strongly expressed in active psoriatic lesions**
  - Complement: See below

TIP

Higher β-defensin 2 levels in psoriatic lesions are associated with more severe disease activity

Cells of the Innate Immune System

- Cellular components: Macrophages, neutrophils, natural killer cells, mast cells, eosinophils
- Phagocytes (macrophages and neutrophils)
  - **Identify microbes using receptors for mannose, opsonins, and TLRs**
  - **Ingest pathogens**
  - **Destroy pathogens by producing reactive oxygen intermediates via phagocyte oxidase, nitric oxide via inducible nitric oxide (NO) synthase, and lysosomal enzymes such as lysozyme, elastase, and collagenase**
  - Activated by $CD4^+$ and $CD8^+$ T cells through IFN-γ and CD40 ligand (CD40L)
  - Phagocytes are unable to kill intracellular organisms (screening test, nitroblue tetrazolium reduction assay)
  - Mononuclear phagocytes
    - **Once localized in tissues, monocytes are called macrophages**
    - In addition to phagocytosis, macrophages degrade foreign antigens or cells into peptide antigens for presentation to T cells
    - **Express Fc receptors for IgG**
    - Produce cytokines that recruit other inflammatory cells
  - Neutrophils
    - **Chemotactic factors: IL-8, C5a, leukotriene B_4 (LTB_4), platelet-activating factor**
    - The most abundant leukocyte
    - Major function is phagocytosis
    - Have **receptors for IgG and complement**
    - Have **many storage granules**
    - Primary granules contain: Myeloperoxidase, lysozyme, neutrophil elastase, defensins
    - Secondary granules contain: Lactoferrin, neutrophil collagenase, neutrophil gelatinase, neutrophil gelatinase-associated lipocalin, and transcobalamin 1
    - Hereditary deficiencies of neutrophil function lead to overwhelming bacterial infection, which can be fatal

TIP

Defect in phagocyte oxidase leads to chronic granulomatous disease

- Granulocytes: Neutrophils, eosinophils, mast cells, and basophils are collectively known as granulocytes
  - **Eosinophils**
    - **Provide protection against helminths**
    - **Function through antibody-dependent cell-mediated cytotoxicity via IgG and IgE** (independent of complement)
    - **Release major basic protein** (toxic to all cells, but particularly helminths) and **leukotrienes**
    - Activated by **IL-5**
  - Mast cells
    - Provide protection against bacteria and parasites
    - **Express high levels of FcΣRI (receptor for IgE)**
    - Bone marrow—derived progenitor cells express CD34 and c-Kit (CD117)
    - Stains: Giemsa, toluidine blue, Leder
    - Preformed mediators: Histamine, proteases (i.e., tryptase, elevated in patients with mastocytosis), heparin
    - Newly formed mediators: Prostaglandin D_2, leukotrienes $C_4/D_4/E_4$, platelet-activating factor
    - Central cell in immediate-type hypersensitivity through IgE-mediated release of histamine
    - Many patients with idiopathic urticaria have circulating autoantibodies directed against the mast cell—expressed chain of the high-affinity IgE receptor
    - **Degranulating stimuli: Dimerized IgE, anti-FcεRI antibody, C5a, substance P, stem cell factor (Kit ligand), drugs (nonsteroidal antiinflammatory drugs [NSAIDs], opiates, vancomycin, polymyxin), ethanol (EtOH), contrast agents**

TIP

Adult mastocytosis is most frequently related to activating mutations in c-Kit tyrosine kinase (but not childhood disease)

TIP

Important to counsel patients to avoid these triggers for mastocytosis and urticaria pigmentosa

- Monocytes
  - Langerhans cells
    - Immature dendritic cells found in epidermis and mucosa
    - Migrate to regional lymph nodes on antigen capture to undergo maturation to become antigen-presenting cells (APCs)
    - **Present processed peptide associated with MHC II to T cells (primarily $CD4^+$), resulting in T cell activation**
    - Express surface marker CD1a, langerin (CD207)
    - Adhesion to keratinocytes mediated by E-cadherin
    - **Express B7 molecules (CD80 or CD86) only after activation by antigen** or other exogenous stimuli
    - TGF-β upregulates E-cadherin expression and maintains Langerhans cells in immature state
    - **Adjuvants work through APCs to increase costimulatory molecule expression and cytokine expression**

TIP

Langerin (CD207) stains Birbeck granules, highly sensitive and specific

THE ADAPTIVE IMMUNE SYSTEM (OVERVIEW)

- Delayed response (initially), high specificity
- **Memory** (stronger elicitation responses on reexposure)
- Receptors
  - **Gene rearrangement leads to randomly generated receptors with ability to recognize millions of antigens**
  - Does not distinguish self from nonself
  - **Requires antigen presentation in context of MHC molecules**
  - Costimulation important aspect of adaptive immunity, which renders checkpoints to autoimmunity
- Noncellular components
  - Antibodies: See below
- Cellular components
  - T cells, B cells, Langerhans cells

TIP

Costimulatory Molecules Used As Immunotherapy Targets for Checkpoint Blockade in Melanoma and Other Cancers

- Cytotoxic T-lymphocyte antigen 4 (CTLA-4; ipilimumab inhibits CTLA-4)
- Programmed death ligand 1 (PD-L1; pembrolizumab inhibits PD-L1)

Cells of the Adaptive Immune System

- Lymphocytes
  - These cells are primarily responsible for the specificity of the immune response
  - Lymphocytes are triggered by a specific antigen to produce antibodies (B cells) or cytokines ($CD4^+$ T cells), or to cause direct cytotoxicity ($CD8^+$ T cells)

TIP

Adaptive Immunity Cytokines
Cytokines: Particularly IL-2, IL-4, IL-5, IFN-γ, TGF-β

  - Natural killer cells
    - **CD56** cell surface marker
    - Identify virally infected or transformed (tumor) host cells via their downregulation of self-MHC I
    - Possess activating and inhibitory receptors
    - Activating receptors bind ligands common to self
    - Inhibitory receptors identify self-MHC I; if stimulated, dominantly inhibit NK cell activity
    - Destroy cells via **perforins and granzymes** (same as T-effector cells)
    - **Activated by IL-12 and IL-15, secrete IFN-γ**
    - **Mediate antibody-dependent cellular cytotoxicity**
  - B cells
    - **CD19/20 cell surface marker**
    - **Progenitors in the bone marrow develop into immature B lymphocytes that express an antigen-specific receptor**
    - Interaction between the antigen and the surface-bound antibody (receptor) initiates B cell activation
    - **Express MHC II molecules, receptors for complement, and Fc receptor**
    - Within lymph node, located in lymphoid follicle
    - In the presence of particular cytokines, undergo **isotype switching of antibodies**

- T cells
  - Progenitors arise in the bone marrow, but migrate to thymus for maturation
  - Subdivided into functionally distinct populations of **helper ($CD4^+$) and cytotoxic ($CD8^+$) T cells**
  - Respond to stimulation by **production of cytokines ($CD4^+$) or causing cell lysis ($CD8^+$)**
  - Require **two signals for activation (costimulation)**
    - **Signal 1 composed of T cell receptor binding to MHC molecule on APC**
    - **Signal 2 involves CD28 on T cell interacting with B7 molecule located on APC**
  - **CTLA-4 binding to B7 causes inhibition of response (checkpoint inhibition)**
    - **Blocked by ipilimumab (enhances immune response to cancer)**
  - MHC/T cell receptor (TCR) engagement in absence of costimulation results in anergy

TIP

T cells located in paracortex of lymph nodes

- $CD4^+$ T cells
  - $CD4^+$ T cells (helper T cells) may be divided into four subtypes: T_H1, T_H2, T_H17, **T_{reg}**
    - **T_H1 cells augment T cell—mediated immunity, activate macrophages, and downregulate T_H2 responses via IFN-γ**
    - **T_H2 cells suppress macrophage activity, activate eosinophils, induce isotype switching to IgE and IgG4, and downregulate T_H1 responses via IL-10**
    - **T_H17 cells are proinflammatory; implicated in the pathogenesis of psoriasis and other autoimmune diseases such as rheumatoid arthritis (RA), multiple sclerosis (MS), and inflammatory bowel disease (IBD)**
    - **T_H17 cells secrete IL-17A, IL-17F, IL-21, IL-22, IL-23, and TNF-α**
    - T_H17 differentiation induced by IL-6 and TGF-β. Proliferation and survival mediated by IL-23

TIP

Antibodies that block IL-17 and IL-23 are effective for psoriasis

  - **T_{reg} cells are important in the downregulation of the immune response,** and likely play a role in diseases associated with autoimmunity, immune dysregulation, and tumor biology
  - **T_{reg} cells express high levels of CD25** (IL-2 receptor α chain) and are characterized by expression of transcription factor **FOXP3**
  - T_{reg} cells suppress immune response through direct contact inhibition or the **secretion of IL-10,** TGF-β, or CTLA-4
  - Mutation of *FOXP3* resulting in **absence of T_{reg} cells is the cause of IPEX syndrome** (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome)

TIP

T_H2 Diseases

- Atopic dermatitis
- Cutaneous T cell lymphoma (CTCL)
- Lepromatous leprosy
- Disseminated cutaneous (chronic) leishmaniasis

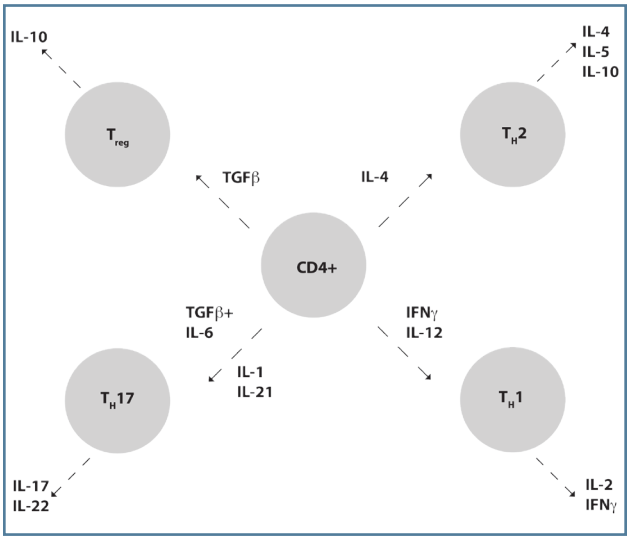

Figure 1.2.1 CD4+ T cell differentiation and associated cytokines.

- $CD8^+$ T cells
  - Recognize cytoplasmic antigens bound to **MHC I**
  - **Kill by releasing granules containing perforin and granzymes, which induce apoptosis**
  - May also induce **apoptosis by presenting Fas ligand (FasL) to Fas receptor on target cells**

- γδT cells
  - **T cells that possess a γδ TCR as opposed to the more common αβ TCR** (as seen in $CD4^+$ and $CD8^+$ T cells)
  - Primarily found in epithelia and appear to play a role in **immunoregulation and immunosurveillance**
  - **Suppress T_H1 cells through release of IL-10**
  - May play important roles in cancer surveillance and resistance to graft-vs-host disease

TABLE 1.2.1 T CELL SURFACE RECEPTORS

Receptor		Binding Partner		
Name	**Location**	**Name**	**Location**	**Effect**
TCR	T cell	Ag-MHC I or II	APC	Activation
CD2	T cell	LFA-3	Endothelial cell, APC	Adhesion, activation
CD4	T cell	MHC II	APC	Activation
CD8	T cell	MHC I	APC	Activation
CD28	T cell	B7 (CD80, CD86)	APC, target cell	Activation (2nd signal)
CTLA-4	Activated T cell	B7 (CD80, CD86)	APC	Inhibition
CD40L	T cell	CD40	APC, B cell	Activation
PD1	Activated T cell	PD-L1, PD-L2	APC, normal tissue	Inhibition
LFA-1 (CD18 + CD11a)*	T cell	ICAM-1	Endothelial cell, APC	Migration, adhesion
Mac-1 (CD18 + CD11b)*	Macrophage, neutrophil, NK cell	ICAM-1	Endothelial cell, APC	Migration, adhesion

APC = antigen-presenting cell; CD40L = CD40 ligand; CTLA-4 = cytotoxic T-lymphocyte antigen 4; ICAM = intercellular adhesion molecule; LFA-1 = lymphocyte function-associated antigen 1; NK = natural killer; PD1 = programmed death 1; PD-L1 = programmed death ligand 1; TCR = T-cell receptor.

*Mutation in CD18 causes leukocyte adhesion deficiency I.

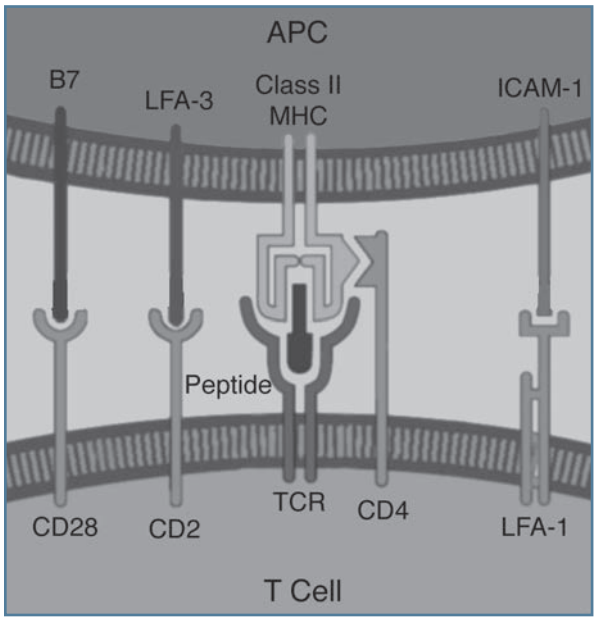

Figure 1.2.2 T-cell receptor.

MAJOR HISTOCOMPATIBILITY COMPLEX AND HLA DISEASE ASSOCIATIONS

The molecules that display peptide antigen to T cells are cell-surface glycoproteins named the major histocompatibility complex (MHC). There are two types of MHC molecules, class I and class II. These differ in several subtle ways but share most of their major structural features. **MHC class I and II molecules display protein antigens for recognition by $CD4_+$ or $CD8_+$ T cells.**

MHC class I molecules bind with stability to peptides derived from proteins synthesized and degraded in the cytosol (all cells), and MHC class II molecules bind with stability to peptides derived from proteins degraded in endocytic vesicles (APCs). The two classes

of MHC are differentially recognized by the two coreceptor molecules, CD8 and CD4. **CD8$^+$ T cells recognize MHC class I peptide complexes, while CD4$^+$ T cells recognize MHC class II peptide complexes.** Every individual is polygenic at the MHC locus and expresses several MHC I and II genes with different peptide-binding specificities.

TIP

HLA-Cw6 has the most definitive genetic association with psoriasis

Class I

- **Expressed on all nucleated cells** (HLA-A, -B, -C)
- **Recognized by CD8 on cytotoxic T cells**
- **Present intracellular proteins** (e.g., viral peptides and tumor cells) to the TCR
- **Ensures that any virally infected or defective (i.e., tumor) cells can be recognized and destroyed by cytotoxic CD8$^+$ T cells**

Class II

- **Expressed on B cells, monocytes, and dendritic cells,** and are inducible on keratinocytes and endothelial cells (HLA-DR, -DQ, -DP)
- **Recognized by CD4 on helper T cells**
- Class II molecules complexed with antigen trigger helper T cells
- Presents peptides derived from extracellular pathogens taken up into vesicles to TCR
- **Expressed on antigen-presenting cells to stimulate the helper arm of the cellular immune response (CD4$^+$ T cells)**

General Information

- Level of class I and II molecule expression is regulated by cytokines
- MHC III region encodes for soluble proteins of the complement cascade and the tumor necrosis family
- **The polygenic and polymorphic nature of the MHC contributes to the ability of the immune system to respond to the multitude of different and rapidly evolving pathogens**
- HLA associations seen in human skin disease reflect the ability of that particular MHC molecule to present a disease-relevant peptide to T cells

HLA Disease Associations

- Class I
  - **Psoriasis: *HLA-Cw6* most linked to psoriasis, *HLA-B17 / B13* to guttate psoriasis, *HLA-B27* psoriatic arthritis** relative risk 10 times normal. Mechanism postulated to be through antigen presentation to CD8$^+$ T cells leading to epidermal migration
  - **Lupus (subacute cutaneous lupus erythematosus [SCLE] + systemic lupus erythematosus [SLE]): *HLA-DR3***
  - **Psoriatic arthritis, Reiter's syndrome: *HLA-B27,*** especially if spondylitis present
  - **Behçet's disease: *HLA-B51***

- Class II
  - Chronic idiopathic urticaria: *HLA-DR4, HLA-DRB4, HLA-DQ8*
  - Pemphigoid gestationis: *HLA-DR3, HLA-DR4*
  - Pemphigus vulgaris: *HLA-DR4, HLA-DRw6*

- Both class I and class II
  - Dermatitis herpetiformis: *HLA-A1, HLA-B8, HLA-DR3, HLA-DQ2*
  - Lichen planus: *HLA-B7, HLA-DR1, HLA-DR10*
  - Vitiligo: *HLA-A33, HLA-B13, HLA-B44, HLA-DRB1, HLA-DR4*

ANTIBODIES

All antibodies have the same overall structure and are known collectively as immunoglobulins (Ig). Antibodies are produced by plasma cells in response to infection or immunization. **They bind to and neutralize toxins or pathogens and prepare them for uptake and destruction by phagocytes.** Each antibody has a unique antigen-binding domain that recognizes the antigen epitope.

- Antibodies are divided into several classes based on differences in the structure of the heavy chain
- Antibody molecules in each class are defined as having the same isotype. The basic structure of antibody molecules is similar between the various classes and is depicted in Figure 1.2.3
- Proteolytic cleavage with papain generates two basic functional domains: two Fab fragments and one Fc fragment

- **The Fab fragment consists of the light chain and the amino-terminal half of the heavy chain, bound to each other by disulfide bonds. The Fab fragment contains antigen-binding activity**
- **The Fc domain functions in complement activation and opsonization mediated by Fc receptors on phagocytes**

Antibody Functions

- **Neutralization of microbes and toxins by direct binding (e.g., staphylococcal toxin; children are more susceptible than adults due to lack of antibodies) (i.e., think SSSS in children)**
- **Enhance opsonization of microbes via Fc receptors on phagocytes or by fixing complement**
- Lysis of microbes and inflammation via complement activation
- In typical humoral response, isotype switching occurs subsequent to exposure to antigen
- **Switching is regulated by T cell—derived cytokines (IgG by IL-4, IL-6, IL-2, and IFN-γ; IgA by IL-5 and TGF-β; IgE by IL-4)**

Distinguishing Features of Isotypes

- **Opsonizing antibodies: IgG1 and IgG3** (but weakly neutralizing)
- **FcγRI has highest affinity for IgG** (isotype 1 and 3) and is located on macrophages, neutrophils, eosinophils, leading to phagocytosis
- **Neutralizing antibodies: IgA1 and IgA2 at mucosal surfaces, IgG2 and IgG4 in tissue**
- **Complement-fixing antibodies: IgG1, IgG3, IgM**
- IgA primarily at mucosal surfaces, prevent colonization by pathogens, important neutralizing function
- IgD functions as antigen receptor on mature B cells
- **IgE binds allergens, stimulates mast cells; increased in atopic individuals**
- **IgG is the predominant antibody in a secondary immune response, most abundant in serum, best for opsonization.** Also neutralizes pathogens and fixes complement

TIP

Hyper-IgE syndrome patients have constitutive high IgE levels, deficient T_H1 responses, and suffer from cold abscesses and eczematous dermatitis

TIP

IgG crosses the placenta

- **IgM is the first antibody produced by B cells, secreted by plasma cells as a pentamer**
- IgM doesn't enter tissue well, due to size; most efficient Ig at fixing complement
- High-affinity receptor for the Fc region of IgE expressed on mast cells, basophils, and Langerhans cells

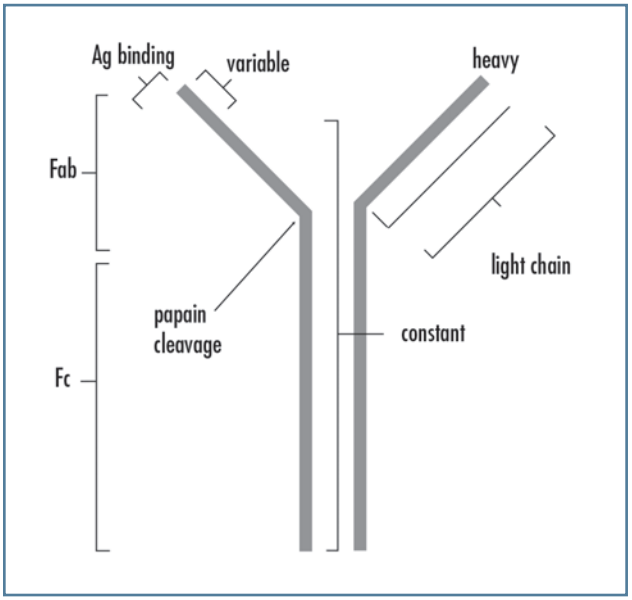

Figure 1.2.3 Schematic of an antibody showing the antigen recognition portion (Fab) and the constant portion (Fc), which binds to antibody receptors.

COMPLEMENT

Complement consists of a series of 25 serum and membrane proteins. These glycoproteins act as effectors in both innate and adaptive immunity. The complement cascade system has two important effects on cells: Opsonization and membrane damage. Biologic activities of complement also include chemotaxis, anaphylaxis, immune complex solubilization, and B-cell activation (provides second signal). The cascade has three pathways: The classical, alternative, and mannose-binding lectin. All act via sequential recruitment, proteolytic activation and assembly, with the ultimate endpoint being formation of the membrane attack complex (MAC), which inserts into lipid membranes and causes osmotic lysis of cells.

TIP

IgG4 does not activate complement

Classical Pathway

- **Activated by antigen-antibody (IgM or IgG) complexes**
- The proteins of the classical pathway are C1, C2, C3, and C4
- C1 binds, recruits C2 and C4 to form C3 convertase, and cleaves C3 and C5
- C1 inhibitor (CI-INH) prevents C1 protease activity
- C3a: Neutrophil chemoattractant (inflammation)
- C3b: Opsonin (binds to pathogen, enhancing phagocytosis)
- C5a: Anaphylatoxin (chemotaxis, increased vascular permeability, mast cell activation)
- C5b: Combines with C6, C7, C8, and C9 to form membrane attack complex

Alternative Pathway

- Activated by bacterial products, including lipopolysaccharide (LPS) from gram-negative bacteria
- Proteins in the alternative complement pathway are factor B, factor D, factor H, properdin, and C3

Mannose-Binding Lectin Pathway

- Activated by inflammatory macrophage cytokines

Complement Receptors

- Eight receptors have been identified
- CR1 (also known as CD35) is main receptor for C3b. Plays important role in mediating clearance of immune complexes, phagocytosis, and immune adherence of antibody-coated bacteria to erythrocytes
- CR2 (also known as CD21) presents antigen to B cells and is a coreceptor for B-cell signaling
- CR3 (CD11b/CD18 heterodimer) and CR4 (CD11c/CD18 heterodimer) are members of the β_2-integrin family (remember, CD11a/CD18 is also known as LFA-1) and bind ICAM-1
- Other receptors include C1qRP, C3aR, C4aR, and C5aR; the latter three mediate anaphylactic reactions
- **Acquired deficiency of CR1 is associated with autoimmune disorders such as SLE**
- **Deficiencies in CR3 and CR4 are found in leukocyte adhesion deficiency (LAD) type 1**

TIP

Epstein-Barr virus (EBV) utilizes the CR2 receptor for cell entry and infection

TIP

LAD type 1 patients suffer from mucositis, poor wound healing, and frequent skin infections without pus or inflammation that can resemble pyoderma gangrenosum

Complement Deficiencies

- Early defects (C1, C2, C3, C5) lead to susceptibility to encapsulated organisms, especially *Pneumococcus*
- Association of C1-C5 deficiency with SLE may be due to genetic linkage
- Late defects (C5-C9) confer susceptibility to *Neisseria*
- C3 deficiency associated with partial lipodystrophy
- Hereditary angioedema (HAE) type I is most common, due to low levels of C1-INH with normal function
- HAE type II is less common, due to normal levels of nonfunctional C1-INH
- Acquired angioedema (AAE) is due to consumptive processes, so C1-INH levels are low
- **To differentiate AAE and HAE, measure C1q (normal in HAE, low in AAE)**

TIP

Late defects (C5-C9) confer susceptibility to *Neisseria*

CYTOKINES

Cytokines are a structurally diverse group of molecules that have important local and systemic effects contributing to both innate and adaptive immunity. There are three major structural families: the hematopoietin family, which includes interleukins and growth hormones, the tumor necrosis factor (TNF) family, and the chemokine family. Most cytokines produced by T cells are given the name interleukin (IL) followed by a number. T_H1 and T_H2 cells release different but overlapping sets of cytokines. **T_H1 cells secrete IFN-α which is**

the main macrophage-activating cytokine, TNF-α, and lymphotoxin. T_H2 cells upregulate humoral immunity by secreting IL-4 and IL-5 and inhibit macrophage activation via IL-10. The main cytokine released by $CD8^+$ effector cells is IFN-γ.

- Small secreted proteins with pleomorphic effects, including cell growth and differentiation, inflammation and immunity (phagocytosis, intracellular killing, effector function), and cell migration (chemokines)
- Cellular response mediated by binding to specific receptors
- Expressed in groups (skewing towards T_H1 or T_H2 responses)

T_H1 Cytokines

- **IFN-γ: Differentiation toward T_H1 cells; increased MHC I and II on APCs; enhanced macrophage activity and downregulation of T_H2**
- IL-2: Proliferation and activation of T cells (clonal expansion), B cells (antibody production), and NK cells
- **IL-12: Heterodimer of p40 and p35 subunits. Increased cytolytic activity and IFN-γ production by T cells and NK cells. IL-12B encodes p40**

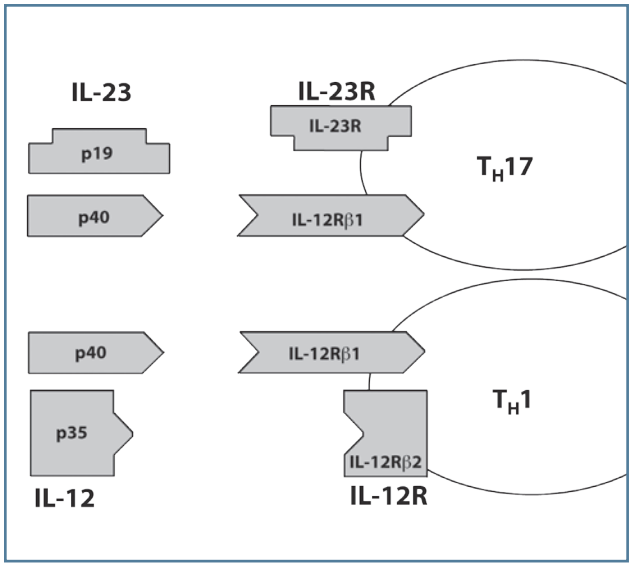

Figure 1.2.4 IL-12 and IL-23 cytokines and receptors share similar subunits.

TIP

Major producers of cytokines are T cells and macrophages

TIP

Ustekinumab binds to the p40 subunit of both IL-12 and IL-23 so that they subsequently cannot bind to their receptors

T_H2 Cytokines

- **IL-4: Differentiation toward T_H2 cells; isotype switching to IgE and IgG4, inhibition of macrophage activation**
- IL-5: Activates eosinophils and B-cell differentiation, increases IgA secretion
- IL-6: Proliferation and differentiation of B cells, induces acute-phase reactants
- IL-10: Decreases expression of MHC II and costimulatory molecules on APCs; decreases IL-12
- IL-13: Related to IL-4; implicated in allergic inflammation
- Dupilumab is a monoclonal antibody against IL4Rα (blocks IL-4 and IL-13) designed for treatment of atopic dermatitis and asthma

T_H17 Cytokines

- **IL-17: Family of cytokines that are proinflammatory, resulting in production of many cytokines including IL-6 and TNF-α**
- IL-17 members include IL-17A and IL-17F, which are implicated in **allergic and autoimmune inflammation as seen in asthma, SLE, and RA**
- IL-22: Member of IL-10 family that mediates inflammation through STAT transcriptional activation pathway; stimulates keratinocyte proliferation
- **IL-23:** Heterodimer of p40 (as in IL-12) and p19 subunits. Required for survival and proliferation of T_H17; **may be key cytokine in development of psoriasis.** IL-23A encodes p19

- IL-36: Member of IL-1 family of cytokines. Expression induced in keratinocytes by IL-17A and TNF-α. Increased gene expression of IL-36 correlates with T_H17 cytokines in psoriatic lesions. IL-36 Ra is a protein antagonist for IL-36 receptor
- Many biologics now exist that block specific cytokines involved in the pathogenesis of psoriasis, including IL-17 and IL-23

TIP

Secukinumab is a human monoclonal antibody and the first biologic to target IL-17, a principal interleukin in psoriatic pathogenesis; approved for psoriasis and psoriatic arthritis

TIP

IL-17 and IL-22 enhance keratinocyte expression of antimicrobial peptides, and IL-22 stimulates keratinocyte proliferation as seen in psoriasis

TIP

Homozygous mutation in IL-36Ra leads to unregulated IL-1 family-mediated inflammation, causing generalized pustular psoriasis

Other

- TNF-α: Primary mediator of acute inflammation, hepatic production of acute-phase reactants

TIP

TNF-α expression inhibited by:
- Thalidomide
- Methotrexate (MTX)
- Hydroxychloroquine
- Pentoxifylline
- TNF inhibitors

TABLE 1.2.2 CYTOKINE ACTIVITIES

Cytokine	Produced By	Target Cells	Action
GM-CSF	Helper T cells	Leukocyte progenitors	Growth and differentiation
IL-1	Macrophages, B cells	Helper T cells B cells	Costimulation Maturation and proliferation
IL-2	T_H1	B, T, NK cells	Growth, proliferation, and activation
IL-4	T_H2	Macrophages B cells Naive $CD4^+$ T cells	Increase MHC II expression Proliferation, IgG4 and IgE synthesis T-cell stimulation; proliferation, differentiation to T_H2
IL-5	T_H2, macrophages	B cells Eosinophils	Proliferation and differentiation, IgA synthesis Activation
IL-6	Macrophages, B cells	Macrophages B cells Naive $CD4^+$ T cells	Inhibit cytokine production Activation Differentiation to T_H17 cells
IL-10	T_H17	T cells Naive $CD4^+$ T cells	Differentiation to effector T cells Differentiation to T_H1 cells

TABLE 1.2.2 CYTOKINE ACTIVITIES CONTINUED

Cytokine	Produced By	Target Cells	Action
IL-12	T_H17	T cells Naive $CD4^+$ T cells	Differentiation to effector T cells Differentiation to T_H1 cells
IL-17	T_H17	Multiple targets	Inflammation
IL-21	Activated APCs	Naive $CD4^+$ T cells	Differentiation to T_H17 cells
IL-22	Leukocytes Fibroblasts	Multiple targets	Inflammation; keratinocyte proliferation
IL-23	T_H1 Cytotoxic T cells NK cells	T_H17	Survival and proliferation
IL-36	Langerhans cells Keratinocytes	$CD4^+$ T cells Dendritic cells	Differentiation to T_H17 cells
IFN-α IFN-β	Leukocytes Fibroblasts	Multiple cell types	Inhibit viral replication; increase MHC I expression
IFN-γ	T_H1 Cytotoxic T cells NK cells	Macrophages T_H2 B cells	Increase MHC expression: killing Inhibit proliferation Switch to IgG2a

APC = antigen-presenting cell; GM-CSF = granulocyte-macrophage colony-stimulating factor; IFN = interferon; IL = interleukin; NK = natural killer; T_H1 = helper T type 1.

WOUND HEALING

Cutaneous Stem Cells

The skin is a complex organ that harbors a multitude of distinct populations of stem cells that are able to regenerate the complex cellularity and structure of the skin and adnexal structures. Stem cells are involved in wound healing, and each subtype of stem cells contributes to regeneration of various components of skin and adnexal structures.

- **Keratinocyte stem cells**
  - **Interfollicular epidermis (between hair follicles): Self-renewing stem cells reside within the basal layer,** which adheres through $\alpha_3\beta_1$- and $\alpha_6\beta_4$-integrins to an underlying basement membrane of laminin-5—rich extracellular matrix that separates the epidermis from the underlying dermis. Secreted factors such as FGF-7, FGF-10, insulin-like growth factor (IGF), EGF ligands, and TGF-α from dermal fibroblasts promote the proliferation of basal epidermal cells. Transition from the basal to the spinous layer requires Notch signaling, a highly conserved pathway involved in a wide variety of developmental processes
- **Hair follicle stem cells**
  - **Hair follicle and melanocyte stem cells reside in the bulge and the hair germ.** In full anagen, hair follicle stem cells (HFSCs) regenerate the lower two-thirds of the follicle, including the matrix. Melanocyte stem cells generate mature melanocytes, which transfer their pigment to differentiating hair cells
  - **HFSCs can be subdivided into two populations: A quiescent one located in the bulge and a primed population within the hair germ just below the bulge, which is more prone to proliferation**
  - HFSCs are maintained in a quiescent state during most of the hair cycle and proliferate only early in anagen. Wnt signaling is also critical for hair germ activation: The downstream Wnt effector, nuclear β-catenin, accumulates in the activated hair germ and leads to target gene activation. With aging, HFSCs maintain their numbers although telogen lengthens with age, suggesting that quiescent HFSCs become increasingly resistant to activation
- **Sebaceous gland stem cells**
  - **Found at or near the bud of the sebaceous gland, and regenerate sebaceous glands during wound repair**

- **Eccrine gland stem cells**
  - **Can form acral epidermis in wound repair**
- **Merkel cell stem cells**
  - **Located in hair skin and regenerate epidermis**
- **Melanocyte stem cells**
  - **Located in the lower bulge region and regenerate hair matrix and epidermal melanocytes**
- Following full-thickness wounds, cells from both the hair follicles and the interfollicular epidermis migrate into the site of damage; however, main role is for keratinocyte stem cell in reepithelialization with minor role for HFSCs

Stages of Wound Healing

Wound healing involves three overlapping phases: Inflammatory, tissue formation, and tissue remodeling.

- Clot formation
  - **Initial step in wound healing**
  - Provisional matrix for cell migration
  - Functions in hemostasis
- Coagulation
  - **Critical event is availability of surface that promotes adsorption and activation of specific coagulation proenzymes**
  - Clot provides a scaffolding for recruitment of cells to injured site
  - Fibrin and fibronectin act as provisional matrix for infiltrating monocytes, fibroblasts, and newly formed blood vessels
  - Clearance of clot matrix is as important as deposition, and inadequate removal of provisional matrix may lead to fibrosis; proteolytic enzymes such as plasminogen and plasmin are the major proteins
- Platelets in wound healing (first response)
  - **Aggregation and adhesion required**
  - Release many mediators, including ADP, and clotting factors
  - Fibrin clot and thrombin act as nidus for further adhesion and aggregation
  - Platelets release platelet-derived growth factor (PDGF), EGF, fibronectin, and TGF-α and TGF-β, which promote new tissue growth
- Neutrophils in wound healing
  - **Migrate with monocytes concurrently, but arrive first in great numbers because of their abundance in circulation**
  - Chemoattractants for polymorphonuclear cells (PMNs): Fibrinogen/fibrin split products, C5a, leukotrienes
  - If wound contamination is controlled, PMN migration ceases within a few days, and PMNs become entrapped within the wound clot, undergo apoptosis or phagocytosis by macrophages
- Monocytes in wound healing
  - **Macrophages are REQUIRED for wound healing—without macrophages, there is no healing**
  - Monocyte chemoattractants include fragments of collagen, elastin, and fibronectin
  - Macrophages debride tissue through phagocytosis and digestion of organisms, tissue debris, and effete PMNs
  - Secrete collagenase
  - **Adherence to matrix stimulates expression of cytokines and growth factors FGF, IL-1, TGF-α, PDGF, and TGF-β, therefore facilitating transition from inflammation to repair**
  - Proliferation phase: Epithelization, granulation (collagen deposit), and angiogenesis. Stimulated by TNF-α
- Epithelialization
  - **Begins hours after injury**
  - Keratinocytes from residual epithelial structures leapfrog each other
  - Wound epidermal cells have lateral mobility by virtue of dissolution of intercellular desmosomes
  - Cells in all layers of migrating epidermis contain keratins 5 and 14 (usually found only in basal epidermis) and keratins 6 and 16; this phenotype resembles that found in lesional psoriatic skin
  - One to two days after injury, cells at wound margin proliferate
  - If basement membrane is destroyed, migration occurs over provisional matrix of collagen type V, fibrin, fibronectin
  - Migrating cells both traverse over wound coated with provisional matrix and through wound using an array of integrin receptors to guide the path
  - Collagenase is produced to assist in migration
  - Migration and dissection result in eschar sloughing
  - Migration is a result of a combination of chemotactic factors, direct guidance by contact, and loss of nearest neighbor, but not of proliferation
  - Once basement membrane proteins reappear, epidermal cells revert to their normal phenotype
  - 1st degree burn: Basement membrane intact
  - 2nd/3rd degree burn: Basement membrane destroyed

- Granulation tissue
  - **Four days after injury, granulation tissue forms**
  - Composed of new capillaries, macrophages, fibroblasts, and blood vessels, which move into wound space as a unit
  - Formation of granulation tissue is dependent on presence of fibronectin
  - Ordered sequence of matrix deposition: fibronectin → collagen III → collagen I
  - Granulation tissue primarily contains collagen type III

SKIN REORGANIZATION FOLLOWING INJURY

Partial Thickness Wounds

- Wound depth affects the ability of the skin to regenerate
  - **Partial-thickness wounds can heal by regenerating the entire epidermis without scarring**
  - **Full-thickness wounds have lost adnexal structures; therefore, reepithelialization only happens at the wound edges leading to scar formation**

Fibroplasia and Wound Contraction

- Fibroplasia is granulation tissue that arises from fibroblasts, and is a mixture of fibroblasts and ECM
- Monocytes → macrophages → secretion of growth factors (also from platelets) → fibroblast proliferation and activation of fibroplasia
- Once migrated into a wound, protein synthesis occurs to create the ECM/collagen matrix
- **Wound contraction ensues during second week of healing → governed by wound fibroblasts' ability to act like smooth muscle cells *(myofibroblasts)*, anchored by collagen bundles**
- Large bundles of actin-containing microfilaments appear in these fibroblasts
- Fibroplasia in wound repair ends with apoptosis of fibroblasts at or around day 10 of healing
- Skin is 30% of normal strength
- **Hyaluronan (hyaluronic acid): Linear polymer (member of glycosaminoglycans); major component of early granulation tissue; produced by fibroblasts**

Neovascularization

- **Soluble factors that stimulate angiogenesis: vascular endothelial cell growth factor (VEGF), TGF, angiogenin, angiotropin, and others**
- **Angiogenesis occurs during first week of wound repair**
- Angiogenesis initiated by plasma leak, release of FGF, and subsequent activation of collagenase to break down the basement membrane on which the endothelial cells rest
- The endothelial cells project pseudopods through the basement membrane and subsequently migrate into the connective tissue space

Tissue Remodeling

- Endothelial cells are first to undergo apoptosis, then myofibroblasts, and macrophages, leaving an acellular scar
- Progression of events over time: Early formation of types I, III, and V collagen
- Collagen bundles grow in size, increasing wound tensile strength; and proteoglycans are deposited, increasing wound resilience to deformation
- **Fibrin: First extracellular matrix to be deposited; for effective hemostasis, interaction must occur with platelets (via glycoprotein BPIIb-IIIa [$\alpha_{IIb}\beta_3$-integrin]); fibroblasts require fibronectin for migration into a fibrin clot**
- Fibronectin: Circulates in blood and binds fibrin

Scars

- Strength of scar
  - 5% at 1 week
  - 20% at 2 weeks
  - 70% at 1 year
- Scar tissue is devoid of adnexal structures
- Keratinocyte stem cells repopulate the epidermis
- Histologic findings: Dense collagen with fibers that run parallel to the DEJ
- Pigmentary alteration: Angiogenesis early on in wound healing leads to blood vessel proliferation, which clinically can be appreciated as erythema and telangiectasia formation. Later, as scars mature, adnexal structures are lost, and normal melanogenesis is disrupted, pigmentary alterations can be seen, often with hypopigmentation of the scar
- Melanocyte stem cells can proliferate and repopulate the melanocytes

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Chapter 2

MEDICAL DERMATOLOGY

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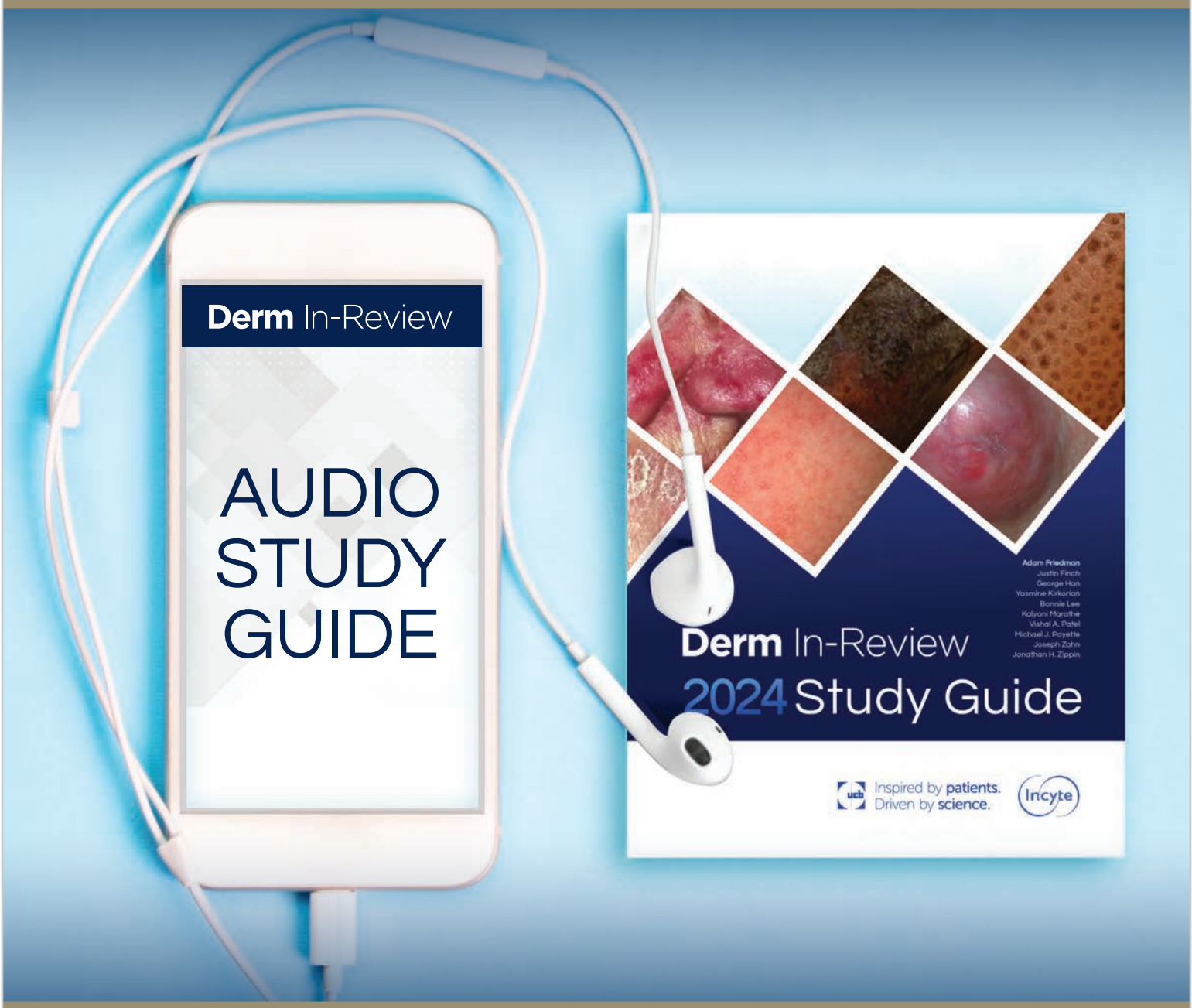


Derm In-Review

2.1 General Dermatology

ADNEXAL DISORDERS

Acne Vulgaris

- Key pathogenic factors
  - Abnormal keratinization (follicular retention hyperkeratosis)
  - Inflammation
  - Sebum production starts at adrenarche
  - Presence of *Cutibacterium acnes* in pilosebaceous unit
- Pathogenesis overview
  - Precursor lesion is the microcomedo
  - *C. acnes:* Bacterium is proinflammatory; activates complement and neutrophil chemotaxis. *C. acnes* lipase cleaves sebum triglycerides into free fatty acids. Activates toll-like receptor (TLR)-2 (these short chain fatty acids impact immune tolerance through inhibition of Histone Deacetylases)
  - Inflammation precedes and is amplified by comedo rupture
- Clinical variants
  - Acne vulgaris
    - Clinically noninflammatory lesions: Microcomedo and the comedo
    - Inflammatory lesions: Papules, pustules, and nodules

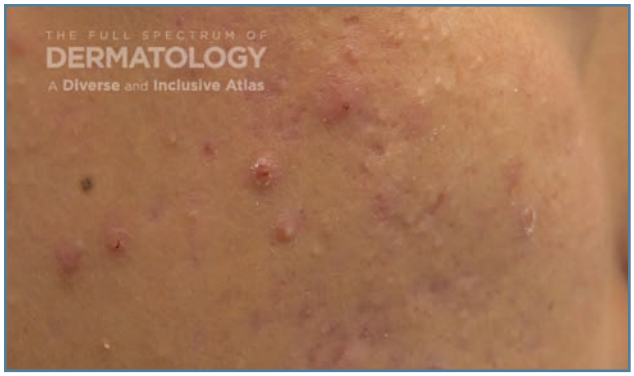


Figure 2.1.1 Acne.

  - Acne conglobata
    - Severe variant characterized by large, multiple comedones; inflammatory nodules; abscesses and sinuses
    - Young male patients
    - Follicular occlusion triad = acne conglobata, hidradenitis suppurativa, dissecting cellulitis of the scalp
    - Treatment: Isotretinoin
  - Acne fulminans
    - Rare, explosive form of severe cystic acne affecting young males
    - Acute, suppurating nodules and plaques that ulcerate and form black eschars
    - Trunk > face
    - May be incited by isotretinoin, especially at higher starting doses
    - Often systemic symptoms: Fever, leukocytosis, arthralgias, and myalgias
    - Lytic changes, indicative of a sterile osteomyelitis, can be seen on X-ray and bone scans. The **sternoclavicular joint and the chest wall** are most frequently affected
    - Treatment: Prednisone, intralesional steroids, antibiotics, and isotretinoin
  - Miscellaneous acne variants
    - Industrial acne
      - Chloracne: Triggered by exposure to chlorinated compounds
      - The malar cheeks and postauricular scalp, as well as the scrotum, are affected. The lesions are characterized by large comedones as well as inflammatory papules, pustules, and cysts
      - **Insoluble cutting oils** are the most frequent cause of industrial acne
      - Dioxin (2,3,7,8-tetrachlorobenzodioxin): Potent trigger of acneiform eruption. Was a well-known contaminant in Agent Orange
- Hormonal considerations
  - Clinical clues: Female patients with hirsutism, alopecia, or irregular menses. Predominance of acne involving the jawline and chin
  - Most common endocrinopathy associated with acne is polycystic ovary syndrome (PCOS), characterized by acne, obesity, hirsutism, amenorrhea, and glucose intolerance
  - Congenital adrenal hyperplasia is also associated with acne
  - Although rare, very high levels of dehydroepiandrosterone sulfate (DHEA-S) may suggest an adrenal androgen-secreting tumor
  - Any suspicion warrants endocrine work-up, including free and total testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and DHEA-S

- Acneiform eruptions
  - Drug-induced acne
    - Halogens, such as bromide and iodide
    - Androgenic hormones
    - Adrenocorticotropic hormone (ACTH)
    - Corticosteroids
    - Isoniazid
    - Lithium
    - Epidermal growth factor receptor (EGFR) antagonists
    - Phenytoin
    - Cyclosporine
    - Vitamins B_2, B_6, B_{12}
    - Mammalian target of rapamycin (mTOR) inhibitors (sirolimus/tacrolimus)
    - MEK inhibitors (trametinib)
    - Sorafenib/sunitinib
- Treatment of acne vulgaris
  - Topical retinoids
    - Tretinoin, adapalene, tazarotene, and trifarotene
    - Comedolytic; normalize follicular epithelial differentiation
  - Topical antibiotics (erythromycin, clindamycin, and minocycline)
    - Decrease the population of *C. acnes* on the skin
    - Use in combination with topical benzoyl peroxide to decrease development of bacterial resistance
  - Benzoyl peroxide (BPO)
    - Bactericidal with direct oxidizing effects. Thus no potential for resistance
    - Irritation, dryness, and bleaching of clothing or hair may occur
    - Recent study found that adapelene + BPO can reduce scarring
  - Topical dapsone
    - Benzoyl peroxide + dapsone may cause yellow or orange discoloration at the site of application
    - Recent study found the adapelene - BPO can reduce scarring
  - Azelaic acid
    - Dicarboxylic acid that has weak activity against *C. acnes*
    - Inhibits tyrosinase, and can be helpful in reducing postinflammatory hyperpigmentation
  - Clascoterone Cortexolone 17alpha-proprionate
    - Topical androgen receptor inhibitor
    - Also being studied for androgenic alopecia
  - Oral antibiotics
    - Tetracyclines
      - Doxycycline, minocycline, sarecycline
      - Doses of tetracyclines below the minimum Inhibitory concentration (MIC) can inhibit neutrophil chemotaxis, proinflammatory cytokine cascades, and reduce *C. acnes* production of lipase
    - Macrolides
      - Include erythromycin and azithromycin
    - Trimethoprim-sulfamethoxazole
  - Systemic retinoids
    - Isotretinoin
      - Gold standard for treating nodular acne and recalcitrant acne
      - Reduces sebum production by reducing sebaceous gland size, normalizes follicular keratinization, and indirectly reduces *C. acnes* and its inflammatory sequelae
      - A potent teratogen
      - Doses range from 0.5 to 2.0 mg/kg/day. Goal cumulative dose 150-220 mg/kg
      - Some possible side effects: increased triglycerides, increased liver enzyme, muscle cramps, rhabdomyolysis (especially in young male athletes with darker skin types) and pyogenic granuloma

TIP

Pseudotumor cerebri occurs more often with coadministration of a tetracycline

  - Hormonal therapies
    - Oral contraceptive pill (OCP)
      - Lead to a decrease in free testosterone levels by increasing the adrenal production of sex hormone—binding globulin (SHBG)
      - Equal efficacy to oral antibiotic after 6 months of therapy
    - Spironolactone
      - Blocks androgen receptors and adrenal androgen synthesis. Side effects include menstrual irregularities, **breast tenderness,** and intestinal symptoms, which can be mitigated by concomitant OCP use. Hyperkalemia is more likely in the setting of renal failure

SAPHO Syndrome

- **S**ynovitis
- **A**cne (acne fulminans or conglobata)
- **P**ustulosis (pustular psoriasis)
- **H**yperostosis
- **O**steomyelitis

Rosacea

- Papules and papulopustules in central face against a background of telangiectases

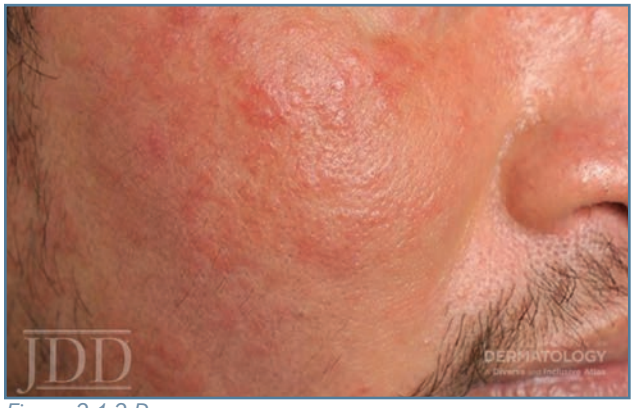


Figure 2.1.2 Rosacea.

- Nose, cheeks, chin, forehead, glabella; less commonly retroauricular, V-shaped chest area, neck, back, scalp
- Flushing and blushing evoked by UV, heat, cold, chemical irritation, strong emotions, alcoholic beverages, hot drinks, and spices
- Variants of rosacea
  - Phymatous rosacea
    - Characterized by prominent pores and fibrous thickening of the skin
      - Treatment: Debulking of the hypertrophic sebaceous skin, using a scalpel and/or laser
      - Occurs almost exclusively in men
    - Rhinophyma: Nose involvement

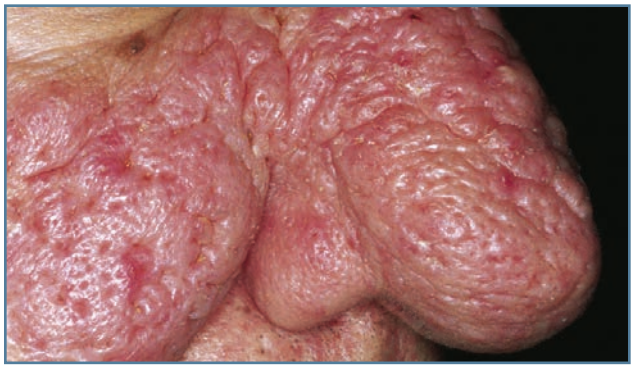


Figure 2.1.3 Rhinophyma.

    - Gnathophyma: Chin involvement
    - Metophyma: Forehead and saddle nose
    - Otophyma: Earlobe involvement
    - Blepharophyma: Eyelid involvement
  - Granulomatous rosacea
    - Dozens of brown-red papules or nodules on diffusely reddened skin, frequently involving lower eyelids
    - Chronic and unremitting
    - Histopathology: Perifollicular and perivascular **noncaseating epithelioid granulomas**
  - Steroid rosacea
    - Caused by topical or systemic steroid use
    - Flaming red, scaling, papule-covered face
    - **Severe pain, discomfort**
    - Withdrawal of steroid causes flare. Slow tapering of steroid over months is required
  - Rosacea fulminans (pyoderma faciale)
    - Occurs almost exclusively in postadolescent women; lots of flushing and blushing
    - Severe inflammation. Huge coalescent nodules and confluent draining sinus occupy most of the face
    - Prognosis is excellent, and recurrences rare
  - Ophthalmic rosacea
    - Blepharitis, conjunctivitis, iritis, keratitis
    - Treatment: Oral antibiotics
  - Perioral dermatitis
    - May be triggered or exacerbated by topical steroid use
    - Treatment: Topical and/or oral antibiotic treatment
  - Persistent edema of rosacea (rosacea lymphedema or Morbihan's disease)
    - Hard, nonpitting edema of face. Often misdiagnosed as cellulitis
    - Treatment: Isotretinoin + prednisone
- Treatment
  - Topical
    - Antibiotics: Often effective
      - Topical clindamycin, erythromycin, or minocycline
      - **Topical metronidazole active against papules and pustules,** but not telangiectasia and flushing
      - Topical sulfur-based preparations
      - Topical ivermectin
    - Azelaic acid
      - Microbiologic activity: Bacteriostatic to staph, strep, *C. acnes, Pseudomonas*
      - Inhibits protein synthesis in susceptible organisms
      - Inhibits keratinocyte differentiation and division
    - Topical α-agonists (brimonidine, oxymetazoline)
    - Sunscreens
    - Green-tinted makeup concealer can neutralize redness

- Systemic
  - Antibiotics: Response is generally good
    - Tetracycline class
    - Inhibit matrix metalloproteinase 7 (MMP7)
    - Macrolides
  - Isotretinoin: Indicated in phymas; but rosacea often rapidly recurs after discontinuation of isotretinoin
- Treatment for rosacea fulminans
  - Prednisone + isotretinoin
  - Do not incise draining abscesses

Hidradenitis Suppurativa (HS)

- Key pathogenic factors
  - Follicular occlusion, follicular rupture, and an associated immune response
- Epidemiology
  - Onset in second or third decade of life
  - Women > men
- Clinical features
  - Involving intertriginous (axillary, groin, perianal, perineal, genital, and inframammary skin) sites mostly. Can occur in any skin area with folliculopilosebaceous units
  - Painful, malodorous, recurrent papules, pustules, inflammatory nodules to deep fluctuant abscesses, draining sinuses, sinus tracts, and scarring

Figure 2.1.4 Hidradenitis suppurativa.

  - Double or multiheaded open comedones in long-standing disease
  - Hurley staging system:
    - Stage I: Single or multiple abscesses without sinus tract and scarring
    - Stage II: Recurrent abscesses with sinus tracts and scarring, single and multiple widely separated lesions
    - Stage III: Diffuse or almost diffuse involvement with multiple interconnected tracts and abscesses across the entire area
  - Unpredictable clinical course
- Association
  - Smoking
  - Metabolic syndrome, obesity
  - Follicular tetrad: HS, acne conglobata, dissecting cellulitis of the scalp, and pilonidal sinus
  - *PSTPIP1* gene mutations
    - PAPASH syndrome: Pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis
    - PASH syndrome: Pyoderma gangrenosum, acne, and suppurative hidradenitis
- Treatment
  - Supportive: Avoid trauma to the area, smoking cessation, weight management, psychosocial support
  - Topical
    - Antiseptic washes (chlorhexidine, benzoyl peroxide)
    - 1% clindamycin
    - 15% resorcinol at site of new, inflamed lesions
  - Intralesional corticosteroids for early painful inflammatory lesions
  - Systemic
    - Oral tetracycline (doxycycline, minocycline, tetracycline)
    - Oral clindamycin + oral rifampin
    - Oral dapsone
    - Oral retinoids
    - Hormonal therapies: Oral contraceptive pills, spironolactone, finasteride
    - Tumor necrosis factor (TNF)-α inhibitors
      - Adalimumab (FDA approved)
      - Ustekinumab
      - Secukinumab (FDA approved)
      - Bimekizumab (under clinical investigation)
    - Ustekinumab
    - Secukinumab (under clinical investigation)
  - Laser: 1064 nm Nd:YAG for hair removal; CO_2 for excision of sinuses
  - Surgical treatment (should be combined with medical therapy)
    - Unroofing of lesions
    - Wide local excision
  - Pain management

Eccrine Disorders: Hyperhidrosis

- Primary hyperhidrosis most commonly affects the axilla, palms, and soles. Increased sweating in localized areas of the body that disappears while sleeping
- The sweat gland is histologically and functionally normal but with an exaggerated response

- Treatment
  - Topical and localized
    - Antiperspirants such as 6.25% or 20% aluminum chloride
    - Topical glycopyrronium
    - Onabotulinum toxin A
    - Microwave thermolysis (axillary hyperhidrosis)
    - Iontophoresis (most commonly used for palmar and plantar hyperhidrosis)
  - Systemic
    - Oral glycopyrrolate
    - Oral oxybutynin
  - Surgical
    - Endoscopic thoracic sympathectomy, reserved for severe refractory cases

PAPULOSQUAMOUS DISORDERS

Psoriasis

- Epidemiology
  - Affects approximately 2% of population of U.S.
  - HLA association with
    - *HLA-B17* (earlier onset and more serious disease)
    - *HLA-Cw6* (most definitive associated HLA type): Relative risk 9-15× normal
    - *HLA-B27*: Psoriatic arthritis
- Pathophysiology
  - Psoriasis is an immune-dysregulatory disease resulting from persistent T cell activation and the resultant release of T_H17- and T_H1-based cytokines. These cytokines cause keratinocytic proliferation (acanthosis), and increased recruitment of inflammatory cells into the psoriatic skin
  - 8-fold shortening of epidermal cell cycle (36 vs. 311 hours for normal)
- Clinical patterns
  - Chronic plaque psoriasis
    - Most frequent pattern
    - Sharply demarcated papules and plaques

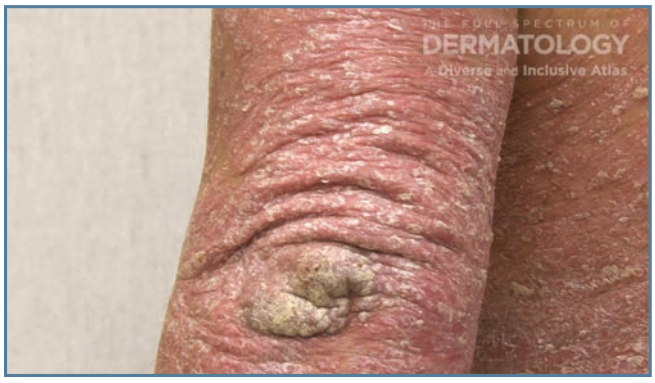


Figure 2.1.5 Psoriasis.

    - Noncoherent silvery scales
    - Koebnerization seen in 20%
    - Areas of predilection: Elbows, knees, scalp, retroauricular region, lumbar area, umbilicus
    - When localized in the major skin folds, scaling is absent
  - Guttate (eruptive) psoriasis
    - Small (0.5 to 1.5 cm) lesions over upper trunk and proximal extremities
    - Early age of onset/young adults
    - Streptococcal throat infection frequently precedes eruption
  - Psoriatic erythroderma
  - Generalized pustular psoriasis
    - Von Zumbusch type = acute variant
    - Usually no other forms on skin at same time
    - Fever + eruption of sterile pustules
    - Pustules arise on highly erythematous skin
    - Distribution: Trunk, extremities including nail beds, palms, and soles
    - **Hypocalcemia, hypoalbuminemia, leukocytosis**
  - Localized pustular psoriasis
    - Systemic symptoms absent
    - Two distinct conditions
      1. Pustulosis palmaris et plantaris
      2. Acrodermatitis continua of Hallopeau
  - Psoriatic nail disease
    - May be of nail matrix or nail bed origin
    - Nail changes more frequent (80-90%) in patients with arthritis
    - Matrix involvement: Nail pits
      - Most common nail change of psoriasis
      - Pits are more randomly distributed (vs regular rows of pits in alopecia areata)
    - Nail bed involvement: Oil spots, onycholysis, subungual hyperkeratosis, and splinter hemorrhages
  - Psoriatic arthritis
    - Asymmetric oligoarthritis, small joints of hands
    - Onycholysis
  - Trigger factors
    - Physical trauma (Koebner reaction)
    - Infection
      - 50% of children exacerbate existing psoriasis during 2- to 3-week interval after upper respiratory infection (URI)
      - Acute guttate psoriasis frequently follows an acute streptococcal infection by 1-2 weeks (56-85%) and streptococcal infections may play a role in exacerbating other forms of psoriasis
      - HIV infection

- Systemic associations
  - Crohn's disease and ulcerative colitis
  - Hypertension (HTN), obesity, diabetes
  - Chronic oropharyngeal infections

- Treatment
  - Topical glucocorticoids: 1st line for mild to moderate disease
  - Tar
    - 2-5% tar in various bases effective in chronic plaque-type psoriasis
  - Narrow-band UVB
    - 1st-line treatment for moderate severity psoriasis
    - Less risk of secondary nonmelanoma skin cancer (NMSC) when compared to psoralen + UVA (PUVA)
    - Excimer laser can be used for limited disease
  - Topical anthralin: Rarely used
  - Vitamin D_3 analogs
    - Calcipotriol, tacalciol, calcitriol
    - Inhibit keratinocyte proliferation and induce terminal differentiation
    - Antiinflammatory
    - Used for plaque-type psoriasis, once daily or twice daily
    - **Calcipotriol inactivated by salicylic acid or lactic acid (Lac-Hydrin)**
  - Tazarotene
    - Retinoid
    - Reduces scaling and plaque thickness, with little effectiveness on erythema
    - Beneficial in combination with phototherapy
    - Available as a combination lotion with 0.01% halobetasol propionate and 0.045% tazarotene
  - Tapinarof
    - Topical aryl hydrocarbon agonist
    - Data showing potential remittive effect in long-term extension studies
  - Roflumilast
    - Topical PDE4 inhibitor
    - Generally well-tolerated
    - Also available as a foam indicated for treatment of seborrheic dermatitis
  - Fixed combination products
    - Calcipotriene 0.005% and betamethasone dipropionate 0.064%
      - Ointment, solution, cream, foam
    - Halobetasol Propionate .01 % And Tazarotene .045%
      - Lotion
  - PUVA
    - Clearing usually occurs after 19 to 25 treatments
    - Decreased utilization due to time commitment as well as increased risk of skin cancer with long term use
  - Methotrexate
    - 10-25 mg every week, by mouth or subcutaneously
    - Also effective in treating psoriatic arthritis
  - Cyclosporine
  - Acitretin
    - Systemic retinoid
    - Effective in pustular and palmoplantar forms of psoriasis
    - Often ineffective as monotherapy for plaque-type psoriasis
      - More effective when combined with phototherapy
    - Usual psoriasis dose: 25-50 mg/day
    - Treatment over 3-4 months necessary
  - Apremilast: Oral PDE4 inhibitor
    - Efficacy similar to methotrexate
  - Deucravacitinib
    - First-in-class TYK2 inhibitor
    - Superior efficacy compared to apremilast
  - Biologic agents
    - TNF-α inhibitors
      - Etanercept
      - Adalimumab
      - Infliximab
      - Certolizumab pegol
      - Golimumab
    - Interleukin (IL)-12/23 inhibitors
      - Ustekinumab
    - IL-23 inhibitors
      - Guselkumab
      - Tildrakizumab
      - Risankizumab
    - IL-17 inhibitors
      - Secukinumab (IL-17A cytokine inhibitor)
      - Ixekizumab (IL-17A cytokine inhibitor)
      - Brodalumab (IL-17 receptor inhibitor)
      - Bimekizumab (IL-17 A/F dual cytokine inhibitor)
    - IL-36 inhibitors
      - Spesolimab (approved for generalized pustular psoriasis)
  - Combination therapies
    - Often desirable, as combinations can limit the toxicities of individual therapies; examples:
      - Topical steroids with UVB or PUVA
      - Retinoids with PUVA ("Re-PUVA") or narrow-band UVB
  - Vitamin D analogs with UVB: Vitamin D analog should be applied after UV light (calcipotriol absorbs UV)

Reactive Arthritis

- Chronic inflammatory disease similar to psoriasis with psoriatic arthritis
- *HLA-B27;* young men much more common than women
- Clinical
  - Urethritis, arthritis, conjunctivitis, oral ulcers, psoriasiform skin lesions
  - 5% have skin lesions
- Causes
  - Urethritis: *Chlamydia trachomatis, Shigella flexneri*
  - Less commonly *Salmonella, Yersinia, Ureaplasma, Borrelia, Cryptosporidium, Campylobacter*

TIP

Shigella flexneri (most common) of nonurethral form of Reiter's, *Salmonella* spp., *Yersinia* spp., *Ureaplasma urealyticum, Borrelia burgdorferi, Cryptosporidium, Campylobacter fetus*

- Skin lesions
  - Multiple small, yellowish vesicles that break, become confluent, and form superficial erosions → frequently on genitals and palms
  - Crusted, hyperkeratotic papules and plaques on plantar surfaces → **keratoderma blennorrhagicum**
  - Penile lesions: Perimeatal balanitis; circinate lesions; similar lesions seen on vaginal mucosa of affected women

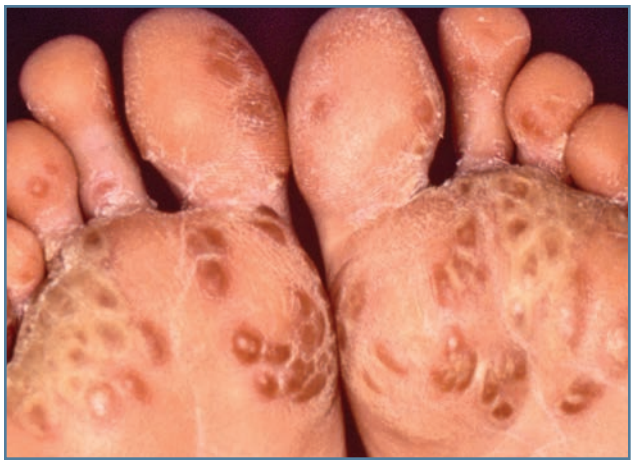


Figure 2.1.6 Reactive arthritis.

  - Buccal, palatal, and lingual mucosa may show painless, shallow, red erosions, and severe stomatitis
  - Nails become thick and brittle with heavy subungual hyperkeratotic deposits
- Treatment
  - Similar to psoriasis and psoriatic arthritis
  - Course of disease marked by exacerbation and remission. A chronic deforming arthritis occurs in 20%

Sneddon-Wilkinson Disease

- Chronic condition, possibly related to psoriasis, with remissions of variable duration
- Subcorneal pustular dermatosis
- Middle-aged women
- Superficial sterile pustules in annular and serpiginous patterns. Abdomen, axillae, groin
- Histology
  - Subcorneal pustules without acantholysis
  - Contains many neutrophils
- Treatment
  - Dapsone
  - Acitretin
  - Narrow-band UVB
  - Monitor for monoclonal gammopathy

TIP

Association with IgA monoclonal gammopathy

Erythema Annulare Centrifugum (EAC)

- Clinical features
  - Erythematous annular or polycyclic plaques that migrate centrifugally with central clearing
  - Superficial EAC: With trailing scales; deep EAC: with infiltrated borders

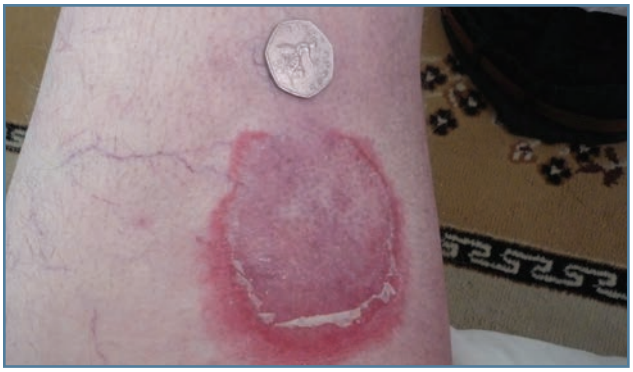


Figure 2.1.7 Erythema annulare centrifugum.

- Most commonly on thighs and hips
- Lasting days to months

- Association
  - Infections: dermatophytes, Candida, poxvirus, and parasites.
  - Drugs: Diuretics, antimalarials, gold
  - Foods: Blue cheese and tomato
  - Autoimmune endocrinopathies
  - Neoplasms: Lymphomas
  - Most are idiopathic
  - Some associated with tinea
- Treatment
  - Topical: Topical steroids
  - Management of pruritus if present

Lichen Planus (LP)

- Inflammatory disorder that affects the skin, mucous membranes, nails, and hair
  - Purple, polygonal, pruritic, planar papules

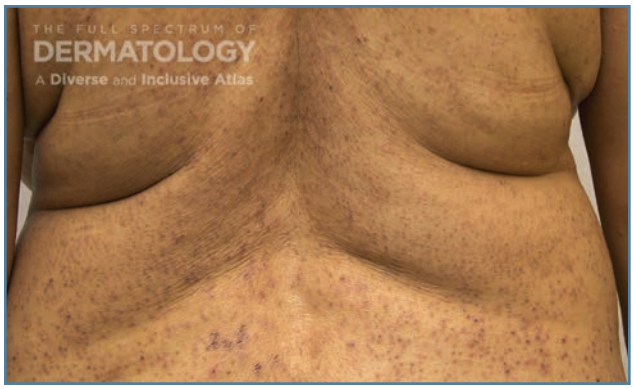


Figure 2.1. 8 Lichen planus.

  - Scaling is not as prominent as in other papulosquamous diseases
  - Prevalence: <1%, no racial preference
  - 2/3 patients between ages 30 and 60
- Etiology and pathogenesis
  - Classification
    - Idiopathic (classic)
    - Drug associated
    - Associated with other diseases (ulcerative colitis, alopecia areata, vitiligo, dermatomyositis, myasthenia gravis)
- Role of infection
  - Hepatitis C implicated in triggering LP (oral erosive)
  - Association with syphilis, herpes simplex virus type 2 (HSV2), HIV, amebiasis, and chronic bladder infections
- Clinical manifestations
  - Erythematous to violaceous, flat-topped, polygonal papule, with occasional small central umbilication
  - Thin, transparent, adherent scale atop the lesion
  - Wickham's striae: Fine, whitish reticulated networks on surface of well-developed plaques
  - Symmetrically involves flexural areas of wrists, arms, legs; also, oral mucosa and genitalia
  - Inverse LP: Axillae, groin, inframammary areas
  - Usually pruritic; oral involvement generally asymptomatic, unless erosive → extremely painful
  - Koebnerization (isomorphic response)

Figure 2.1.9 Oral lichen planus with Wickham's striae.

- Clinical variants
  - Configuration
    - Annular LP
      - African Americans more commonly affected
      - On penis and scrotum
      - Larger lesions reach 2-3 cm in diameter and become hyperpigmented with raised outer rim
    - Linear LP
      - Secondary to trauma (Koebner), often. May occur in Blaschkoid band
    - Hypertrophic LP
      - Shins, interphalangeal joints
      - Most pruritic
      - Heals with scar formation and hyper/hypopigmentation
    - Atrophic LP
      - Rare
      - White, bluish papules or plaques with central superficial atrophy

Figure 2.1.10 Atrophic lichen planus.

      - Most common on lower extremities and trunk
      - Resembles lichen sclerosus
    - Vesiculobullous LP
      - Rare
      - Vesicles and bullae within lesions of LP
      - **Bullae arise from papules of LP**, not normal skin
      - Subepidermal separation
    - Erosive ulcerative LP
      - Chronic and painful bullae and ulcerations on **feet**
      - Usually associated with more typical LP lesions of nails, mucosal surfaces, and skin

- Loss of toenails and alopecia common
- In oral LP, oral mucosa, gingiva, and tongue may be affected. Desquamative gingivitis may occur

- Follicular LP (lichen planopilaris)
  - Individual keratotic and follicular papules and studded plaques
  - Trunk and medial aspects of proximal extremities
  - Affects scalp: Cicatricial alopecia
  - Graham-Little-Piccardi-Lassueur syndrome
    - Triad of:
      1. Follicular LP of skin and/or scalp
      2. Multifocal cicatricial alopecia of scalp
      3. Nonscarring alopecia of axillary and pubic areas
- Lichen planus pigmentosus
  - Uncommon
  - Hyperpigmented, dark brown macules in sun-exposed areas and flexural folds
  - Occurs in darker-pigmented people
  - Clinically similar to erythema dyschromicum perstans
- Actinic LP
  - More common in Middle Eastern countries in spring/summer
  - Annular plaques with bluish center on sun-exposed skin
  - Affects sun-exposed areas
  - Pruritus and scaling minimal

- Sites of involvement
  - LP of the scalp
    - Lichen planopilaris or follicular LP: Individual keratotic papules that coalesce and merge to form patches
    - Women > men
    - Uni- or multifocal hair loss
    - End-stage: Scarring alopecia
  - Mucosal LP
    - Mouth, vagina, esophagus, conjunctiva, urethra, anus, nose, and larynx
    - Occurs in 60-70% of patients with LP
    - Is the sole manifestation of LP in 20-30%
    - Forms: Reticular, plaque-like, atrophic, papular, erosive-ulcerative, and bullous forms
    - Male genitalia: Glans penis most common site, (frequently) annular
    - Female genitalia: Leukoplakia/erythroplakia, erosive, or generalized desquamative vaginitis
    - Vulvar and gingival LP can exist together: Erythema and erosions of gingivae and tongue and white reticulated plaques
    - Conjunctival LP: Cicatricial conjunctivitis
  - Nail LP
    - 10-15% of cases
    - Usually in combination with other LP lesions on skin
    - 20-nail dystrophy can be seen
    - Thinning, longitudinal ridging, rough nails (trachyonychia) and distal splitting of nail plate (onychoschizia), onycholysis, longitudinal ridging (onychorrhexis), subungual hyperkeratosis, or anonychia
    - **Classic finding: Dorsal pterygium** (forward growth of the eponychium with adherence of proximal nail plate); also "tenting" sign as nail plate is elevated with longitudinal splitting
    - Pits common

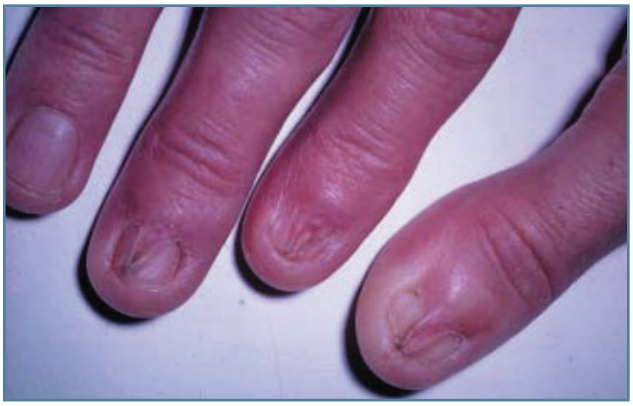


Figure 2.1.11 Nail lichen planus.

  - Inverse LP
    - Rare
    - Occurs in flexural areas such as axilla, under breast, groin
    - Reddish-brown, discrete papules
  - Palmoplantar LP
    - Yellowish, compact keratotic papules and papulonodules on lateral margins of fingers and hand surfaces

- Special forms of LP/lichenoid eruption
  - Drug-induced LP
    - May be typical or atypical for classic LP, localized or generalized
    - Typically manifest postinflammatory hyperpigmentation, alopecia, without Wickham's striae

- Symmetric eruption on trunk and extremities—photodistribution common with these drugs: 5-fluorouracil (5-FU), carbamazepine, chlorpromazine, diazoxide, ethambutol, quinine/quinidine, tetracyclines, thiazides, and furosemide
- Mucous membrane involvement often associated with specific drugs and chemicals—amalgam containing mercury; gold more common

- LP-lupus overlap
  - Classic lesions of LP not usually seen
  - Photosensitivity, pruritus, follicular plugging also uncommon
  - Lesions on extremities, commonly: Atrophic plaques and patches with hypopigmentation and a livid red-to-blue violet color with telangiectasia and minimal scaling; bullae may develop
  - May progress to systemic lupus erythematosus (SLE)
  - Prolonged course
  - Histology: Lichenoid reaction and histologic features of LE seen in same biopsy
- Lichen planus pemphigoides
  - Tense blisters atop lesions of LP, or **development of vesicle de novo on uninvolved skin** (vs bullous LP, which only vesiculates on involved skin)
  - Histologically like LP, with linear deposition of IgG and C3 at dermo-epidermal (DE) junction
  - Circulating IgG autoantibodies react to 180/200-kDa antigen within basement membrane (BM) zone
- Keratosis lichenoides chronica (Nekam disease)
  - Violaceous papular and nodular lesions; hyperpigmented and hyperkeratotic, covered with gray scales. Facial seborrheic dermatitis-like eruption
  - Often, linear and reticulate pattern on the dorsal hands and feet, extremities, and buttocks
  - Very refractory to treatment
- LP and malignant transformation
  - Squamous cell carcinoma (SCC) risk is very low to none at all
  - Risk increased by longstanding disease, erosive or atrophic types of LP, and tobacco use
  - Most common sites for malignant transformation are tongue, gingiva, and buccal mucosa
  - Most patients developing SCC in cutaneous LP had a history of either arsenic or X-ray exposure
- Lichenoid keratosis (lichen planus–like keratosis)
  - Brown to red scaling papule or plaque found on sun-exposed skin of extremities
  - Histological features of LP with additional finding of **parakeratosis**

- Associated conditions
  - Autoimmune chronic active hepatitis
  - Primary biliary cirrhosis
  - Postviral chronic active hepatitis
  - Hepatitis C virus (HCV) in some populations
- Treatment
  - Topical high-potency steroids for mucosal and limited cutaneous disease
  - Topical immunomodulators such as tacrolimus ointment for oral/genital disease
  - Intralesional triamcinolone acetonide (TAC)
  - Systemic steroids for refractory cases
  - Oral/mucosal LP: Replacement of gold or amalgam dental restorations
  - Topical anesthetics for oral pain
  - PUVA photochemotherapy successful in generalized LP
  - **Oral retinoids**
  - Oral metronidazole
- Course and prognosis
  - Typically persists 1-2 years
  - May follow chronic, relapsing course
  - Spontaneous remission on average after 15 months
  - Lichen planopilaris most chronic and progressive with little potential for hair regrowth
  - Hypertrophic LP follows protracted unremitting course
  - Oral LP does not usually spontaneously regress

Pityriasis Rubra Pilaris

- Chronic inflammatory skin disorder
- Small follicular papules, salmon-orange to red-dish-brown color, pinhead size, and topped with scaly plugs giving a "nutmeg grater" texture
- Yellowish pink scaling patches, often begins on scalp
- Solid confluent palmoplantar hyperkeratosis
- Usually idiopathic but some cases due to activating mutations in *CARD14* gene
- Clinical features
  - Involvement generally symmetrical and diffuse, with characteristic small islands of normal skin within the affected areas, islands of sparing
  - Palms and soles will be hyperkeratotic, orangish color, with fissuring
  - Nails: Dull, rough, thickened, brittle, and striated; may crack and break; no pitting
  - No nail pits (differentiates it from psoriasis)

TABLE 2.1.1 TYPES OF PITYRIASIS RUBRA PILARIS

Type	Designation	Features
I	Classic adult	Follicular papules starting on face and progressing caudally → generalized keratoderma with islands of sparing; typically resolves within 3 years
II	Atypical adult	More ichthyosiform scaling, longer duration
III	Classic juvenile	Same as type I
IV	Circumscribed juvenile	Thick plaques on elbows, knees, palms, soles
V	Atypical juvenile	Sclerodermatous changes on palms and soles
VI	HIV-related	Nodulocystic and lichen spinulosus—like lesions; erythroderma

- Treatment: Difficult
- Topical keratolytics
- Systemic retinoids
- Vitamin A: 500,000 units daily
- Phototherapy
- Systemic steroids for short-term management
- Methotrexate
- Azathioprine
- Cyclosporine
- Biologics: TNF-α inhibitors, ustekinumab

Figure 2.1.12 Pityriasis rubra pilaris.

Pityriasis Lichenoides

- PLEVA/PLC considered a spectrum of disease
- PLEVA = pityriasis lichenoides et varioliformis acuta, Mucha-Habermann disease
- PLC = pityriasis lichenoides chronica
- Most commonly seen in young adults and children
- Clinical features
  - PLEVA
    - Acute eruption of inflammatory papules and papulovesicles with hemorrhagic or necrotic crusts

Figure 2.1.13 Pityriasis lichenoides et varioliformis acuta.

    - New lesions may continue to present as older lesions resolve → lesions in various stages of development
    - Heals with varioliform scars
    - **Febrile, ulceronecrotic form** is potentially life-threatening. May also have arthralgias; GI, pulmonary, CNS involvement. May have mucosal involvement
  - PLC
    - Multiple scaly, red-brown papules
    - Heals with dyspigmentation (hypo), no scarring
- Pathology
  - PLEVA
    - Parakeratosis, spongiosis, mild to moderate epidermal acanthosis
    - Vacuolar alteration at the basal layer
    - Exocytosis of lymphocytes and erythrocytes into epidermis
    - Dense, wedge-shaped lymphohistiocytic infiltrate extending from papillary into reticular dermis
  - PLC: Same features as PLEVA but less pronounced
- Treatment
  - Topical
    - Mid to high-potency topical steroids
    - Topical calcineurin inhibitors
  - Systemic
    - Oral antibiotics (doxycycline, minocycline, tetracycline, azithromycin, erythromycin)
    - Phototherapy (narrow-band UVB or PUVA)
    - Refractory or febrile ulceronecrotic Mucha-Habermann disease: Methotrexate, cyclosporine, dapsone, acitretin, systemic steroids

ECZEMATOUS DISORDERS

Atopic Dermatitis (AD)

- Pathogenesis
  - Includes abnormalities of epidermal structure and function **(Filaggrin gene mutations)**, along with cutaneous inflammation
  - Cytokine imbalances can lead to further barrier defects
    - Cytokine imbalances, such as increased Th2 and Th22, reduce the terminal differentiation of keratinocytes
    - Increased signaling by IL-4 and IL-13 is associated with
      - Increased signaling of Th2 cytokines and chemokines
      - Inappropriate IgE class switching
      - Weakened epidermal barrier function
      - Decreased AMPs
      - Decreased keratinocyte differentiation
      - Decreased epidermal lipids
    - Acute lesion: Significant increase in expression of key Th2 cytokines, IL-4 and IL-13, and also Th22 cytokines (eg, IL-22)
    - Chronic lesion: Intensified Th2-related inflammation à increases in IL-5, IL-13, IL-10, IL-31, CCL5, CCL13, and CCL18.
- Clinical manifestations
  - Typically begins in infancy; 50% in first year of life
  - Xerosis
  - ↑ Serum IgE levels
  - Infancy
    - AD generally more acute and primarily involves the **face, scalp, and the extensor surfaces of the extremities**
    - Facial erythema or pallor
    - Diaper area spared
    - Pityriasis alba

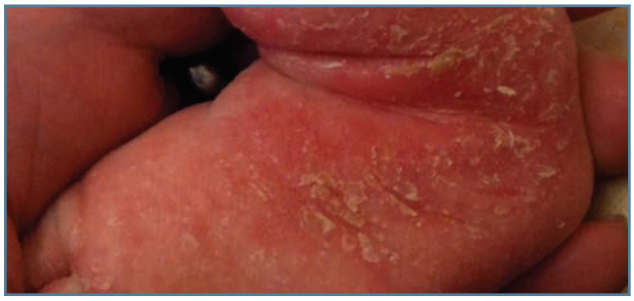


Figure 2.1.14 Atopic dermatitis in a child.

  - Older children
    - Patient develops chronic AD with lichenification and localization of the rash to the **flexural folds of the extremities**

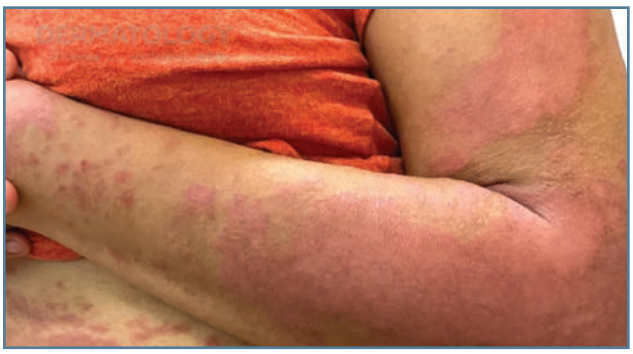


Figure 2.1.15 Atopic dermatitis.

    - Dennie-Morgan infraorbital folds
    - Orbital darkening
  - Adults
    - 1/3 of AD persists to adulthood
      - The estimated number of adults with moderate and severe AD who have been diagnosed and treated but remain uncontrolled was 1.6 million
  - Garmhausen D, et al. Allergy. 2013;68:498-506.
    - Subsides as patient grows older, leaving adult with skin that is prone to itching and inflammation
    - Chronic hand eczema may be the primary manifestation of adults with AD
- Complications
  - Ocular problems
    - Eyelid dermatitis and blepharitis, atopic keratoconjunctivitis, keratoconus: Conical deformity of cornea, cataracts
  - Infections
    - Frequently complicated by recurrent skin infections:
      - *Staphylococcus aureus:* Found in over 90% of AD skin lesions. Impetiginization results in honey- colored crusting, folliculitis, and pyoderma. Deep-seated *S. aureus* infections may indicate hyper-IgE syndrome
      - Herpes simplex: Results in eczema herpeticum—multiple, itchy, vesiculopustular lesions erupt in a disseminated pattern → often become hemorrhagic and crusted
      - Molluscum contagiosum
      - HPV
      - Superficial fungal infections: *Trichophyton rubrum* and *Pityrosporum ovale*

TIP

Innate antimicrobial peptides include human β-defensins (HBD) and cathelicidins, such as LL-37. Ong et al found a deficiency of HBD-2 and LL-37 in lesions from patients with atopic dermatitis compared to those with psoriasis. This decreased expression of innate antimicrobial peptides may explain the increased susceptibility to colonization and skin infection with *S. aureus* in patients with atopic dermatitis

- Foods
  - **Most AD patients do NOT have food allergy**
    - When involved, eggs, milk, peanuts, soybeans, tree nuts, fish, and wheat are the most common allergens implicated

- Management
  - Topical corticosteroids
  - Topical calcineurin inhibitor
  - Topical crisaborole
  - Systemic glucocorticoids
    - Rarely indicated, and risk of rebound flare after discontinuation
    - Short courses can be done while other modalities are started, and tapering dosage is critical
  - UV phototherapy
    - UVB
    - High-intensity UVA can be fast-acting and effective with acute exacerbations of AD
  - Dupilumab
    - Anti-IL-14 Rx IL-4r alpha
    - Modulates IL-4 and IL-13
  - Systemic cyclosporine or tacrolimus
    - Oral cyclosporine or tacrolimus for severe AD
    - Discontinuation of treatment may result in rapid relapse of skin disease
  - Systemic mycophenolate mofetil
  - Systemic azathioprine
  - Allergens
    - Dust mites, molds, animal dander, pollens
    - Avoidance of triggering foods
  - Antibiotics
    - Antistaphylococcal antibiotics helpful in those colonized
  - Pruritus
    - Antihistamines

- Prognosis
  - Disease more severe and persistent in young children
  - Periods of remission grow longer as patient ages
  - Mild disease at infancy: Spontaneous resolution occurs in 40% of patients after age 5
  - Topical JAK Inhibitor
    - Ruxolitinib cream
    - Approved for up to 20% BSA in patients 12 and older
  - Tralokinumab
    - Inhibits IL-13 only
    - Efficacy lower than dupilumab, but optional dosing regimen for once-monthly injection
  - Lebrikizumab
    - Investigational IL-13 inhibitor

Nummular Dermatitis

- Clinical features: Chronic, well-demarcated, coin-shaped, eczematous papules or plaques, most commonly seen on lower extremities
- Can be seen as a feature of atopic dermatitis, asteatotic eczema, and stasis dermatitis
- Treatment: Same as atopic dermatitis

Contact Dermatitis

- Irritant contact dermatitis
  - Irritants produce a reaction in almost all people exposed to the irritant and is not dependent on an immunologic (memory) reaction
  - More common than allergic contact dermatitis (~4:1)
  - Common irritants include acids (including phenol, which can be neutralized by isopropyl alcohol), alkalis, detergents, fiberglass (removed with talcum powder), hydrocarbons, mace, metal salts, tear gas (chloroacetophenone), water
- Allergic contact dermatitis (ACD)
  - Type IV hypersensitivity reaction (delayed hypersensitivity) (cell-mediated)
    - A hapten combines with a protein within Langerhans cells to produce the reaction
  - Patch testing is the gold standard for diagnosis: T.R.U.E. Test (35 allergens) versus North American 80 Comprehensive Series (>80 allergens)
    - Patch testing is different from prick testing (which tests for type 1 IgE hypersensitivity and is generally done in allergist's office)
    - Patch test results
      - 1+ reaction: Weak reaction with erythema, ± papules
      - 2+ reaction: Strong reaction with vesicles, erythema, and papules
      - 3+ reaction: Bullous reaction

TIP

Myth Busters Regarding ACD

Urushiol can remain antigenic for months (e.g., oils on clothing, tools, gloves). Once the plant oils have been washed off, it CANNOT keep spreading. There is no allergen in vesicle fluid. Patients can develop allergy to something they previously tolerated (e.g., neomycin)

- Common allergens
  - Fragrance mix
    - Contains **cinnamic alcohol and aldehyde,** hydroxycitronellal, isoeugenol, eugenol, oak moss absolute, α-amyl cinnamic aldehyde, geraniol
    - Found in perfumes, cinnamon oil/powder, cassia oil, flavoring agents, toilet soaps, bath tissue
    - Balsam of Peru, another allergen, is also fragrance; from the *Myroxylon pereirae* tree; is found naturally in tomatoes/citrus; in cola
    - Detects 70% of fragrance allergies
    - Fragrance is most common allergen in personal care products (2nd is preservatives)

TIP

Formaldehyde-Releasing Preservatives

- Quaternium-15
- 2-Bromo-2-nitropropane-1,3-diol (Bronopol)
- Diazolidinyl urea (Germall II)
- Imidazolidinyl urea (Germall 115)
- DMDM hydantoin
- Of note: Quaternium compounds other than quaternium-15 do NOT release formaldehyde and do NOT cross-react

TIP

Urushiol is found in mango peel, poison ivy (*Toxicodendron radicans*), poison oak (*Toxicodendron diversilobum* in western U.S.), sumac, gingko fruit (allergen is a cross-reactor—ginkgolic acid), lacquer tree, cashew nut, Indian marking nut, black varnish tree, Brazilian pepper tree

  - Glutaraldehyde
    - Cold sterilization; Used to disinfect medical/dental equipment
    - Also is a preservative
  - Gold
    - Patients allergic to gold often also react to nickel and cobalt
    - Titanium dioxide in makeup or sunscreen releases gold from jewelry
  - Cobalt
    - Patients often also react to gold/nickel
    - Found in jewelry, cosmetics, cements
  - Imidazolidinyl urea = Germall 115 = Tristat 1U
    - A preservative, a formaldehyde releaser
    - Found in cosmetics/creams/lotions/hair conditioner/shampoo/deodorants, OTC medications, adhesives, bubble baths, cleaning agents, latex emulsions, inks, soaps
    - Cross-reacts with formaldehyde and other formaldehyde releasers, including quaternium-15, diazolidinyl urea (Germall II), DMDM hydantoin, 2-bromo-2-nitropropane-1,3-diol (Bronopol)
  - Lanolin
    - Found in wool alcohol, wool wax, wool fat, adhesives, cosmetics, topical medications (creams/lotions/ ointments), soaps
    - From sheep fleece
    - Lanolin-sensitive patients can sometimes tolerate one formulation but not another
    - Common allergy among leg ulcer patients
  - Methylchloroisothiazolinone = Kathon CG = 5-chloro-2-methyl-4-isothiazolin-3-one
    - Found in cosmetics, skin/hair products, "acid" permanent waves, industrial water systems, cooling oils, soaps, latex emulsions, moist toilet paper, mascara, biocides
    - A preservative
    - May cause airborne contact dermatitis
  - Neomycin
    - Most common sensitizing topical antibiotic
    - Found in topical antibiotics, first-aid creams, ear drops, nose drops
    - Cross-reactivity with other aminoglycosides; allergy to bacitracin often coexists
  - Nickel
    - Most common allergen
    - Jewelry is safe to wear if it is ≥12 ct gold, sterling silver, platinum, or titanium
    - Found in jewelry, alloys, pigments, dentures, orthopedic appliances, scissors, razors, eyeglass frames, eating utensils, eyelash curlers, tweezers
    - Can test for the presence of nickel by using dimethylglyoxime
  - *para*-Phenylenediamine
    - Penetrates latex gloves, but nitrile is protective
    - Found in hair dyes, inks, photodeveloping solutions, textile dyes
    - Found in black henna tattoos (but NOT pure henna)

TIP

***para*-Phenylenediamine**
Cross-reactivity with azo- and aniline dyes, procaine, benzocaine, *para*-aminobenzoic acid (PABA), *para*-aminosalicylic acid, sulfonamides (see AA SSTEPP mnemonic box)

MNEMONIC

AA SSTEPP

Azo
Aniline dyes
Sulfonamides
Sulfonylurea
Thiazides
Esters (e.g., benzocaine)
Procainamide
PABA and PABA esters

- *para*-tert-Butylphenol (PTBP) formaldehyde resin
  - Found in shoes, watch straps, do-it-yourself glues, plywood, insulation, automobiles, motor oils, inks, papers, film developers, disinfectants, deodorants, dental bonding, rubber, raincoat
  - May cause depigmentation

TIP

Causes of Shoe Dermatitis

- Leather (potassium dichromate)
- Adhesives (PTBP formaldehyde resin and colophony rosin)
- Rubber accelerators (mercaptobenzothiazole; thiuram)
- Topicals patient is applying (neomycin)
- Mercaptobenzothiazole (rubber)*

*Mercaptobenzothiazole (rubber) is most common cause of shoe dermatitis

- Quaternium-15 = Dowicil 200
  - Most common cosmetic preservative to cause ACD
  - A preservative, a formaldehyde releaser
  - Found in cosmetics, household cleaners/polishes, creams/lotions, shampoo, latex paints, topical meds, metal-working fluids, adhesives
  - Not all patients allergic to this are allergic to formaldehyde
- Rosin (colophony)
  - Found in adhesive tape, cosmetics, insulating tape, glossy paper, flypaper, polish, paints, inks, epilation wax, rosin bags for baseball players, varnishes, violin bows, chewing gum
  - From *Pinus palustris* and *Pinus caribaea* (conifers)
  - Also called abietic acid
- Thimerosal (Merthiolate)
  - Preservative in vaccines (e.g., hepatitis), eyedrop solutions, cosmetics, nasal sprays, contact lens solution
  - Cross-reactivity with mercury or due to the thiosalicylic acid component
  - Cross-reacts with piroxicam
- Chromate
  - Found in leather, cements, some green felts (pool tables)
- Thiuram mix
  - In rubber (prevents degradation), latex, adhesives, pesticides, medications like disulfiram (Antabuse)
  - Found in condoms, adhesives, diaphragms, repellents, fungicides
  - Includes four chemicals
  - Cross-reacts with disulfiram
- Dimethyl fumarate
  - Contact Allergen of the Year: 2011
  - Present in sachets to prevent mold formation on shipped furniture ("sofa dermatitis")

Stasis Dermatitis

- Key pathogenic factors
  - Triggered by venous hypertension, venous insufficiency, and incompetence of deep leg vein valves
- Clinical features
  - Edema on the lower third of lower extremities; hemosiderin deposition; erythematous, scaly ill-defined patches and plaques
    - Hemosiderin deposition in established areas
  - Usually more pronounced in the medial aspects
  - Skin may appear weepy or dry and itchy
  - Often most prominent when ulcers are present
  - Can be complicated by allergic contact dermatitis
    - Neomycin
  - Can have autosensitization
- Association: Seen with other signs of venous hypertension (varicose veins, chronic edema, venous ulceration, hemosiderin deposition, lipodermatosclerosis)
- Treatment
  - Must address underlying venous insufficiency: Compression stockings, leg elevations; surgical options include ligation and removal of insufficient veins
  - Topical: Emollients, topical corticosteroids, topical calcineurin inhibitor

Autosensitization/Id Reaction

- Secondary eczema distant from primary site of involvement, usually appears days to weeks after primary lesions
- Clinical features
  - Symmetrical eczematous eruption at site distant from primary dermatitis
  - Commonly seen in the setting of allergic contact dermatitis, stasis dermatitis and tinea
- Treatment: Address primary dermatitis

Seborrheic Dermatitis

- Key pathogenic factors
  - Active sebaceous glands, abnormal sebum composition, and commensal yeast *Malassezia furfur*
- Epidemiology
  - Infant: 0-3 months
  - Adults: Peak in the fourth to sixth decades; men > women
- Clinical features
  - Pink-yellow to dull red to red-brown sharply demarcated patches or thin plaques with bran-like or greasy scales

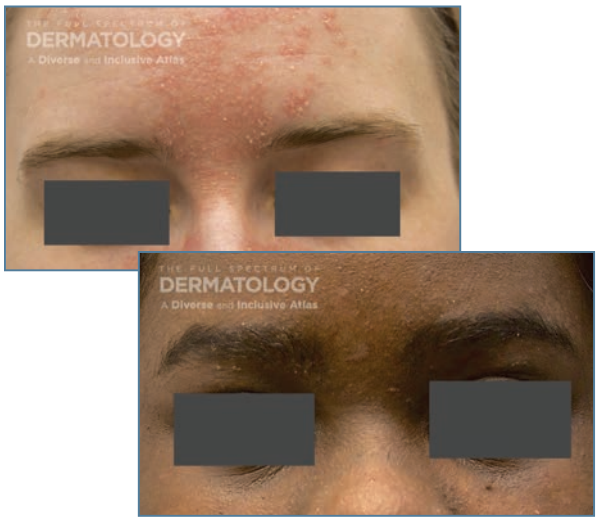


Figure 2.1.16 Seborrheic dermatitis.

  - Can be crusted
  - At areas rich in sebaceous glands: Scalp, face, ears, presternal region, and less often in the intertriginous areas
  - Most often in limited form but can be generalized and even erythrodermic
- Association: Can be a sign of HIV infection when severe and therapy resistant; Parkinson's disease
- Treatment
  - Infantile: Self-limited. Emollients, topical 2% ketoconazole cream, low-potency topical steroids; avoid mechanical removal of scales
  - Adults:
    - Topical ketoconazole 2% cream or shampoo
    - Low-potency topical steroids
    - Zinc pyrithione shampoo
    - Tar or salicylic acid shampoo
    - Ciclopirox cream or shampoo
    - Topical calcineurin inhibitors

PIGMENTARY DISORDERS

Vitiligo

- Epidemiology
  - Half of all cases begin before age 20
- Pathogenesis
  - Likely autoimmune
  - 30% of vitiligo patients have an affected relative
- Clinical
  - Depigmented white patches surrounded by normal or hyperpigmented border

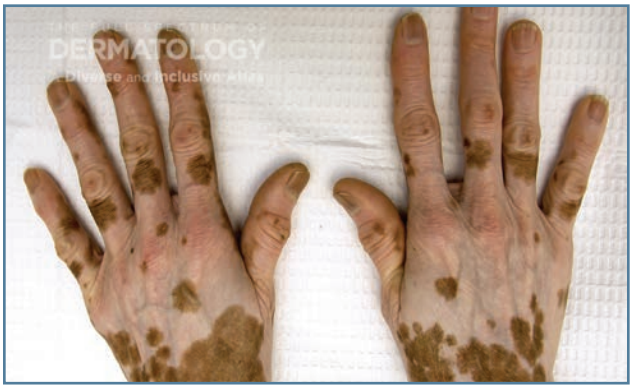


Figure 2.1.17 Vitiligo.

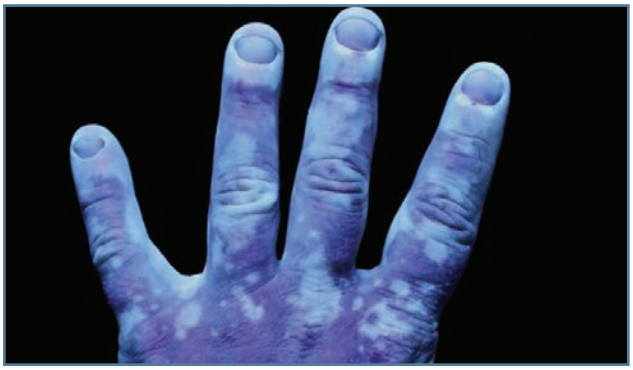


Figure 2.1.18 Vitiligo under Wood's lamp.

- Trichrome vitiligo: Intermediate tan zones halfway between the normal skin color and the depigmentation
- Hairs in vitiliginous areas become white
- Four types
  - Localized or focal (includes segmental)
    - Asymmetric
    - Often treatment resistant
    - 5% of adult, 20% of childhood cases of vitiligo
  - Generalized (most common)
    - Symmetrical
    - Face, upper chest, dorsal hands, axillae, groin
    - Skin around all orifices
    - Areas of trauma (knees and elbows)
  - Universal
    - Entire body surface depigmented
  - Acrofacial

Figure 2.1.19 Acrofacial vitiligo.

- Associations
  - Insulin-dependent diabetes
  - Pernicious anemia
  - Hashimoto's thyroiditis
  - Graves' disease
  - Addison's disease

- Treatment
  - Topical corticosteroids
  - Ultraviolet phototherapy (narrow-band UVB [NBUVB], PUVA)
  - Laser (308 nm excimer)
  - Topical calcineurin inhibitor
  - Ruxolitinib cream
  - Systemic Janus kinase (JAK) inhibitor + NBUVB
  - Repigmentation surgery with punch minigrafts, dermoscopic dermal grafts
  - IL-15 inhibitors - potential treatment avenue under study that may inhibit autoimmune memory T cells

CONNECTIVE TISSUE DISEASES

Lupus Erythematosus (LE)

- Classification
  - Acute
    - Systemic lupus erythematosus
    - Transient malar erythema
    - Bullous lupus
  - Subacute cutaneous LE (SCLE)
    - Papulosquamous
    - Annular
    - Neonatal
    - Complement deficiency syndromes
  - Chronic cutaneous LE
    - Discoid (DLE)
    - Verrucous (hypertrophic)
    - Tumid
    - Lupus panniculitis (LP)
    - Chilblain
    - LE-LP overlap
    - Childhood DLE

- Systemic LE
  - Epidemiology
    - Young middle-aged women; skin involved in 80% cases
  - Criteria: 4 of 11 needed (see mnemonic)
    - Malar erythema
    - DLE
    - Serositis (carditis or pleurisy)
    - Oral ulcers
    - Arthritis, nonerosive
    - Photosensitivity
    - Neurologic (seizure or psychosis)
    - Hematologic disorder
    - Anti-nuclear antibody (ANA)
    - Immunologic disorder (positive LE cell preparation, **anti-dsDNA** or **Sm,** false-positive RPR)
    - Renal (**nephritis,** proteinuria)
  - Cutaneous findings
    - Butterfly facial erythema, may be associated with edema → lasts days to weeks and heals without scarring

MNEMONIC

MD SOAP N HAIR

Malar erythema
Discoid LE
Serositis (carditis or pleurisy)
Oral ulcers
Arthritis, nonerosive
Photosensitivity
Neurologic (seizure or psychosis)
Hematologic disorder
ANA
Immunologic disorder
Renal

Figure 2.1.20 Malar erythema in lupus erythematosus.

- Bullous lesions, sun-exposed areas → **histologically like epidermolysis bullosa acquisita (EBA) with antibodies against collagen type VII,** but responds to dapsone (EBA does not)
- Tips of fingers and toes → show puffy erythema, telangiectasias
- Periungual telangiectasias
- Red lunulae
- Erythematous to purplish palms and soles
- Telangiectasias on face or elsewhere
- Diffuse nonscarring hair loss with short, broken-off hairs in frontal region
- Multiple (>15) dermatofibromas
- Vasculitis secondary to anti-phospholipid antibody
- Cryoglobulinemia, livedo reticularis, thrombophlebitis, cutaneous infarction
- Erythema multiforme/toxic epidermal necrolysis (EM/TEN)-like lesions
  - Acute syndrome of apoptotic pan-epidermolysis; Rowell syndrome
- Calcinosis cutis
- Plaque-like depositions of mucin

▸ Variants

- Pregnancy and SLE
  - Miscarriages occur with greater frequency
  - LE may worsen, or go into remission during pregnancy
  - **Fetal death risk increased with anticardiolipin or anti-Ro antibodies**
  - Postpartum period shows the highest risk to the patient

TIP

Hydrochlorothiazide (HCTZ) and terbinafine induce SCLE

- Drug-induced LE
  - Usually benign course
  - Drug-induced LE not usually associated with skin, renal, and CNS manifestations
  - Anti-histone antibody closely associated with symptomatic disease
  - **I**NH, **h**ydralazine, **minocycline**/**m**ethyldopa, **c**hlorpromazine, **q**uinidine, **p**rocainamide

MNEMONIC

I Hate Multiple Meds Causing Queer Problems

INH
Hydralazine
Minocycline
Methyldopa
Chlorpromazine
Quinidine
Procainamide

TIP

Histone Antibodies

- Characteristic of drug-induced SLE → >90% of patients
- 30% of patients with idiopathic SLE have anti-histone Abs

  - Other associations
    - Hydralazine → 14%, with slow acetylators (*HLA-DR4*) more prone
    - Procainamide → 50% of treated patients
    - Penicillamine induces native disease, with anti-dsDNA Abs
- Bullous SLE
  - Sun-exposed sites
  - **Ab against collagen VII**
  - Higher association with SLE
  - Pathology: **Subepidermal blister with neutrophils (looks like dermatitis herpetiformis [DH])**
  - Treatment: Dapsone

- Subacute cutaneous lupus

▸ Papulosquamous

- Scaly papules that evolve into either psoriasiform or polycyclic annular lesions (more commonly)
- No follicular involvement
- No scarring
- Occurs on sun-exposed surfaces of face and neck, inner arms, axillae, and flanks
- Spares knuckles
- Arthritis common
- Hard palate may be involved

- May have concomitant DLE
- 50% meet American College of Rheumatology (ACR) criteria for SLE (usually have arthralgia, arthritis, leukopenia, positive ANA)
- **Anti-Ro (+) in >70%**
- Disease runs a mild course

TIP

Common causes of drug-induced SCLE

- Majority positive for anti-Ro
- Drugs that may induce: HCTZ, penicillamine, glyburide, griseofulvin, piroxicam, spironolactone, diltiazem, angiotensin-converting enzyme (ACE) inhibitors, terbinafine

- Neonatal LE
  - *HLA-DR3*
  - Annular scaling erythematous macules and plaques on **head and extremities** **(racoon eyes)** within the first few months of life
  - Occurs in babies born to mothers with LE, rheumatic disease, or other connective tissue disorders **(anti-Ro positivity most common)**
  - 50% of mothers asymptomatic at delivery
  - Lesions resolve spontaneously by 6 months, heal without scarring
  - Photosensitivity may be prominent
  - 75% of cases involve girls
  - Associations
    - **3rd degree congenital heart block** (± cardiomyopathy)
      - Present at birth
      - 20% mortality, 2/3 require pacemakers
      - Absent if anti-U1RNP (+)

TIP

Heart block in neontal SLE

50% have congenital heart block, which is permanent (this may be the only manifestation of disease)

    - **Hepatobiliary disease**
      - 1st few weeks
      - May present as liver failure, conjugated hyperbilirubinemia, or mildly elevated aminotransferases
    - **Thrombocytopenia**
      - 1st few weeks
    - 25% risk that a second child will have neonatal lupus
  - Complement deficiency syndromes
    - Most commonly C2 and C4
    - Photosensitivity
    - Annular SCLE lesions
    - Ro antibody formation
- Discoid lupus
  - Epidemiology
    - Young adults; women:men, 2:1
  - Clinical
    - Dull red macules with adherent scales extending into follicles
    - **Ear (concha and external canal most common sites)**
    - Plugged follicles (carpet tacking)
    - Patches heal with atrophy, scarring, dyspigmentation, and telangiectasia

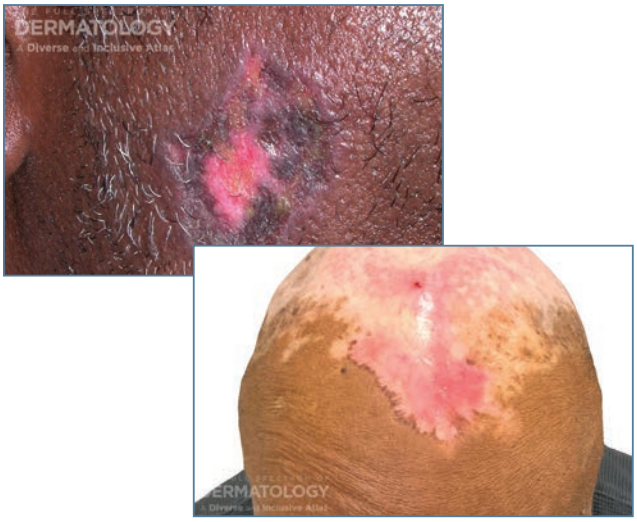


Figure 2.1.21 Discoid lupus.

    - Variants
      - Localized
        - Above neck (scalp, nose, malar, lips, ears)
        - Pruritus and tenderness common
        - Mucosal involvement of mouth, nose, eyes, vulva common
      - Generalized
        - Less common than localized
        - Thorax and upper extremities, in addition to usual sites above the neck
        - Elevated erythrocyte sedimentation rate (ESR), positive ANA, or leukopenia more common

- Course
  - Benlysta is not approved for DLE, rather SLE.
  - Up to 28% of DLE pts may turn into SLE
  - Abnormal laboratory results, such as ANA, leukopenia, hematuria, or albuminuria, identify those who are apt to progress; also, rash above and below the neck
  - Relapses are common
  - Basal cell carcinoma (BCC) or SCC can occur in scars, and a favored site is the lower lip
- Treatment
  - Sun avoidance
  - Topical corticosteroids (potent) with or without occlusion
  - Intralesional (IL) steroids
  - Antimalarials (hydroxychloroquine, chloroquine, quinacrine)
  - "Belimumab", fully human IgG1λ recombinant monoclonal antibody directed against B lymphocyte stimulator (BLyS)
- Other forms of cutaneous LE
  - Verrucous LE (hypertrophic)
    - Nonpruritic, papulonodular lesions on arms and hands
    - Resembles keratoacanthomas (KAs) or LP
    - Treat with IL TAC
  - Tumid lupus
    - Face, trunk most common; no scarring
    - Pathology shows pronounced lymphohistiocytic dermal infiltrate and **marked dermal mucin**
  - LE panniculitis (lupus profundus)
    - Deep dermal and subcutaneous nodules, rubbery-firm, sharply defined, and nontender
    - Head, face, upper arms, chest, buttocks, thighs
    - Heals with **severe fat atrophy** → disfiguring, depressed plaques
    - Overlying discoid lesions in 50% (**lupus profundus**)
    - Pathology shows **lobular panniculitis with lymphoid follicles in septae, hyaline degeneration of fat**
    - Treat with antimalarials for many months
  - Chilblain lupus erythematosus
    - Chronic, unremitting form with lesions on fingertips, ears, calves, and heels
    - Lesions are due to cold
    - Lesions evolve into DLE-like lesions
  - LE-LP overlap syndrome
    - LE and LP lesions
  - Childhood DLE
    - Lacks female predominance, less photosensitivity, ↑ **progression to SLE**

Dermatomyositis (DM)

- With or without skin lesions, **weakness of proximal muscle groups** is the prominent feature
  - Skin eruption precedes muscle symptoms by 2 to 3 months
- Epidemiology
  - Twice as prevalent in women
  - Small peak in children and large peak in adults between 40 and 65
- Pathogenesis
  - Lymphocyte-mediated muscle damage + cutaneous lesions from keratinocyte apoptosis
  - Immune reaction likely triggered by malignancy, drug, infectious agent
- Cutaneous findings
  - **Heliotrope rash:** Violaceous erythema and swelling of periorbital skin

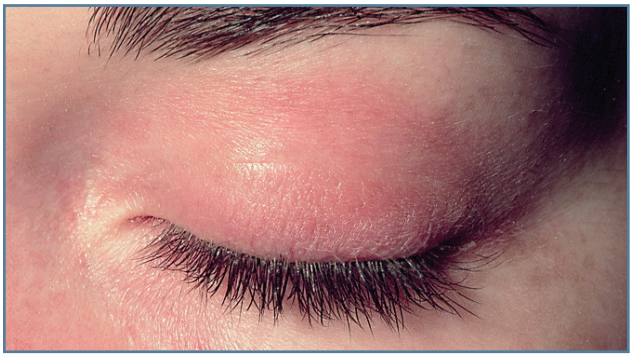


Figure 2.1.22 Heliotrope rash in dermatomyositis.

  - **Gottron's papules:** Flat-topped, violaceous papules over metacarpophalangeal (MCP), proximal interphalangeal (PIP), distal interphalangeal (DIP) joints
  - Periungual telangiectasias with frayed or ragged cuticles

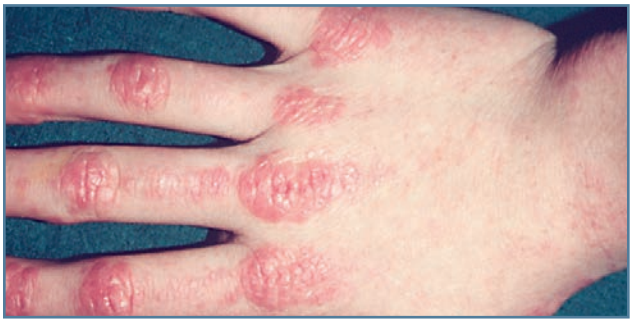


Figure 2.1.23 Gottron's papules in dermatomyositis.

- Erythematous or urticarial patches and plaques on upper portion of face and extremities
- Photosensitivity
- Hyperkeratosis, scaling, fissuring, and hyperpigmentation over the fingertips, sides of thumb, and fingers ("mechanic's hands")
- Raynaud's phenomenon
- Poikiloderma of chest or back (shawl sign), or on lateral thighs (holster sign)

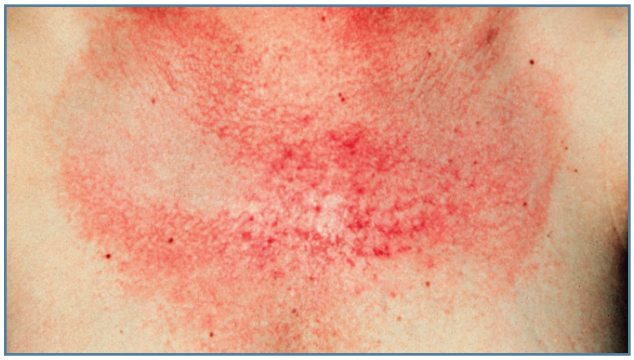


Figure 2.1.24 Poikiloderma on the chest in dermatomyositis.

- Calcinosis cutis: More often in children with DM
- **Bullous lesions**
  - **May predict poor prognosis (associated with severe myopathy or lung disease)**

- Muscle findings
  - Symmetric weakness with swelling and pain, especially involving shoulder
  - **Difficulty swallowing,** talking, or breathing
  - Cardiac disease late in disease
  - Amyopathic dermatomyositis: Lack of muscle inflammation after a year or longer
- Associated diseases
  - Sclerodermatous changes → sclerodermatomyositis (anti-Ku antibodies)
  - Other collagen vascular diseases
  - Presence of anti-Jo-1 antibody, as well as anti-PL-7, anti-PL-12 (anti-synthetase antibodies), correlates well with **pulmonary disease**
- Cancer risk
  - Cancer can precede, occur simultaneously as, or follow DM
  - 25% of DM associated with occult malignancy
    - **Ovarian, colon, genitourinary (GU)** > breast, lung, gastric, pancreatic, lymphoma (non-Hodgkin), other female genital cancers
  - Malignancy usually in **5th or 6th decade of life,** and more common in women
  - Patients should be monitored for all cancer screenings: Fecal occult blood test (FOBT), colonoscopy, transvaginal ultrasound, and Pap
- Laboratory tests
  - Creatinine kinase, aldolase, lactate dehydrogenase (LDH), and transaminase elevations (aspartate transaminase [AST] > alanine transaminase [ALT])
  - Perform EMG and MRI to find disease activity
  - Pulmonary function tests
  - Barium swallow for esophageal dysmotility
  - **Triceps muscle biopsy (gold standard)**
- Myositis-specific autoantibodies
  - Positive ANA in 60-80% of patients
  - **Anti-Mi-2** (good prognosis)
  - **Anti-TIF-1γ** (higher risk of underlying cancer)
  - **Anti-Jo-1** (anti-synthetase syndrome; pulmonary fibrosis)
  - **Anti-MDA-5** (in patients with amyopathic DM; rapidly progressive interstitial lung disease; cutaneous ulcerations, palmar papules)
  - Anti-Ku (sclerodermatomyositis)
  - Anti-signal recognition particle (SRP) (fulminant DM/polymyositis [PM], cardiac involvement, poor prognosis)

TIP

Anti-Mi-2 Abs correlate with shawl sign, cuticular changes, and good prognosis

Anti-Jo-1 Abs correlate with pulmonary fibrosis, Raynaud's, polyarthritis

Anti-SRP Abs correlate with cardiac disease and poor prognosis

Anti-Ku Abs correlate with sclerodermatomyositis

- Course
  - Major causes of death are cancer, ischemic heart disease, and lung disease
- Treatment
  - Systemic corticosteroids
  - Azathioprine, methotrexate, antimalarials, mycophenolate mofetil, cyclophosphamide
    - **Hydroxychloroquine: Increased incidence of cutaneous drug reactions in patients with DM**
  - Treat calcinosis with aluminum hydroxide, diphosphonates, diltiazem, colchicine, low-dose warfarin
  - Sunscreens

Juvenile Dermatomyositis (JDM)

- Epidemiology
  - 2 peaks (2-5 years, 12-13 years)
  - *HLA-DQA1*0501*
  - Antecedent illness 3-4 months before disease (viral, strep)
- Pathogenesis
  - Occlusive, small-vessel vasculopathy affecting small arterioles and capillaries
  - **TNF-α-308A allele: ↑ thombospondin 1 (antiangiogenic) → small-vessel occlusion**
- Clinical features
  - Periorbital edema in association with facial rash
  - **Lipodystrophy (distinguishing feature of JDM)**
  - Panniculitis
  - **Calcinosis cutis:** Associated with delay in starting steroid therapy or therapy-resistant disease
  - Variants
    - **Brunsting type:** More common, slow course; progressive weakness, calcinosis, steroid responsive
    - **Banker type:** Vasculitis of GI tract and muscles; rapid-onset severe weakness, steroid unresponsive
- Specific JDM markers
  - Neopterin (indicator of macrophage activation)
    - Increased in JDM; correlates with disease activity
  - von Willebrand factor antigen (elevated before muscle enzymes in JDM)
  - Annexin XI (56 kDa) (most sensitive JDM marker)

TIP

Childhood DM

Brunsting type: More common, slow course, progressive weakness, calcinosis, steroid responsive

Banker type: Vasculitis of muscles and GI tract, rapid onset of severe weakness, steroid unresponsive, and death

Scleroderma

- Classification: Limited/localized scleroderma and systemic sclerosis (SSc)
  - See discussion of systemic sclerosis below

Localized Scleroderma

- Epidemiology
  - Women:men, 3:1
  - More common in whites
- Clinical
  - Localized plaque morphea
    - Circumscribed sclerotic plaques with ivory-colored centers and violaceous borders (if disease active)
    - Plaques may be elevated or depressed, are indurated but not bound to the deeper structures
    - May occur after radiation therapy
    - All forms of localized morphea have good prognosis, with disease becoming inactive in 3-5 years
  - Generalized morphea
    - Widespread involvement
    - Multiple indurated plaques and hyperpigmentation

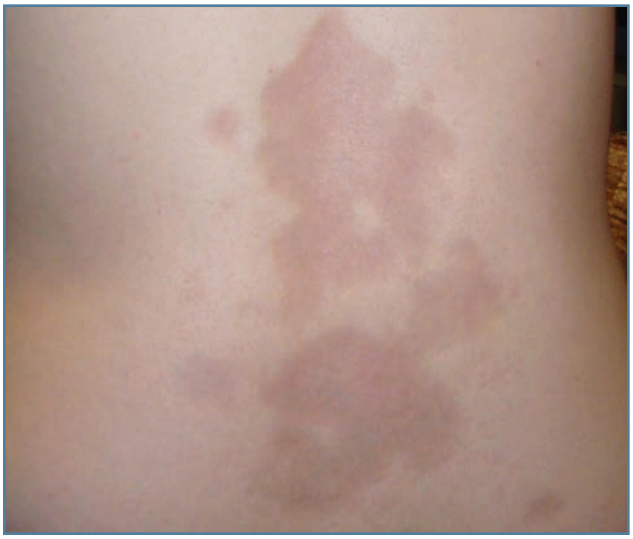


Figure 2.1.25 Morphea.

    - Upper trunk, abdomen, buttocks, and legs
    - Not associated with systemic disease
  - Guttate morphea (lichen sclerosus et atrophicus [LS&A])
    - Multiple small chalk-white lesions that lack the firm character of morphea
  - Nodular morphea
    - Lesions resemble keloids
    - May coexist with more typical lesions of morphea
  - Morphea profunda (subcutaneous morphea)
    - Deep, bound-down, sclerotic plaques

- Atrophoderma of Pierini and Pasini
  - Idiopathic atrophy of the skin characterized by single or several depressed areas of skin
  - Lesions are well defined with a "cliff drop" border
- Linear scleroderma
  - Single, unilateral linear band
  - Lower extremities are most frequent site

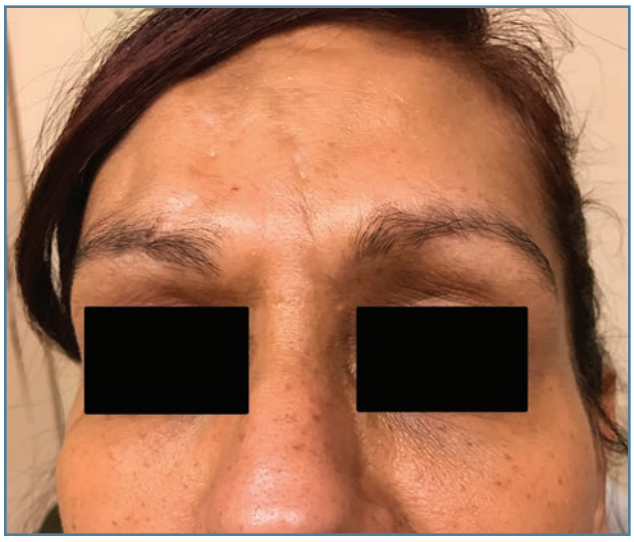


Figure 2.1.26 Linear morphea on the face: en coup de sabre.

  - Upper extremities, **frontal head (*coup de sabre*)**, thorax also involved
  - Differentiate from morphea by involvement of deeper layers of skin with fixation to underlying structures
  - Associated with anti-ssDNA Ab
  - Need to diagnose and treat urgently with prednisone and methotrexate
  - May cause severe deformity
  - May be associated with spina bifida occulta
- Melorheostosis (candle wax)
  - Linear, dense, cortical hyperostosis
  - Affects an involved limb usually, but may be widespread
- Parry-Romberg syndrome
  - Facial hemiatrophy; may be form of linear scleroderma

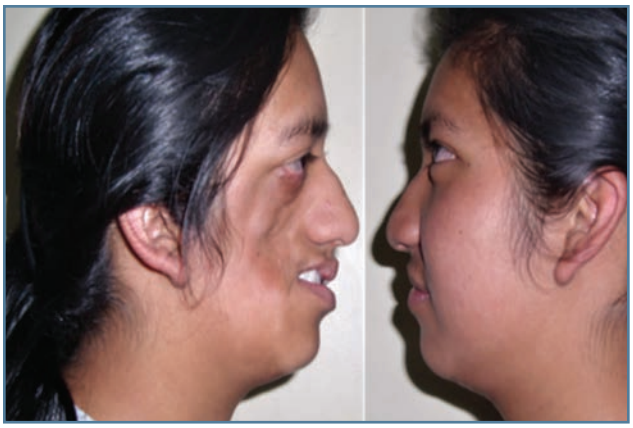


Figure 2.1.27 Parry-Romberg syndrome.

  - Hyperpigmentation followed by atrophy of the dermis, subcutaneous fat, muscle, and sometimes the bone
- Scleroderma-like disorders
  - **Bleomycin:** Pulmonary fibrosis, Raynaud's, and cutaneous changes indistinguishable from SSc (reversible on discontinuation of drug)
  - Scleroderma-like skin changes seen in scleromyxedema, porphyria cutanea tarda (PCT), graft-versus-host disease (GVHD)

- Course
  - Morphea and linear scleroderma → few months to many years
  - 50% of patients with lesions that disappear are left with areas of hypo- or depigmentation
  - *Coup de sabre* lesions may remain unchanged or become more extensive
  - Limited SSc rarely progresses to diffuse SSc
- Treatment
  - Generally self-limited, so no treatment necessary
  - High-potency topical steroids + intralesional steroids
  - D-Penicillamine may soften skin, allow the resumption of skin growth, and the cessation of new lesions
  - High-dose UVA1 (340-450 nm) or NBUVB, methotrexate (MTX), cyclosporine for morphea

Systemic Sclerosis (SSc)

- Epidemiology
  - Women:men, 4:1
  - More common in black women, with diffuse disease more likely to affect black women
  - 10-year survival < 70%

- Pathogenesis
  - **Vascular dysfunction and endothelial injury:** Hypoxia → synthesis of profibrotic cytokines, fibroblast activation, and collagen production
  - **Fibrosis:** Transforming growth factor (TGF)-β → release of connective tissue growth factor (CTGF) → sustained collagen synthesis
  - **Immune activation**
    - Topoisomerase I—antitopoisomerase I complexes bind to fibroblasts → monocyte adhesion and activation
    - Oligoclonal helper T type 2 (T_H2)-cell expansion → increased profibrotic cytokines (**IL-4 → TGF-β synthesis**)

TIP

Polyvinyl chloride

Causes scleroderma with hepatic & pulmonary fibrosis

- Diagnosis
  - Diagnosis (need 1 major, 2 minor)
    - Major criterion
      - Symmetric sclerosis proximal to the MCP/metatarsophalangeal (MTP) joints
    - Minor criteria
      - Sclerodactyly, digital pitting scars, bibasilar pulmonary fibrosis on X-ray

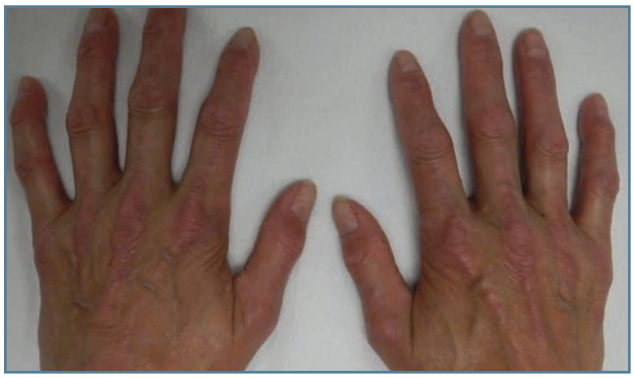


Figure 2.1.28 Sclerodactyly.

- Clinical
  - Cutaneous
    - Skin changes usually precede systemic disease
      - Dyspigmentation
        - Diffuse hyperpigmentation most common (accentuated in areas of pressure)
        - No associated adrenal insufficiency
      - Leukoderma: Depigmentation with sparing of perifollicular skin **(salt and pepper sign)**
        - Upper trunk and central face most common
      - Telangiectasias: Lips and palms most common; matted or squared-off (vs. raised as in hereditary hemorrhagic telangiectasia [HHT])
      - Facial: **Microstomia,** lip retraction, perioral furrows, beaked nose
      - **Neck sign:** Ridging and tightening of neck on neck extension (90% of patients)
      - Nail fold capillary abnormalities
        - Capillary loss alternating with dilated loops characteristic; seen in 90% of patients
        - Also seen in SLE, DM, HHT
      - **Pterygium inversum unguis:** Adherence of the distal portion of the nail bed to the ventral surface of the nail plate
      - Calcinosis cutis: Joints, distal extremities (fingertips) most common
      - Cutaneous ulcers
        - Due to ischemia (fingertips), fibrotic tissue, trauma (joints)
        - Can lead to osteomyelitis, amputation
      - Secondary Raynaud's phenomenon

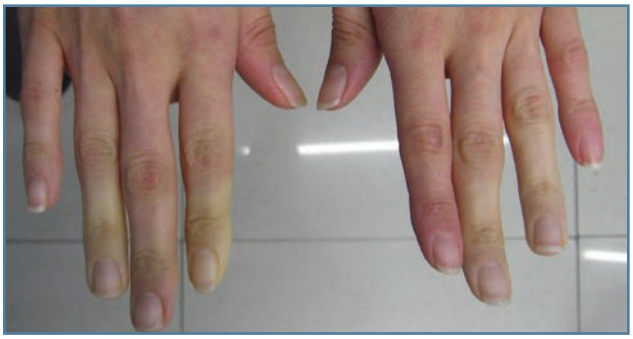


Figure 2.1.29 Raynaud's of the hand.

        - Episodic vasospasm of digital arteries
        - Most common finding (90% diffuse SSc, 99% limited SSc)
        - Vs. primary Raynaud's (young women; no associated diseases)
      - Thinning or complete loss of hair and anhidrosis

- Extracutaneous
  - Polyarthritis may be first manifestation
  - Pulmonary
    - **Interstitial lung disease (alveolitis → pulmonary fibrosis)**
      - Most common cause of death in **diffuse SSc**
      - Diagnose/monitor by pulmonary function tests (PFTs), CT scan every 6-12 months
    - **Pulmonary arterial hypertension**
      - Most common cause of death in **limited SSc**
      - Diagnose by echocardiography or right heart catheterization

TIP

Mortality in SSc

- **Pulmonary fibrosis and renal hypertensive crisis in diffuse SSc**
- **Pulmonary hypertension in limited SSc**

  - GI
    - **Esophageal disease (most common systemic finding, 90%)**
    - **Small-intestine involvement gives rise to constipation, diarrhea, bloating, and malabsorption**
  - Cardiac
    - Myocardium sclerosis → conduction defects
    - Most common cause of death in children
  - Renal
    - Hypertension
    - Common cause of death in diffuse SSc
- CREST syndrome
  - **C**alcinosis, **R**aynaud's, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasia
  - Esophageal dysfunction similar to that of more severe disease
  - Mat telangiectasias
    - Face, trunk, dorsal hands
    - Smoother outline than **Osler-Weber-Rendu (HHT)**
  - Affects acral/distal parts of body (head, hands, feet, forearms)
  - **Anti-centromere Ab (+)** very specific for CREST
  - Mortality = **pulmonary HTN**
- Mixed connective tissue disease (MCTD)
  - Combined features of scleroderma, LE, and myositis
- Autoantibodies
  - **Anti-topoisomerase-I (Scl-70)** = increased risk diffuse SSc, interstitial lung disease
  - Anti-RNA polymerase I and III = associated with diffuse SSc
  - Anti-fibrillarin = associated with diffuse SSc (seen in <10%)
  - **Anti-centromere** = limited SSc

- Course
  - Visceral involvement ultimately develops in diffuse SSc
  - **5-year mortality for diffuse SSc is about 50%**
- Treatment
  - Azathioprine, chlorambucil, MTX, cyclophosphamide variably successful
  - Systemic steroids do not alter the overall disease course
  - Cyclosporine may result in decrease in skin thickness, but pulmonary function remains unchanged and renal function may worsen
  - Extracorporeal photopheresis very controversial
  - D-Penicillamine may be effective if used in early disease, with improved survival curves in patients because of lower incidence of renal disease
    - Side effects limit long-term use:
      - Autoimmune lupus/polymyositis, pemphigus, nephrotic syndrome, myasthenia gravis, and Goodpasture syndrome
  - **ACE inhibitors markedly improve survival by treating renal disease**
  - Peripheral vasospasm treated with diltiazem
  - Calcinosis treated with calcium channel blockers
  - Reflux esophagitis with proton-pump inhibitors
  - Physical therapy
  - Cessation of smoking decreases morbidity in those patients with documented Raynaud's

Lichen Sclerosus

- Epidemiology
  - Presents from childhood to old age, and occurs in all races
  - Females predominate
- Pathogenesis
  - Associated with *HLA-DQ7*
  - **IgG1 autoantibodies against ECM-1** in 80%
- Clinical
  - White, polygonal, and flat-topped papules or plaques surrounded by erythema

- Later, lesions coalesce into large atrophic patches, becoming smooth, slightly wrinkled, and white
- Females
  - Begins as slightly elevated, well-demarcated erythema → dry, hypopigmented sclerotic lesions

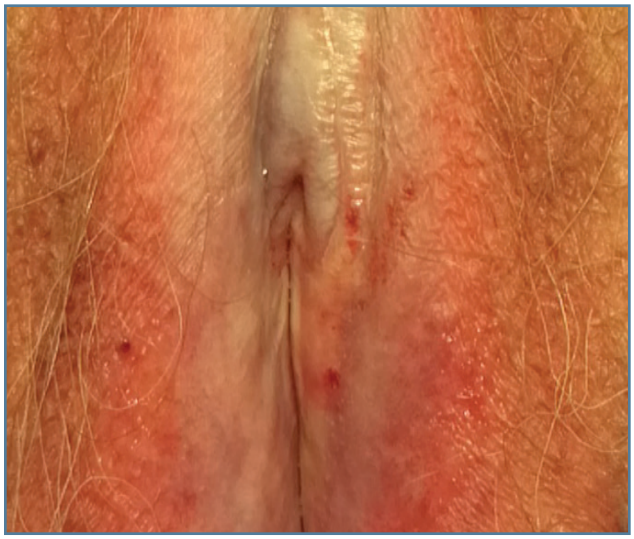


Figure 2.1.30 Vulvar lichen sclerosus.

  - Kraurosis vulvae (atrophy and shrinkage of the skin of the vagina and vulva)
  - Anogenital area affected in 85% ("figure-eight" appearance)
  - Normal anatomic structures may be obliterated
- Males
  - **Balanitis xerotica obliterans:** Male involvement of the glans penis
- Extragenital
  - Upper back, chest, and breasts; usually asymptomatic
- **+ Koebnerization**
- Cancer risk
  - Increased risk of genital SCC in both men and women
  - Lifetime risk for women less than 5%

- Childhood LS
  - Onset in childhood in 10-15% of cases
  - Girls outnumber boys, 10:1
  - Genital disease represents 90% of childhood LS
  - In girls
    - Symptoms include difficulty with defecation, dysuria, perineal pruritus, and perineal skin lesions
  - In boys
    - Phimosis is most common presenting sign
  - May resolve spontaneously, especially around puberty (50% of girls, after circumcision in boys)
- Treatment
  - Superpotent topical steroids 1st line may induce periods of remission
  - Calcineurin inhibitors

Nephrogenic Systemic Fibrosis

- Pathogenesis - previously known as "nephrogenic fibrosing dermopathy"
  - **Impaired renal function** (often dialysis patients) + **gadolinium contrast medium** or thrombotic event, surgical procedure
- Clinical
  - Induration, thickening, hardening of skin with brawny hyperpigmentation
  - Flexion contractures, stiffening of the hands
  - Pain, pruritus common
  - Extremities most commonly involved
  - Face always spared
  - Affected skin is shiny, with peau d'orange appearance
  - Extracutaneous features
    - **Eye: Yellow scleral plaques**
    - Systemic fibrosis of heart, lungs, skeletal muscle
  - Fibroblast-like cells that stain with **CD34** and **procollagen I** in dermis
- Treatment
  - Renal transplant most effective
  - Extracorporeal photopheresis, plasmapheresis, high-dose intravenous immunoglobulin (IVIg)

Sjögren's Syndrome

- Epidemiology
  - More than 90% women
- Pathogenesis
  - Unknown; autoimmune disorder against secretory glands
- Clinical
  - **Triad of keratoconjunctivitis sicca, xerostomia, arthritis**
  - Xerophthalmia (photophobia, blurred vision, burning)
    - Schirmer test (+) if <5-mm tear migration

- Xerostomia (difficulty swallowing, absent infralingual salivary pool, perlèche, thrush, dental caries)
  - Bilateral parotid swelling most common sign in children
- Vaginal xerosis (dryness, burning, dyspareunia, candida, bacterial overgrowth)
- Cutaneous findings
  - Xerosis/pruritus most common
  - Purpura, urticarial vasculitis, erythema nodosum, nodular amyloidosis, Sweet's syndrome
  - **Increased risk of marginal zone B-cell lymphoma such as non-Hodgkin's lymphoma (NHL)**

TIP

Xerostomia Dx

- Elderly
- Anticholinergic meds
- Radiation
- Salivary stones

Xerophthalmia Dx

- Ocular rosacea
- Sarcoid/amyloid infiltration
- Radiation
- Estrogen deficiency
- Vitamin A deficiency
- GVHD
- Parkinson's disease
- Cicatricial pemphigoid

- Laboratory
  - Labial salivary gland biopsy
  - Schirmer test for xerostomia
  - Rheumatoid factor (RF) positive
  - Positive cryoglobulins
  - Anti-Ro > anti-LA
  - **Antibodies to fodrin** (93% specific)
- Treatment
  - Symptomatic (artificial tears, frequent fluids), strict dental care, antifungal troches, chlorhexidine rinses
  - Muscarinic receptor agonists (pilocarpine, cevimeline)

Connective Tissue Serologies

- ANA
  - Substrate → human Hep-2 cells (human laryngeal SCC)
  - ANA: High negative predictive value, low positive predictive value
    - Less than 1:80 has no diagnostic value
    - 5% healthy young people and 15% people > 55 years old have ANA >1:160
    - Almost all patients with SLE are positive for ANA
      - ANA-negative SLE → determined often on animal substrates, yet later found to be positive on human cells, or if patient only makes antibodies to ssDNA (not detected by most tests)
  - Patterns
    - Peripheral/rim: Stains native DNA (**dsDNA**) → SLE
      - Most specific pattern for SLE
      - "Rimming is a double-standard"
    - Homogeneous: Stains histones → drug-induced SLE
    - Nucleolar: Stains nucleolar RNA → SSc, SLE
    - Centromere: Stains kinetochore → CREST
    - Speckled: Stains ribonucleoproteins → MCTD, SLE, SSc, Sjögren's
- dsDNA antibodies
  - Enzyme-linked immunosorbent assay (ELISA) used more than immunofluorescence (IF)
  - Performed on *Crithidia luciliae* → possesses giant mitochondrion with no ssDNA
  - Positivity highly characteristic of SLE → highly correlative with positive direct immunofluorescence (DIF) in patient's normal skin (lupus band), low complement levels, **renal disease,** and poor prognosis
  - Highly positive levels confirm diagnosis of SLE; low levels found in RA, Hashimoto's, Graves', Waldenström's, MCTD, SSc, Sjögren's, autoimmune liver disease
  - Negative test does not exclude SLE (50-83% sensitive)
- Single-stranded antibodies
  - Very low diagnostic value → detected in LE and other CTDs (DM, morphea, Sjögren's, and linear morphea of children)
- RNP antibodies
  - Small ribonucleoproteins (SRNPs)
  - SS-A (Ro), SS-B (La), SM, and U1RNP
  - Anti-Ro antibodies

        - Found in LE (varying percentages based on subset of LE) and Sjögren's (50%)
    - Strongly associated with **photosensitivity** (especially in SCLE)
    - Anti-La antibodies
        - More than 90% with positive anti-La also positive for anti-Ro
    - Ro and La helpful in workup of photosensitivity
        - Confirm clinical diagnosis of SCLE, Sjögren's, or **neonatal LE**
        - Useful in testing ANA-negative patients with clinical manifestations of SLE or SCLE
    - Anti-U1RNP
        - 30% of patients with SLE; patients with SLE and anti-U1RNP also have other positive serologies
        - Majority of patients with positive U1RNP have SLE rather than MCTD
        - Presence associated with sclerodactyly, Raynaud's, esophageal dysmotility
- Anti-Sm
    - Diagnostic of SLE, and not reported in patients with other CTDs
    - Found in 15-40% of patients with SLE
    - Most patients with anti-SM also have antibodies to U1RNP (converse is not true)
- Anti-phospholipid antibodies
    - Also called the lupus anticoagulant and anti-cardiolipin antibodies
    - **Associated with thrombosis** (not bleeding)
    - Most prevalent in SLE patients
    - Seen in patients taking certain drugs (cocaine, interferon [IFN]-γ, procainamide, hydralazine, quinine, quinidine, phenytoin, sulfadoxine/pyrimethamine [Fansidar], phenothiazines), chronic infections
    - Indications for testing
        - Livedo reticularis
        - Purpura and necrosis
        - Ulcers
        - Internal organ thrombosis
        - Recurrent miscarriages
- Cardiolipin
    - Recurrent spontaneous abortions, thrombocytopenia, hypercoagulable state
    - Livedo reticularis, leg ulcers, acral infarction/ulceration, hemorrhagic cutaneous necrosis
- β_2-Glycoprotein 1
    - Cofactor for cardiolipin (more specific)
    - High risk of thrombosis in SLE
- Ku
    - Myositis with scleroderma
- α-Fodrin
    - Most specific for Sjögren's
- Jo-1
    - Histidyl-tRNA synthetase
    - Anti-synthetase syndrome (arthritis, Raynaud's phenomenon, interstitial lung disease)
- Also PL-7 (threonyl-tRNA synthetase) and PL-12 (alanyl-tRNA synthetase)
- Mi-2
    - Helicase nuclear proteins
    - Classic DM (Gottron's papules, shawl sign, periungual telangiectasias, cuticular overgrowth)
    - Associated with a good prognosis
- SRP
    - Signal recognition particle
    - Fulminant DM/PM with cardiac involvement
    - High mortality
- Mas
    - Polymyositis
    - Alcoholic rhabdomyositis
- Scl-70
    - Topoisomerase I (unwinds DNA)
    - SSc with diffuse scleroderma (60%)
    - CREST syndrome
- Fibrillin-1
    - Major component of microfibrils in the extracellular matrix
    - Localized scleroderma (30%)
    - CREST syndrome (10%)
    - SSc with diffuse scleroderma (5%)
- Anti-cyclic citrullinated protein (CCP) antibodies
    - Predictor for the development of RA
    - Increased severity of RA, including radiologic progression of erosive arthritic changes

TABLE 2.1.2 ANTI-NUCLEAR ANTIBODY PATTERNS

Pattern	Associated Antibody	Associated Disorder
Homogeneous	Anti-histone	SLE false +, Drug-induced LE, SLE
Rim (peripheral)	Anti-dsDNA	SLE nephritis
Speckled (fine speckled)	Anti-Sm Anti-Ro and -La (SSA/B) anti-U1RNP Anti-Ku Anti-topoisomerase (Scl-70)	SLE SLE, Sjögren's syndrome SLE, MCTD SLE, scleroderma, myositis Scleroderma, SLE
Centromere (discrete speckled)	Anti-kinetochore	CREST
Nucleolar Anti-RNA polymerase Anti-PM/Scl	Anti-U1RNP	SSc, SLE

CREST = calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, telangiectasia; dsDNA = double-stranded DNA; LE = lupus erythematosus; MCTD = mixed connective tissue disease; SLE = systemic lupus erythematosus; SSc = systemic sclerosis.

VASCULAR DISORDERS

Livedo Reticularis

- Appearance of sluggish blood flow through the 3-dimensional structure of the dermal and subcutaneous vasculature

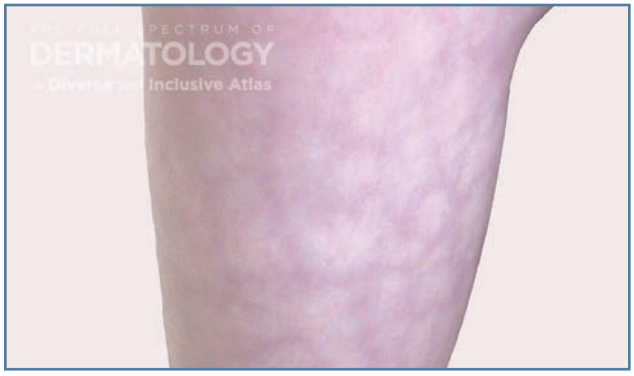


Figure 2.1.31 Livedo reticularis.

- Causes
  - Physiologic
    - Cutis marmorata
  - Intravascular obstruction
    - Stasis
    - Cardiac failure
    - Emboli
    - Cryoglobulinemia
    - Antiphospholipid syndrome
    - Hyperoxaluria
    - Arteriosclerosis
    - Hyperparathyroidism
    - Arteritis (polyarteritis nodosa [PAN], rheumatoid arthritis [RA], lupus erythematosus [LE], diabetes mellitus [DM], syphilis, tuberculosis [TB], pancreatitis)
  - Drugs
    - **Amantadine,** quinine, quinidine
  - Sneddon's syndrome
    - Idiopathic livedo reticularis with cerebrovascular attacks
    - Women usually, onset in 3rd or 4th decade
    - Clinical
      - Persistent and widespread livedo reticularis
      - Labile hypertension (HTN), CNS disease (transient ischemic attacks [TIAs], cerebrovascular accident [CVA], dementia)
      - ***Livedo racemosa*** = more brawny/thicker/broken livedo
      - Poor prognosis

Livedoid Vasculitis (Atrophie Blanche)

- Pathogenesis
  - Unknown; fibrin thrombi focally deposited in superficial dermal vessels
  - Occlusive proclivity in some (factor V Leiden, hyperhomocysteinemia, anti-phospholipid antibodies, altered fibrinolysis, platelet activation, chronic venous HTN, varicose veins)

- Clinical
  - Recurrent painful ulcers of lower extremities in association with persistent livedo reticularis; often deep purple in color
  - Atrophie blanche: Healed lesions result in sclerotic pale areas surrounded by telangiectasias
  - Associated with arteriosclerosis or stasis
- Treatment
  - Aspirin, dipyridamole, colchicine, low-dose heparin, systemic glucocorticoids, and low molecular weight dextran, nifedipine, pentoxifylline

Small-Vessel Vasculitis

- Diverse group of disorders that combine segmental inflammation with necrosis of blood vessels
- May be primary, a feature of a systemic disorder, or idiopathic
- Pathogenesis
  - Postulated that circulating immune complexes are locally deposited → complement activation → neutrophil chemotaxis → release of lysosomal enzymes → damage tissue
- Clinical
  - Palpable purpura: Nonblanching erythematous papules
  - Papules, urticaria, pustules, vesicles, ulcers, necrosis, and livedo reticularis
  - Usually occurs on lower extremities or over dependent areas such as the back and gluteal regions
    - Uncommon on face, palms, soles, and mucous membranes
  - Palpable purpura persists 1-4 weeks, resolving often with transient hyperpigmentation and/or atrophy

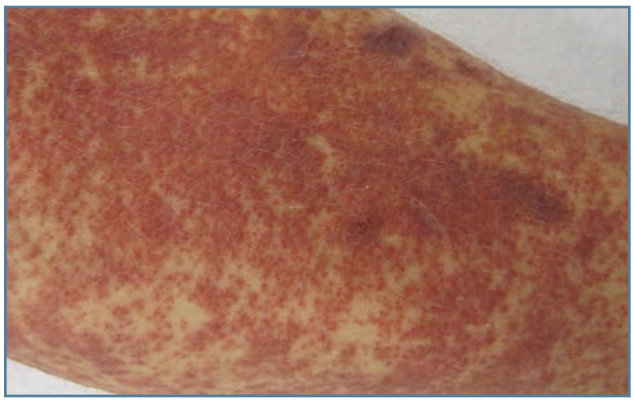


Figure 2.1.32 Leukocytoclastic vasculitis.

  - Symptoms
    - Pruritus, burning, and pain less commonly
    - Episodes associated with fever, malaise, arthralgias, and myalgias
- Associated conditions
  - Rheumatoid arthritis
  - Sjögren's syndrome
  - Systemic lupus erythematosus (SLE)
  - Dermatomyositis
  - Hypergammaglobulinemic purpura
  - Mixed connective tissue disease
  - Relapsing polychondritis
  - Scleroderma
  - Paraneoplastic vasculitis
  - Associated malignancies
    - Hodgkin's, lymphosarcoma, adult T cell leukemia, mycosis fungoides, myelofibrosis, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), IgA myeloma, diffuse large cell leukemia, hairy cell leukemia, squamous cell bronchogenic carcinoma, prostate cancer, renal cell carcinoma, and colon carcinoma
  - Cryoglobulinemia
    - Particularly mixed types II and III
  - Cystic fibrosis
  - Crohn's, ulcerative colitis
  - Behçet's disease
  - Anti-neutrophil cytoplasmic antibodies (ANCAs)
    - Seen with hepatitis C infection
    - Palpable purpura
  - Anti-phospholipid antibodies
    - Livedo reticularis is most common finding
  - Precipitating infections
    - Group A β-hemolytic streptococci
    - *Staphylococcus aureus*
    - *Mycobacterium leprae:* Erythema nodosum leprosum
    - Hepatitis B
    - HIV
    - *Neisseria meningitidis*
    - Rocky Mountain spotted fever
    - Catheter infections
  - Precipitating drugs
    - Penicillin
    - Sulfonamides
    - Thiazides
    - Allopurinol
    - Phenytoin

- Nonsteroidal antiinflammatory drugs (NSAIDs)
- Propylthiouracil (PTU) and hydralazine in association with ANCAs
- Streptokinase
- Radiocontrast media
- Monoclonal antibodies

Henoch-Schönlein Purpura

- Epidemiology
  - Most widely recognized subgroup
  - Mostly children
- Clinical
  - **Recent upper respiratory tract infection (URI) in 75% (group A β-hemolytic streptococci)**
  - Tetrad of:
    - **Nonthrombocytopenic palpable purpura** (lower legs and buttocks)
    - **Transient arthritis** (ankles/knees)
    - **Abdominal pain** (gastrointestinal [GI] bleeding, vomiting, intussusception)
    - **Glomerulonephritis/microscopic hematuria**
  - Skin lesions of adults show blisters and necrosis

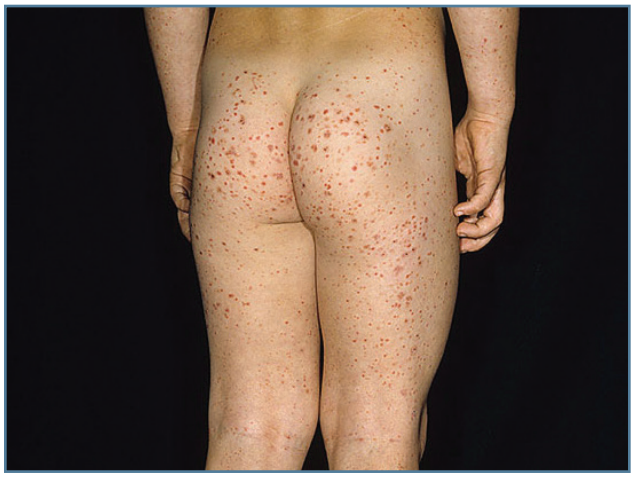


Figure 2.1.33 Henoch-Schönlein purpura.

  - Long-term morbidity from **kidney disease**
    - Involvement of purpura on the upper trunk and initial renal insufficiency predict probability
- Labs
  - 33% have elevated serum IgA
  - **Must monitor urinalysis (UA), blood urea nitrogen/creatinine (BUN/Cr) ratio for at least 3 months**
- Treatment
  - Self-limited over 4-6 weeks
  - NSAIDs for arthritis
  - Systemic steroids for severe GI, joint, renal, or scrotal involvement
  - Intravenous immunoglobulin (IVIg)

Acute Hemorrhagic Edema of Childhood

- Epidemiology
  - Children and infants < 2 years of age
- Clinical
  - Causes
    - Infection most common (75%): Staphylococci, streptococci, adenovirus > Escherichia coli, mycobacteria, *Campylobacter sputorum* subsp. *mucosalis*, coxsackievirus, rotavirus
    - Drug exposure (penicillin [PCN], sulfamethoxazole-trimethoprim [Bactrim], NSAIDs)
    - Immunization
  - Abrupt onset of fever, painful, edematous, coin-shaped or cockade petechial/purpuric plaques with scalloped borders and central clearing
  - Favors face, ears, distal extremities; often scrotum in boys
  - No systemic features
  - Patients often appear well

Urticarial Vasculitis

- Epidemiology
  - Middle-aged women
- Clinical
  - Causes
    - Autoimmune connective tissue diseases (CTDs) most common (**Sjögren's, SLE**)
    - Infections (hepatitis B virus [HBV], hepatitis C virus [HCV], Epstein-Barr virus [EBV], Lyme)
    - Drugs (potassium iodide, fluoxetine, NSAIDs, cimetidine, diltiazem, angiotensin-converting enzyme [ACE] inhibitors, PCN, sulfonamides, thiazides, polymyxin, ciprofloxacin, rifampin, vancomycin, β-lactams)
    - Malignancies (IgM or IgG monogammopathies, IgA multiple myeloma, colon cancer, renal carcinoma)
    - Serum sickness-like reactions to drugs, cryoglobulinemia, HCV
  - Resembles urticaria but lesions last > 24 hours

- **Burning, pain** > pruritus; resolves with postinflammatory hyperpigmentation
- **Trunk, proximal extremities** more common
- Fever, malaise, and myalgia, with possible lymphadenopathy and hepatosplenomegaly
- Associated symptoms
  - Episodic arthralgias
  - Renal: Diffuse glomerulonephritis or glomerulitis
  - GI: Diarrhea, nausea, vomiting
  - Pulmonary: Laryngeal edema
  - Eye: Conjunctivitis, uveitis, episcleritis
  - CNS: Headaches, pseudotumor cerebri
- Variants
  - **Normocomplementemic urticarial vasculitis**
    - 80%; less severe
    - Tend to have skin-limited disease
    - Arthralgias/arthritis most common finding (migratory and transient, peripheral joints)
    - Usually benign course and resolves after 3 years
  - **Hypocomplementemic urticarial vasculitis**
    - 20%; more severe
    - **Strong association with SLE**
    - Joints (50%): Transient/migratory arthralgias/arthritis
    - **Angioedema** (40%)
    - Pulmonary (20%): **Chronic obstructive pulmonary disease (COPD)** (associated with smoking and most life-threatening), effusions; hemosiderosis and hemorrhage in children
    - GI (20%): Nausea/vomiting/diarrhea (N/V/D), abdominal pain, no GI bleeding or ischemia
    - Renal (5-10%): **Glomerulonephritis** most common; interstitial nephritis, necrotizing vasculitis
    - Ocular: Conjunctivitis, episcleritis, iritis, uveitis
    - Cardiac: Valvular heart disease, pericarditis with tamponade, myositis
    - Labs: Low complement levels, low C1q, anti-C1q Abs (100%), + anti-nuclear Ab (ANA) (75%), anti-double-stranded DNA (dsDNA) Abs (25%)
  - **Schnitzler's syndrome**
    - Urticarial vasculitis + monoclonal IgM gammopathy + ≥ 2 of any of the following:
      - Intermittent fever, arthralgias/arthritis, bone pain with osteosclerosis, lymphadenopathy (LAD), hepatosplenomegaly (HSM), ↑erythrocyte sedimentation rate (ESR), ↑white blood cell (WBC) count, sensorimotor neuropathy
      - Risk of developing lymphoproliferative disease (Waldenström macroglobulinemia most common)

TIP

Schnitzler's Syndrome

Schnitzler's syndrome: Episodes of urticarial vasculitis that occur in association with monoclonal IgM M component. Fever, lymphadenopathy, hepatosplenomegaly, bone pain, and sensorimotor neuropathy

- Treatment
  - H_1 blockers, indomethacin, colchicine
  - Systemic steroids, mycophenolate

ANCA-Associated Vasculitides

- Pathogenesis
  - Abs against neutrophilic intracellular antigens
  - c-ANCAs (cytoplasmic): Specific for **proteinase 3 (PR3)**
    - **Anti-PR3 c-ANCAs occur in 80% of Wegner's granulomatosis, 30% of microscopic polyangiitis**
  - p-ANCAs (perinuclear): Specific for **myeloperoxidase (MPO)**
    - **Anti-MPO p-ANCAs occur in 60% of microscopic polyangiitis, 60% Churg-Strauss syndrome**

Microscopic Polyangiitis

- Pathogenesis
  - Unknown; not associated with HBV (vs. polyarteritis nodosa)
  - **p-ANCA** > **c-ANCA**
- Clinical features
  - Fever, weight loss, arthralgias, myalgias for months-years before other symptoms
  - Palpable purpura (50%) > splinter hemorrhages, tender erythematous nodules, ulcers, necrotizing livedo reticularis
  - **Pauci-immune, crescentic, necrotizing glomerulonephritis (90%)**; renal infarcts, arterial aneurysms in PAN
  - Pulmonary capillaritis (33%) → dyspnea, pulmonary infiltrates
    - **Severe alveolar hemorrhage in 10% → order chest X-ray (CXR)**
- Treatment
  - Systemic steroids + cyclophosphamide

Granulomatosis with Polyangiitis (formerly known as Wegner's)

- Pathogenesis
  - Unknown; *S. aureus* may play role in nasal/pulmonary Wegner's → nasal carriage associated with recurrence
  - **c-ANCA** > **p-ANCA**
- Clinical
  - Mucocutaneous disease in 40%; presenting symptom in 10%
  - Palpable purpura > oral ulcers
  - Papulonecrotic lesions favor the extremities (esp. elbows)
  - Red, friable, hyperplastic gingival tissue (esp. interdental papillae) = **strawberry gingiva**
  - Painful subcutaneous (SQ) nodules/ulcers (resemble pyoderma gangrenosum)
  - Upper and lower respiratory tract involvement in 90%
    - Nasal/sinus/tracheal/ear involvement in 70%
    - Recurrent epistaxis, mucosal ulcerations, nasal septal perforations, **saddle nose deformity**
    - Subglottic stenosis in children
    - Pulmonary symptoms (dyspnea, cough, pleuritis, hemoptysis)
    - CXRs show upper/lower irregular infiltrates or nodular cavitary lesions
  - Renal disease in 20% at presentation (70% develop glomerulonephritis)
- Treatment
  - Systemic steroids + cyclophosphamide
  - Infliximab, rituximab

Eosinophilic Granulomatosis with Polyangiitis (formerly known as Churg-Strauss)

- Pathogenesis
  - Immediate hypersensitivity reaction + cytotoxic reactions with activation of helper T type 2 (T_H2) lymphocytes → mast cell and eosinophil degranulation + ANCA-induced neutrophil activation
    - Associated with vaccination, desensitization therapy, leukotriene inhibitors, rapid discontinuation of steroids
    - **p-ANCA** > **c-ANCA**
- Clinical
  - 6 criteria
    - Eosinophilia
    - Asthma
    - Neuropathy
    - Sinus abnormalities
    - Allergies
    - Perivascular eosinophils
  - Initial phase: **Allergic rhinitis,** nasal polyps, late-onset (~age 35) **asthma**
  - Second phase: **Peripheral eosinophilia,** respiratory infections, GI symptoms
  - Third phase: Systemic vasculitis, granulomatous inflammation
    - Palpable purpura in 55%
  - Other symptoms
    - Neurological: Mononeuritis multiplex (70%) = asymmetric asynchronous sensory and motor peripheral neuropathy involving isolated damage to at least 2 separate nerve areas
    - Cardiovascular: Myocarditis with congestive heart failure (CHF) = most common cause of death
    - Renal: Necrotizing glomerulonephritis (35%)
    - **Löffler's syndrome:** Eosinophilic pneumonitis
- Treatment
  - Systemic steroids + cyclophosphamide
  - Prognosis is good; usually have residual steroid-dependent asthma

Other Vasculopathic Disorders

- Eosinophilic vasculitis
  - Idiopathic syndrome with recurrent pruritic, purpuric, papular skin lesions with angioedema
  - Urticarial plaques and palpable purpura present
  - Infiltrate of eosinophils
- Nodular vasculitis
  - Women between 30 and 40
  - Recurrent, tender, red, subcutaneous nodules over lower extremities, especially the calves; lesions can occur on thighs, buttocks, trunk, and arms
  - No systemic manifestations
  - **Erythema induratum:** Form of nodular vasculitis associated with ***Mycobacterium tuberculosis***
    - Treat with thalidomide

Cryoglobulinemia

- Pathogenesis
  - Immune complexes form from circulating cryoglobulins → deposited on vessel walls → activate complement
  - Reversibly precipitate in cold

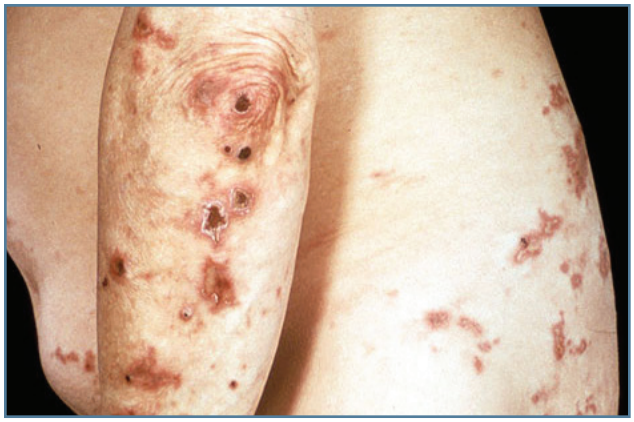


Figure 2.1.34 Cryoglobulinemia.

- Clinical
  - Purpura, livedo, Raynaud's, distal ulcerations
  - Affected organs are skin, kidneys, liver, musculoskeletal, and nervous systems
  - Subtypes
    - Type I
      - **Cold induced**
      - **Monoclonal immunoglobulin (IgG or IgM > IgA or only light chains)**
      - **Usually an underlying lymphoproliferative disorder such as myeloma, Waldenström's macroglobulinemia, or lymphoma**
      - Vascular occlusion and necrosis
      - Purpura, acrocyanosis, retinal hemorrhage, Raynaud's phenomenon, and arterial thrombosis
    - Type II (mixed cryoglobulinemia)
      - **Monoclonal immunoglobulin (IgM > IgG >> IgA) that binds the Fc portion of polyclonal IgG rheumatoid factor**
      - Infection, **esp. HCV,** also rheumatoid arthritis (RA), Sjögren's, malignancy
    - Type III (mixed cryoglobulinemia)
      - **Polyclonal immunoglobulin (IgM) that binds polyclonal IgG rheumatoid factor**
      - Associated with SLE, RA, Sjögren's, infectious mononucleosis, cytomegalovirus (CMV) infection, primary biliary cirrhosis, hepatitis B, hepatitis C
      - Leukocytoclastic vasculitis (LCV) with palpable purpura, arthritis/arthralgias, and vascular purpura
    - Essential mixed cryoglobulinemia
      - Cryoglobulins and the manifestation of symptoms without an identifiable connective tissue, neoplastic, or infectious process
      - Often HCV infection coincides

Cryofibrinogenemia

- Pathogenesis
  - Cryoproteins in anticoagulated blood or plasma that reversibly precipitate in the cold
  - Composed of fibrinogen
- Clinical
  - Purpura, ecchymoses, gangrene, ulcers
  - Associated with malignancy, thromboembolic disease, diabetes, pregnancy, oral contraception, and pseudotumor cerebri
- Treatment
  - Moderate: cold avoidance, corticosteroids, low-dose aspirin; or stanozolol
  - Severe: Immunosuppressive therapies, plasmapheresis, and/or intravenous fibrinolysis
  - Secondary cryofibrinogenemia: treat associated disease(s)

Erythema Elevatum Diutinum

- Epidemiology
  - Middle-aged or older adults (30-60 years old)
- Pathogenesis
  - Immune complex deposition
- Clinical features
  - Symmetric violaceous, red-brown, or yellowish papules, plaques, nodules on extensor surfaces (esp. hands, knees)
  - Arthralgias possible in underlying joints; extracutaneous involvement rare
  - Chronic, waxing/waning course
  - Majority resolve over 5-10 years
- Associations
  - Infections (β-hemolytic streptococci, HBV, **HIV**)
  - Autoimmune/inflammatory diseases (Wegner's granulomatosis, inflammatory bowel disease [IBD], relapsing polychondritis, SLE, RA)
  - Hematologic disorders (**IgA monoclonal gammopathy,** multiple myeloma, myelodysplasia, polycythemia vera, hairy cell leukemia)
  - Other (familial Mediterranean fever, hyper-IgD syndrome)
- Treatment
  - NSAIDs, intralesional (IL) steroids, **dapsone**, sulfapyridine

Calcific Uremic Arteriolopathy (Calciphylaxis)

- Pathogenesis
  - Vascular calcification → occlusion of microvessels in dermis and subcutaneous tissue
  - Metastatic cutaneous calcification from increased parathyroid hormone (and increased calcium phosphate product) secondary to renal failure
- Clinical
  - Painful reticulated violaceous eschar-like plaques associated with soft tissue necrosis

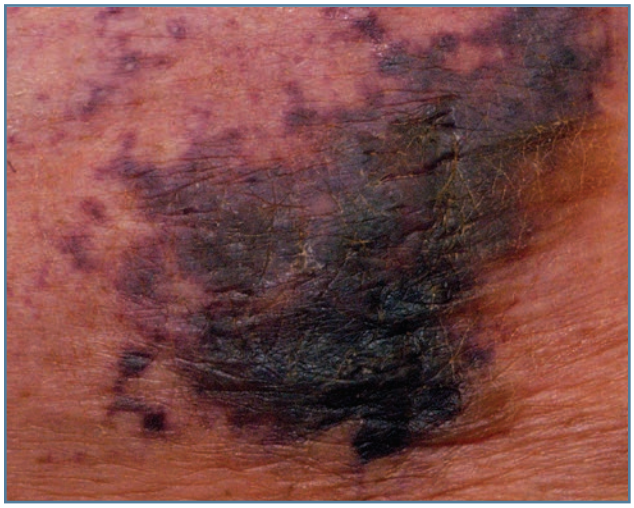


Figure 2.1.35 Calciphylaxis.

  - Most commonly seen in end-stage renal disease patients who are on dialysis
  - Need a wedge or deep (a punch within a punch) biopsy
- Treatment
  - Treat underlying abnormalities of calcium, phosphorus, and hyperparathyroidism (phosphate-binding agents, calcimimetic, parathyroidectomy)
  - IV sodium thiosulfate
  - Local wound care
  - Pain management

DEPOSITION DISORDERS

Amyloidosis

- Pathogenesis
  - Abnormal extracellular deposition of amyloid (fibrillar proteinaceous material)
  - Precursor proteins (soluble proteins) → aggregate, polymerize, form fibrils → extracellular deposition → pressure atrophy if deposited in organs → organ failure
  - **Characteristic cross-β-pleated sheet on X-ray crystallography**
- Classification
  - Primary (often has skin findings)
    - Localized
    - Systemic
  - Secondary (rare skin findings)
    - Cutaneous or tumor associated
  - Familial
- Pathology
  - Periodic acid—Schiff (PAS) positive, diastase resistant
  - Congo-red positive
    - Orange/red (light microscopy)
    - Green birefringence (polarized light)
  - Purple with crystal violet
  - Thioflavin T
  - Secondary systemic amyloid A (AA) loses its birefringence after treatment with potassium permanganate, but primary and localized forms do not

TIP

Protein AL

Derived from Ig light chains (λ subtype); AL also found in nodular amyloidosis produced by a plasmacytoma

- Primary systemic amyloidosis
  - AL (amyloid light chain)
  - Clinical
    - Usually associated with underlying plasma cell dyscrasia > multiple myeloma
    - Shiny, smooth, firm, flat-topped papules of waxy color that coalesce into nodules or plaques
    - Commonly around nose, eyes, mouth, and mucocutaneous junctions

- **Macroglossia + carpal tunnel + pinch purpura = strongly suggestive of systemic amyloidosis**
  - Glossitis: May lead to dysphagia; lateral aspects of tongue shows indentations from teeth
  - Carpal tunnel: RA-like arthropathy
  - Pinch purpura: Purpuric lesions result from amyloid infiltration of blood vessels; occurs after trauma (eyelids, neck, axillae, anogenital region common sites)

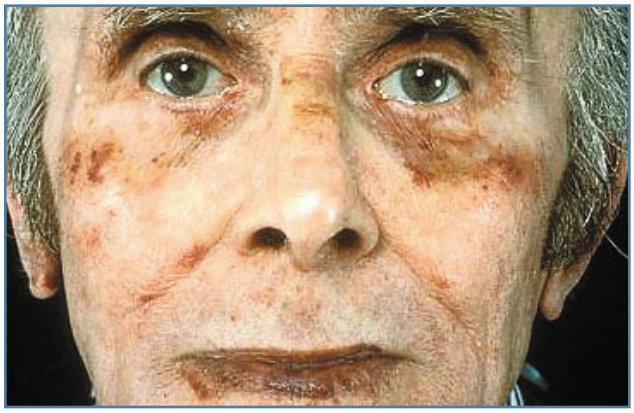


Figure 2.1.36 Purpura seen in primary systemic amyloidosis.

- Other organ involvement
  - Renal: Proteinuria → hypoalbuminemia, edema
  - Cardiac: Congestive heart failure, arrhythmias
  - Neurological: Bilateral/symmetric sensory neuropathy, autonomic instability (postural hypotension, impotence, gastrointestinal instability)
  - Hepatic: Irregular, firm, enlarged liver (seen in 50%)

- Secondary systemic amyloidosis
  - AA (amyloid-associated) amyloid
  - Skin not involved
  - Deposits in adrenals, liver, spleen, and kidney as a result of some chronic disease
    - TB, leprosy, Hodgkin's, Behçet's, rheumatoid arthritis, ulcerative colitis, schistosomiasis, or syphilis

TIP

AA amyloid fibrils

Derived from serum amyloid A (SAA) protein, an acute-phase reactant

- Also seen in Muckle-Wells syndrome (renal amyloidosis, urticaria, fevers, limb pains, and deafness) and familial Mediterranean fever
- Dialysis-related amyloidosis: β_2-microglobulin is the protein component altered by uremia → carpal tunnel syndrome, bone cysts, and spondyloarthropathy
- Primary cutaneous amyloidosis
  - **Keratin** is the protein component (except in nodular)
  - No amyloid around the blood vessels
    - Macular amyloid
      - Moderately pruritic, brown, rippled macules in interscapular region of the back

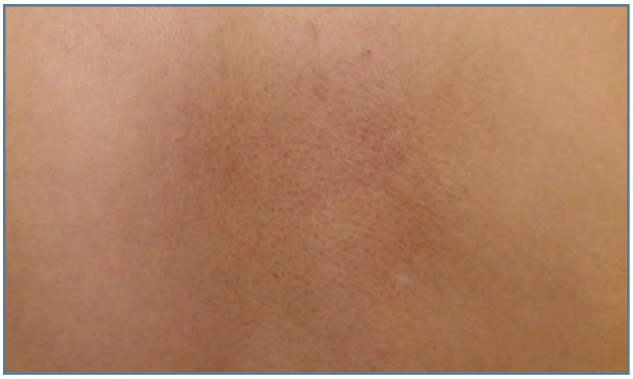


Figure 2.1.37 Macular amyloid.

      - May have associated notalgia paresthetica
    - Lichen amyloid
      - Small, brown, discrete, scaly papules often on bilateral shins

Figure 2.1.38 Lichen amyloid.

      - Seen in type IIa MEN (multiple endocrine neoplasia)
    - Nodular amyloidosis
      - **AL amyloid**

  - Single or multiple nodules on extremities, trunk, genitals, or face
  - Numerous plasma cells
    - Amyloid is produced by plasma cells (plasmacytoma) and contains γ light chains and β_2-microglobulin
- Secondary cutaneous amyloidosis
  - Also, **keratin-derived**
  - Incidental findings in benign and malignant neoplasms (nonmelanoma skin cancers, dermatofibromas, seborrheic keratoses, trichoepitheliomas, etc.)
  - After PUVA (psoralen and UVA) therapy
- Familial syndromes associated with amyloidosis
  - Familial Mediterranean fever and Muckle-Wells syndrome → show AA protein
  - MEN IIa → keratin-derived amyloid
- Familial amyloidotic polyneuropathy
  - Types I and II: Mutations in transthyretin
  - Type III: Apolipoprotein A1
  - Type IV: Gelsolin mutation

TABLE 2.1.3 AMYLOIDOSIS

Type	Fibril Protein	Other Features
Systemic		
Primary	AL (amyloid light chain)	Involves tongue, heart, GI tract, and skin. Petechiae, purpura, waxy skin-colored papules, alopecia, carpal tunnel syndrome, neuropathy, arthropathy
Secondary	AA (amyloid associated)	Result of chronic disease: TB, leprosy, Hodgkin's, RA, Reiter's, syphilis No skin involvement Amyloid in the adrenals, liver, spleen, and kidney
Cutaneous		
Macular	Altered keratin	Rippled brown macules in interscapular region on back, notalgia paresthetica
Lichen	Altered keratin	Brown, scaly papules on bilateral shins
Nodular	AL chains	Single or multiple nodules on extremities, genitals, trunk, or face
Hereditary		
Familial Mediterranean fever	AA	AR, intermittent fevers, renal amyloidosis, peritonitis, pleurisy *MEFV* gene; marenostrin/pyrin protein
Muckle-Wells	AA	AD, periodic attacks of urticaria, fever, deafness, renal amyloidosis
Hemodialysis associated	β_2-Microglobulin	Arthritis (esp. scapulohumeral and carpal bones)
Senile	Amyloid β (Aβ precursor) protein	Senile or neuritic plaques, Alzheimer's disease
Familial Amyloidotic Polyneuropathy		
Types I and II	Transthyretin	
Type III	Apolipoprotein	
Type IV	Gelsolin	Also has cutis laxa

AD = autosomal dominant; AR = autosomal recessive; GI = gastrointestinal; RA = rheumatoid arthritis; TB = tuberculosis.

Mucinoses

- Scleromyxedema (papular mucinosis)
  - Pathogenesis
    - **Unknown; increased dermal mucin and collagen**
  - Clinical
    - Numerous, symmetrically distributed, 2- to 3-mm firm, waxy papules, often in linear arrays
    - Hands, forearms, head/neck, upper trunk, thighs
    - Glabella often has deep vertical furrows
    - Systemic manifestations
      - Dysphagia from esophageal involvement
      - Muscular, neurologic, pulmonary, renal, cardiovascular involvement
      - **Visceral disease can be fatal**
      - **leonine facies**
    - **Almost always associated with a paraproteinemia (usually IgGλ)**
  - Treatment
    - Melphalan + thalidomide and oral steroids
    - Combinations of dexamethasone, lenalidomide, bortezomib, autologous hematopoietic stem cell transplant
- Scleredema
  - Pathogenesis
    - Unknown
    - Strong association with diabetes, infection
  - Clinical manifestations
    - Marked, nonpitting, symmetric induration of the skin with mucin deposition
    - Induration is waxy white or shiny, and diffuse without sharp demarcation between involved and uninvolved areas
    - Posterior and lateral aspects of neck, spreads to face, shoulders, back, arms, and trunk
    - Skin involvement may be preceded by prodrome of low-grade fever, malaise, myalgia, arthralgia
    - 3 subtypes
      - Type I
        - Middle-aged women > children
        - Preceded by fever, malaise, **URI (strep)**
        - Sudden hardening of cervicofacial skin with progression to trunk/upper extremities (UE)
        - Resolves in 6-24 months
      - Type II
        - More subtle onset than type I with no preceding illness
        - **(+) monoclonal gammopathy (IgGκ)**
      - Type III
        - **Obese middle-aged men with diabetes**
        - Peau d'orange of upper back and neck; persists for years
        - May be fatal with internal involvement

TIP

Scleredema Subtypes

Type I:	Women and children, head and neck following infection
Type II:	Associated with monoclonal gammopathy
Type III:	Associated with diabetes, difficult to treat

  - Laboratory findings
    - Increase in anti-streptolysin O (ASO) titer in some patients
    - Glucose tolerance test may be warranted
    - Hyperinsulinemia may be present
  - Treatment
    - None; type I spontaneously resolves
- Pretibial myxedema
  - Pathogenesis
    - Associated with hyperthyroidism
    - Graves' disease most common (1-5%, 25% if exophthalmos)
    - Other: Hashimoto's without thyrotoxicosis, hypothyroidism, even euthyroidism
  - Clinical features
    - Cutaneous induration of the shins from mucin deposition
    - Erythematous to skin-colored, brown, or yellow waxy indurated nodules/plaques, with peau d'orange appearance
    - Shins > other sites (face, shoulders, UE, abdomen, grafts, scars)
    - Diffuse nonpitting edema → elephantiasis
    - Entrapment of nerves → foot drop
    - Hypertrichosis, hyperhidrosis confined to myxedematous skin
  - Treatment
    - Topical or IL steroids
    - Pneumatic compression
    - Octreotide
    - Therapy for hyperthyroidism does not cure myxedema, nor does grafting
- Generalized myxedema
  - Pathogenesis
    - Severe hypothyroidism (quantitative or functional deficiency in thyroxine) → impaired degradation of mucin

- Clinical features
  - 3 types
    - Adult hypothyroidism
      - Most common
      - Usually from autoimmune disease (Hashimoto's, treatment for Graves')
    - Juvenile hypothyroidism
    - Congenital hypothyroidism (cretinism) → clavicular fat pad diagnostic
  - Systemic symptoms
    - Sluggishness, weight gain, constipation, leg cramps, poor appetite, cold intolerance
  - Skin manifestations
    - Pale, cool, waxy, dry skin
    - Absence of sweating
    - Yellowish discoloration of palms/soles (from carotenemia)
    - Dry/brittle hair and nails
    - Diffuse nonscarring alopecia (esp. lateral third of the eyebrow)
    - Purpura on extremities, blue telangiectasias of fingers
  - Systemic manifestations
    - Cardiomegaly, megacolon, bowel obstruction, Alzheimer's-like symptoms, serositis, carpal tunnel, 7th nerve paralysis
- Labs
  - Free thyroxine (T_4); thyroid-stimulating hormone (TSH) = high in primary, low in secondary
- Treatment
  - Symptoms subside with thyroid treatment (thyroxine)

TABLE 2.1.4 MONOCLONAL GAMMOPATHY AND DISEASE ASSOCIATIONS

Type	Disease
IgA	EED, pyoderma gangrenosum, subcorneal pustular dermatosis, IgA pemphigus, POEMS, Sweet's syndrome
IgM	Schnitzler syndrome, Waldenström macroglobulinemia
IgG	NXG (IgGκ), scleredema (IgGκ > IgGλ), scleromyxedema (IgGλ > IgGκ)

EED = erythema elevatum diutinum; NXG = necrobiotic xanthogranuloma; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes.

NEUTROPHILIC DISORDERS

Pyoderma Gangrenosum

- Epidemiology
  - 20-50 years old
  - More common in women
- Pathogenesis
  - Idiopathic usually
  - 50% associated with systemic disease
    - **Crohn's, ulcerative colitis (UC) most common**
    - Rheumatoid arthritis
    - Hematologic diseases (AML, CML, hairy cell leukemia, IgA monoclonal gammopathy)
    - Infections (chronic active hepatitis, HCV, HIV)
    - Other (SLE, pregnancy, Takayasu's arteritis)

TIP

Pyoderma Gangrenosum

50% have associated disease, most common is IBD (UC > Crohn's)

- Clinical features
  - Tender papulopustule with surrounding erythema or induration or an erythematous nodule or bulla that evolves into a necrotic painful ulcer with undermined violaceous borders

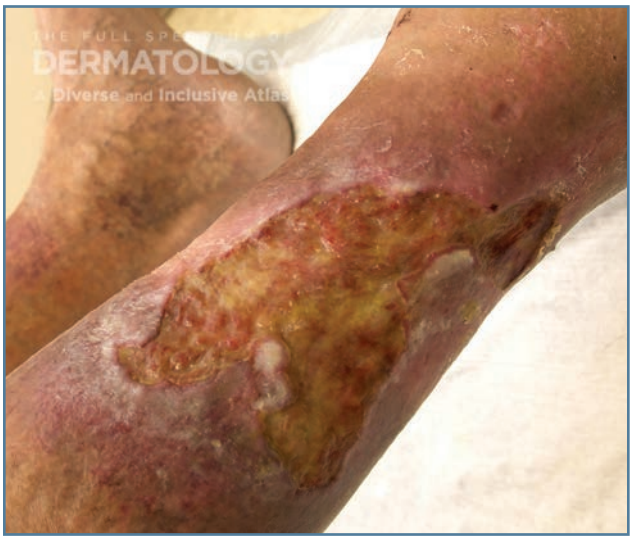


Figure 2.1.39 Pyoderma gangrenosum.

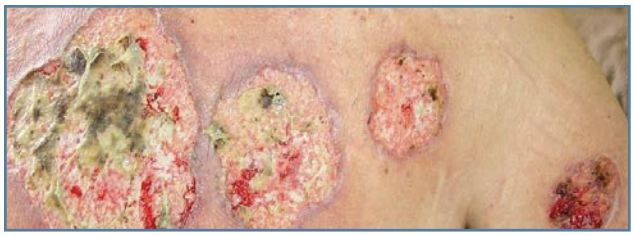


Figure 2.1.40 Multiple pyoderma gangrenosum lesions on the back.

- Many lesions begin at sites of trauma (pathergy)
- Subtypes
  - Ulcerative
    - Most common
    - Distinct rolled edges with violaceous borders
    - Heal with thin, atrophic scars
  - Vesiculobullous
    - Less destructive, more superficial
    - Looks like Sweet's
    - More commonly associated with leukemia, **polycythemia vera**
  - Pustular
    - More commonly associated with IBD, pyostomatitis vegetans, and subcorneal pustular dermatosis
  - Vegetative
    - Least aggressive
    - Cribriform chronic superficial ulcerations on the trunk, usually
    - Often no associated underlying disease
- **PAPA syndrome** (Pyogenic Arthritis, Pyoderma gangrenosum, severe cystic Acne)
  - AD mutation in CD2 binding protein 1
  - Early-onset severe arthritis; multiple joint replacements

- Treatment
  - Treat underlying disease
  - Potent topical steroids, calcineurin inhibitors
  - Intralesional steroids at advancing edge
  - Systemic steroids, cyclosporine, anti-tumor necrosis factor (TNF)-α, sulfapyridine, sulfasalazine, dapsone
  - Other agents: Mycophenolate mofetil, methotrexate, azathioprine, minocycline, thalidomide, saturated solution of potassium iodide (SSKI), azathioprine, cyclophosphamide, chlorambucil, clofazimine

Relapsing Polychondritis

- Epidemiology
  - 4th-5th decade
  - Both sexes equally affected
- Pathogenesis
  - Likely antibody-mediated **(type II collagen)**
  - Intermittent episodes of inflammation of the articular and nonarticular cartilage
  - Results in chondrolysis, dystrophy, and atrophy of the cartilage
- Clinical features
  - Unilateral erythema, edema, and pain of ear auricle with **sparing of the lobe**

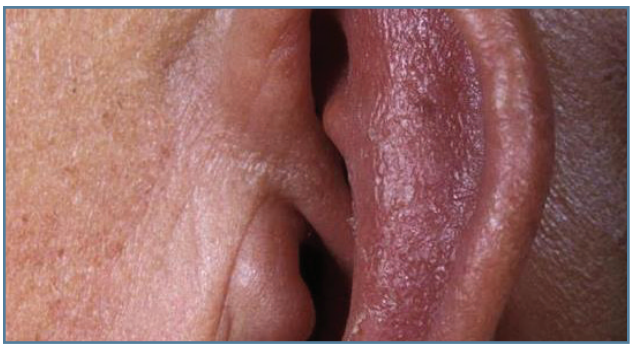


Figure 2.1.41 Relapsing polychondritis.

  - Acute flare of inflammation lasts 1-2 weeks
  - 85-90% of patients develop auricular chondritis
    - Can develop conductive deafness because of swollen cartilage
  - Recurrent episodes result in cartilage destruction and fibrosis (floppy or cauliflower ear)
  - Other findings
    - **Migratory arthritis** seen in 50-80%
    - **Nasal septal chondritis** in 50-70% (rhinitis, crusting, bleeding, and saddle-nose deformity)

TIP

DDx saddle-nose

Syphilis, granulomatosis with polyangiitis (GPA), relapsing polychondritis, leprosy

    - Ocular conjunctivitis, scleritis, iritis
    - Respiratory bronchitis results in hoarseness, coughing, and dyspnea
    - Cardiovascular inflammation causes aortic regurgitation and aortic aneurysm
    - 1/3 have associated rheumatic or autoimmune disease and many have LCV
  - **MAGIC Syndrome**
    - Behçet's and relapsing polychondritis simultaneously (**M**outh **A**nd **G**enital ulcers with **I**nflamed **C**artilage)

- Labs
  - **IgG anti-type II collagen antibody** titers correspond to disease activity
- Course
  - Unpredictable; chronic and variable with episodic flares (usually 1-4 weeks) and spontaneous remissions
  - Peripheral arthritis predicts a worse course
  - **Causes death in 1/3 of patients secondary to airway collapse, cardiovascular complications,** and infection (secondary to systemic steroids)
- Treatment
  - Systemic steroids, dapsone, cyclosporine, NSAIDs

Behçet's Disease

- Epidemiology
  - Young adults
  - Turkey (highest prevalence), Japan, Middle East, Mediterranean
  - *HLA-B51*
- Pathogenesis
  - Circulating immune complexes and overactive neutrophils
- Diagnostic criteria
  - Major
    - Recurrent aphthous stomatitis

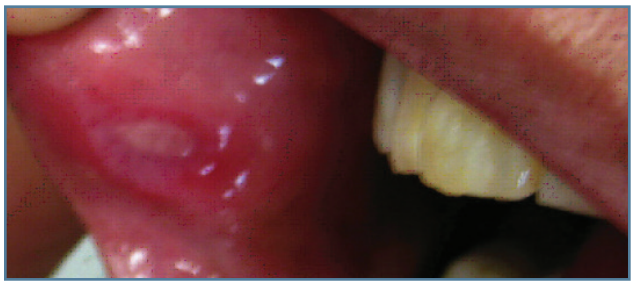


Figure 2.1.42 Behçet's disease.

    - 3 episodes in 12 months
    - First symptom in 65-70%
  - Plus 2 minor criteria
    - Eye lesions (posterior uveitis) most common
    - Recurrent genital ulceration
    - Skin lesions (erythema nodosum, pseudofolliculitis, papulopustular lesions, or acneiform nodules)
    - Positive pathergy test
- Clinical features
  - Skin
    - Painful
    - Anogenital ulcers (esp. scrotum, vulva)
    - Erythema nodosum (EN)—like lesions
    - Pseudofolliculitis/acneiform lesions
  - Systemic
    - Nonerosive mono/polyarticular (knees, wrists, ankles)
    - GI pain, hemorrhage, intestinal perforation
    - Acute meningoencephalitis
    - Aneurysms, deep vein thromboses (DVTs), coronary arteritis, valve disease, arrhythmias
    - Pulmonary aneurysms, superior vena cava thrombosis
    - Glomerulonephritis
- Treatment
  - Topical steroids, calcineurin inhibitors for mucocutaneous disease
  - Systemic steroids
  - Dapsone, colchicine, thalidomide, azathioprine, cyclosporine, anti-TNF-α

Sweet's Syndrome (Acute Febrile Neutrophilic Dermatosis)

- Diagnostic criteria
  - Need both major and two of four minor criteria
  - Major criteria:
    - Abrupt onset of painful erythematous plaques or nodules
    - Histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis
  - Minor criteria
    - Fever >38°C
    - Association with underlying hematologic or visceral malignancy, inflammatory disease or pregnancy, OR preceded by upper respiratory infection, gastrointestinal infection, or vaccination
    - Excellent response to treatment with systemic glucocorticoids or potassium iodide
    - Abnormal laboratory values at presentation (three of four of the following: ESR >20 mm/hour, positive CRP, >8000 leukocytes, >70 percent neutrophils)
- Clinical features
  - Skin
    - Sudden eruption of tender, juicy/edematous, nonpruritic, erythematous papules and plaques

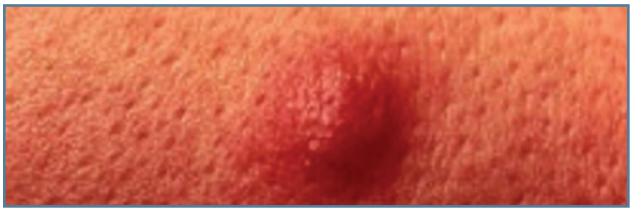


Figure 2.1.43 Acute febrile neutrophilic dermatosis.

- Face, neck, upper extremities
  - **Neutrophilic dermatosis of the dorsal hands** (localized variant with histologic overlap)
- Coalesce to form irregular sharply bordered plaques ("relief of a mountain range")
- Transparent vesicular appearance, though solid ("illusion of vesiculation")
- Resolves in 5-12 weeks

- Systemic
  - Look and feel ill (fever, leukocytosis, headache, arthralgia, myalgia, and general malaise)
  - Ocular: Conjunctivitis and episcleritis
  - Bone: Sterile osteomyelitis
  - Neurologic: Aseptic meningitis, neurologic and psychiatric symptoms, with neutrophils in the CSF
  - Renal: Proteinuria, hematuria, glomerulonephritis
  - Hepatic: Infiltration of portal triad and tracts with elevated liver function test (LFT) results
  - Pulmonary: Culture-negative infiltrates

- Associated causes
  - Malignancy most common (paraneoplastic, **acute myelogenous leukemia,** genitourinary [GU]/breast/colon)
  - Inflammatory bowel disease (IBD)
  - Drugs (granulocyte-macrophage colony-stimulating factor [GM-CSF], furosemide [Lasix], hydralazine, minocycline, Bactrim)
  - Infection (strep URI, *Yersinia*)
  - Pregnancy

TIP

Sweet's Syndrome

Malignancy, most commonly hematologic (AML); lesions may precede diagnosis of leukemia

- Laboratory
  - Leukocytosis with neutrophilia
  - Elevated ESR
  - Malignancy-associated Sweet's: Anemia, normal or low neutrophil count and abnormal platelet count
- Pathology
  - Diffuse nodular and perivascular infiltrates of neutrophils with massive dermal papillary edema
- Treatment
  - Oral steroids
  - Dapsone, potassium iodide, colchicine

Neutrophilic Eccrine Hidradenitis

- Epidemiology
  - Mostly in patients receiving chemotherapy for malignancy, especially AML
    - Cytarabine and anthracyclines involved in most cases
    - Can precede malignancy diagnosis or associate with relapse
  - Infectious associations (*Serratia, Enterobacter* species, *Staphylococcus aureus, Nocardia* species, and *Mycobacterium chelonae*)
- Clinical features
  - Asymptomatic or tender erythematous papules or plaque
  - Most commonly on trunk > extremities
  - May be febrile
  - Neutrophilic infiltrate and necrosis of eccrine glands on pathology
- Treatment
  - Spontaneous resolution after stopping chemotherapy or treating infection
  - Systemic steroids, dapsone may help

PANNICULITIS

Erythema Nodosum

- Clinical features
  - Prototypical **septal panniculitis**
  - Any age, but most prevalent between 20 and 30 years of age
  - Erythematous, tender nonulcerating nodules that progress to violaceous bruise-like color

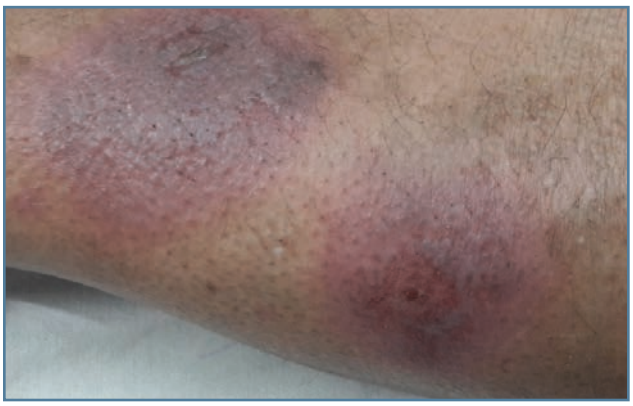


Figure 2.1.44 Erythema nodosum.

- Anterior shins > thighs, forearms
- Onset of new lesions often accompanied by fever, chills, arthralgias, malaise, and leukocytosis

TIP

Erythema Nodosum

SHOUT BCG

Sarcoid, sulfa, strep
Histoplasmosis
Oral contraceptives
Ulcerative colitis
TB

Behçet's
Crohn's
GI (Yersinia)

- Causes
  - Results from immunologic reaction triggered by drugs, systemic illness, bacterial, viral, and fungal infections
  - Infections
    - *Streptococcus* most common infectious cause
    - Tuberculosis (primary infection)
    - GI bacteria (*Yersinia* > *Salmonella, Campylobacter*)
    - Other bacteria (leptospirosis, tularemia, brucellosis, lymphogranuloma venereum, cat-scratch disease)
    - Fungal (blastomycosis, coccidioidomycosis, histoplasmosis)
    - Dermatophytes (particularly those causing tinea capitis with kerion formation)
    - Viruses (paravaccinia, infectious mononucleosis, hepatitis B)
  - Sarcoidosis
    - **Löfgren's syndrome:** Acute sarcoidosis, erythema nodosum (good prognosis)
  - Drugs
    - **Oral contraceptives**
    - Sulfonamides
    - Penicillins
    - Bromides
  - Inflammatory bowel disease
    - Crohn's, ulcerative colitis
  - Miscellaneous causes
    - Behçet's syndrome
    - Sweet's syndrome
    - Malignancy (lymphoma, leukemia, cervical cancer)
    - Onset of radiation therapy for cancer
- Treatment
  - Spontaneous resolution usually occurs within 3-6 weeks
  - NSAIDs
  - Potassium iodide
  - Systemic steroids, cyclosporine, TNF-α (avoid if infectious etiology)

α_1-Antitrypsin Deficiency Panniculitis

- α_1-Antitrypsin = glycoprotein produced in the liver, most abundant circulating serine protease inhibitor
- Pathogenesis
  - Trauma may trigger unregulated effects of α_1-antitrypsin → attack fat and connective tissue
  - Majority of abnormal protein accumulates in endoplasmic reticulum of hepatocytes; small amounts of protein that enter the circulation tend to form inactive polymers and attract polymorphonuclear leukocytes (PMNs)
- Clinical features
  - Large, erythematous/purpuric, tender nodules/plaques → **deep, necrotic ulcers with oily discharge** → heal with scarring and SQ atrophy
  - Antecedent trauma in 33% of cases
  - Lower trunk, proximal extremities (flanks, buttocks, thighs) most common sites
  - ±Fever, pleural effusions, pulmonary emboli
  - Prolonged course, resistant to therapy
  - Other sequelae: Liver cirrhosis, emphysema, pancreatitis, membranoproliferative glomerulonephritis (MPGN), RA, c-ANCA vasculitis, angioedema
  - **Pathology shows liquefactive necrosis of dermis and SQ septa**

Erythema Induratum (Nodular Vasculitis, Erythema Induratum of Bazin)

- Epidemiology
  - Female >> male
- Pathogenesis
  - Type IV cell-mediated response to various antigens
    - **Tuberculosis most common;** other infections (*Nocardia*), drugs (propylthiouracil)
- Clinical features
  - Tender, erythematous/violaceous nodules/plaques that are persistent, heal with scarring, and can recur
  - **Calves** > feet, thighs, buttocks, arms
  - Can ulcerate
- Treatment
  - Steroids, NSAIDs, SSKI, tetracycline, gold, mycophenolate mofetil (CellCept), bed rest, avoid smoking

Pancreatic Panniculitis (Pancreatic Fat Necrosis)

- Epidemiology
  - 2% patients with pancreatic disorders
- Pathogenesis
  - Lipase: Main contributor; hydrolyzes neutral fat into glycerol and free fatty acids (FFAs) → fat necrosis and inflammation
  - Amylase: Peaks 2-3 days after skin eruption; normalizes 2-3 days after regression
  - Trypsin: Causes ↑ vessel permeability, which allows lipase to access fat
- Clinical features
  - Associated with acute/chronic pancreatitis, pancreatic carcinoma (acinar > other), pseudocysts, pancreas divisum, or traumatic pancreatitis
    - May precede detection of pancreatic disease by 1-7 months
  - Erythematous, edematous, painful SQ nodules that can migrate, become fluctuant, ulcerate, and have oily discharge
  - **Legs (exacerbated by edema)** > abdomen, chest, arms, scalp
    - Can involve visceral fat (omentum, peritoneum)
  - **Schmid's triad:** SQ nodules, polyarthritis, eosinophilia (poor prognosis)
  - Associated findings: Fever, abdominal pain, inflammatory polyarthritis, ascites, pleural effusions
  - Pathology shows **ghost cells** (lipocytes that have lost their nuclei and have thick, shadowy walls)
    - Saponification of fat by calcium salts → deposition of granular or homogeneous basophilic material

Lipodermatosclerosis (Sclerosing Panniculitis)

- Epidemiology
  - Women older than 40 years old
- Pathogenesis
  - Venous HTN/insufficiency → increased capillary permeability → leakage of fibrinogen → fibrin cuffs around vessels → tissue hypoxia
- Clinical features
  - Pain, warmth, erythema, induration of medial ankle (sometimes of abdominal pannus)
  - Sharply demarcated hyperpigmented (from hemosiderin) induration (inverted wine bottle) of lower leg
  - Pathology shows **lipomembranous change** (thickened, undulating membranes that form cysts lined with feathery eosinophilic remnants of adipocytes)
- Treatment
  - Leg elevation, compression stockings, stanozolol (enhances fibrinolysis; side effects = Na^+ retention, lipid abnormalities, hepatotoxicity, virilization), oxandrolone, pentoxifylline, ultrasound

Cytophagic Histiocytic Panniculitis

- Epidemiology
  - Young to middle-aged adults
- Pathogenesis
  - Likely related to SQ panniculitis–like T-cell lymphoma, but other cases not related to lymphoma (SLE, infection)
- Clinical features
  - Skin colored to erythematous, sometimes painful SQ nodules or hemorrhagic plaques
  - Extremities and trunk most common sites
  - May have fever, hepatosplenomegaly, mucosal ulcers, serosal effusions, pancytopenia, intravascular coagulation, liver failure, hemorrhagic diathesis, death
  - Pathology shows **bean bag cells** (macrophages that contain erythrocytes, lymphocytes, karyorrhectic debris)
    - Bean bag cells also seen in Rosai-Dorfman
- Treatment
  - Prednisone, cyclosporine, dapsone

GRANULOMATOUS DISORDERS

Granuloma Annulare (GA)

- Asymptomatic, arciform, or annular skin-colored, pink, or violaceous small papules that coalesce into plaques

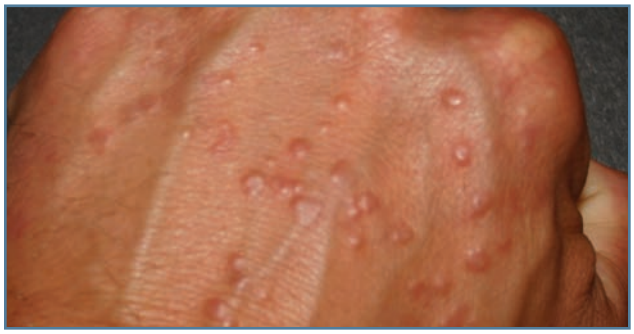


Figure 2.1.45 Granuloma annulare.

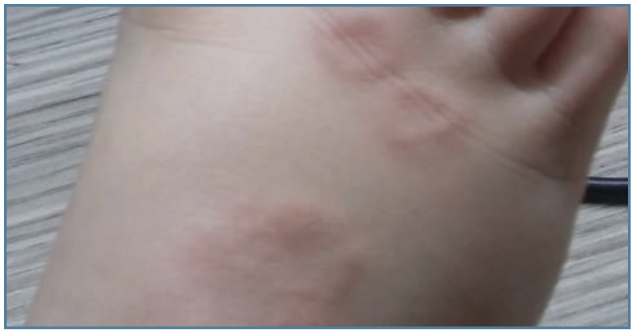


Figure 2.1.46 Granuloma annulare in a child.

- Subtypes
  - Localized GA
    - Children, young adults
    - Lateral or dorsal surfaces of fingers, hands, elbows, feet, ankles
    - 75% clear within 2 years
  - Generalized GA

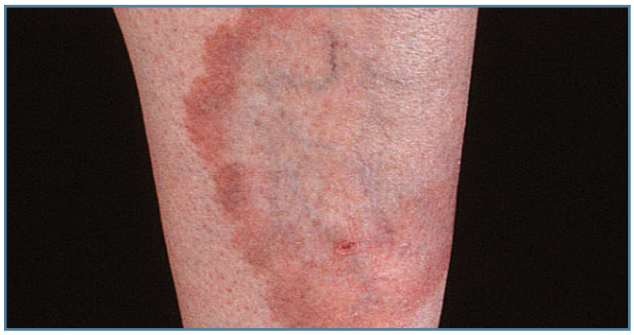


Figure 2.1.47 Generalized granuloma annulare.

    - May be associated with lipid abnormalities, thyroid disease, and diabetes (less likely based on recent evidence)
    - Diffuse papules
    - Longer duration, poorer response to treatment
  - Subcutaneous GA
    - More common in children
    - Palms, hands, anterior tibial surfaces, feet, buttocks
    - Often a history of trauma to area
  - Perforating GA
    - Dorsum of hands
    - Transepidermal elimination of degenerating collagen
- Treatment
  - Topical or intralesional steroids
  - For generalized or refractory cases: Prednisone, cyclosporine, methotrexate, anti-TNF-α, narrow-band UVB (NBUVB)

Cutaneous Sarcoidosis

- Skin lesions occur in 25% of patients with sarcoidosis
- Red-brown, symmetric, flat-topped, dermal papules/plaques without scale
- Face, lips, neck, upper trunk, extremities common sites
- Often occur in preexisting scars, trauma sites
- **Erythema nodosum** = most important nonspecific cutaneous finding
  - Associated with subacute, transient sarcoidosis that usually resolves spontaneously
- Systemic manifestations
  - Lymphadenopathy (esp. hilar/paratracheal)
  - Bone: Punched-out lytic lesions in distal fingers and toes (esp. lupus pernio); arthralgias
  - Ocular: Iris, ciliary body, choroid, retina, optic nerve, conjunctiva, lacrimal glands
  - Neurologic: CN VII palsy most common (esp. Heerfordt's)
    - **Uhthoff phenomenon** = vision loss after heat exposure
- Other: Liver, spleen, kidney, upper/lower GI tract, peripheral lymph nodes (LNs), muscle, heart, pituitary, testes/ovary
- Lab abnormalities
  - Hypercalcemia
    - Increased histiocytic production of 1,25-dihydroxyvitamin D leads to increased absorption (can cause hypercalciuria, kidney stones, renal failure)
  - Elevated ACE level
    - ACE derived from epithelioid cells of granulomas and thus reflects granuloma load in the body
  - Used for monitoring disease severity, not for diagnosis

- Clinical variants:
  - Lupus pernio
    - Chronic, violaceous, indurated papules
    - Predilection for nose, ears, lips, and face

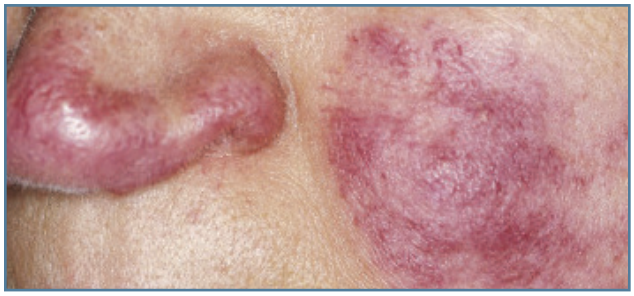


Figure 2.1.48 Lupus pernio.

      - **Beaded appearance around nasal rim**
    - Associations:
      - Pulmonary fibrosis and upper respiratory
      - Saddle-nose deformity
      - Cystic bony lesions, especially distal fingers
  - Löfgren's syndrome
    - Erythema nodosum, hilar adenopathy, fever, migrating polyarthritis, acute iritis
  - Subcutaneous nodules/Darier-Roussy sarcoidosis
    - Oval, firm, painless
    - Arise deep in dermis and subcutis
    - Found on trunk and extremities
  - **Heerfordt's syndrome**
    - Parotid gland enlargement, uveitis, fever, cranial nerve palsy (esp. **facial nerve**)
  - **Mikulicz syndrome**
    - Bilateral sarcoidosis of parotid, submandibular, sublingual, and lacrimal glands
- Treatment
  - Corticosteroids 1st line (oral, IL > topical)
  - Antimalarials
  - Methotrexate (MTX), thalidomide, isotretinoin, minocycline, allopurinol, TNF-α inhibitors

Necrobiosis Lipoidica (Diabeticorum)

- Clinical features
  - Well-demarcated firm, waxy, yellowish brown plaques with central depression and telangiectasia

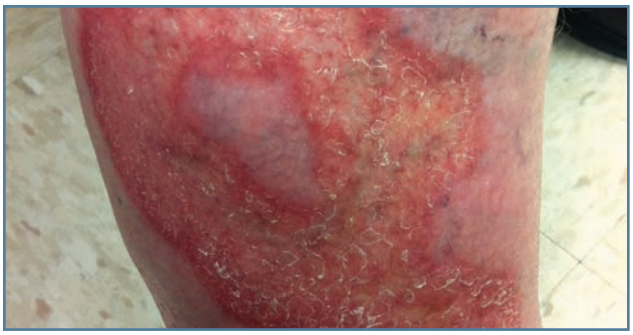


Figure 2.1.49 Necrobiosis lipoidica.

  - Can ulcerate
  - Pretibial most common site
  - Strong association with diabetes
    - Controlling diabetes doesn't alter disease
- Pathology
  - Palisaded granulomas with pale pink degenerated collagen
  - Horizontal tiers of degenerated/irregular collagen between layers of inflammation
  - No mucin at the center
- Treatment: Often unsatisfactory
  - IL steroids
  - Topical
    - Steroids, calcineurin inhibitors
  - Systemic
    - Aspirin ± dipyridamole, pentoxifylline, niacinamide, cyclosporine
  - Surgical

HEMATOPOIETIC DISORDERS

Hyperlipoproteinemias/Xanthomatosis

- Hyperlipoproteinemias
- Familial LPL deficiency (type I)
  - Autosomal recessive (AR); decreased or abnormal lipoprotein lipase (LPL) or apolipoprotein C-II (Apo C-II) mutation
    - Same phenotype because Apo C-II is a cofactor for LPL
  - ↓ (low-density lipoprotein [LDL], high-density lipoprotein [HDL]); ↑ (chylomicrons, triglycerides [TGs])
  - Clinical features
    - Eruptive xanthomas, **lipemia retinalis (opaque yellow retinal vessels)**

- Associated with hepatomegaly, pancreatitis, abdominal pain (horrible, screaming pain)
- No increased risk of coronary artery disease (CAD)

- Familial hypercholesterolemia; Apo B-100 deficiency (type II)
  - Autosomal dominant (AD); LDL receptor defect (or reduced affinity of LDL for receptor) or Apo B-100 mutation
    - **Most common hyperlipoproteinemia** (1:500 heterozygous)
    - Accelerated degradation of LDL receptor
  - ↑ (LDL, cholesterol)
  - Clinical features
    - Tendinous, tuberoeruptive, tuberous, or plane xanthomas
      - **Plane xanthomas of finger webs: Pathognomonic for homozygous Apo B-100 mutation**
    - Xanthelasma
      - **Arcus juvenilis: White ring due to lipid deposition in the peripheral cornea**
    - Atherosclerosis
    - Secondary causes
      - IIa: Hepatoma, obstructive biliary disease, porphyria, hypothyroidism, anorexia, nephrotic syndrome, Cushing's
      - IIb: Nephrotic syndrome, Cushing's
    - Homozygotes: Need liver transplantation to survive
- Familial dysbetalipoproteinemia; Apo E deficiency (type III)
  - AR; *APOE* gene or apolipoprotein E deficiency
    - Patients have apolipoprotein E2, but it is poor ligand for B-100/E receptor (compared to E1 and E3)
  - ↑ (chylomicron remnants, intermediate-density lipoprotein [IDL], cholesterol, TGs)
    - β-VLDL (very low-density lipoprotein) on electrophoresis
  - Clinical features
    - Tuberoeruptive/tuberous xanthomas in 80%
      - **Xanthoma striatum palmare = plane xanthomas of palmar creases (66%)**
    - Associated with atherosclerosis, diabetes, gout, obesity
- Endogenous familial hypertriglyceridemia (type IV)
  - AD; elevated production of VLDLs
  - ↑ (VLDL, TGs)
  - Clinical features
    - Eruptive, tendinous, tuberous xanthomas
    - Atherosclerosis
    - Secondarily caused by type II non—insulin-dependent diabetes mellitus (NIDDM), uremia, paraproteinemia, alcoholism, lipodystrophy, obesity
- Type V
  - AD; elevated chylomicrons and VLDLs from unknown cause
  - ↑ (VLDLs, chylomicrons, TGs, cholesterol); ↓ (LDL, HDL)
  - Clinical features
    - Eruptive xanthomas, **lipemia retinalis**
    - Associated hepatomegaly
    - No increased risk of CAD

TIP

Characteristic Features Seen in Hyperlipoproteinemias/Xanthomatosis

Lipemia retinalis	I, V
Plane xanthomas	II
Eruptive xanthomas	I, II, V
Xanthelasma	II, III
Tendinous xanthomas	II
Xanthoma striatum palmare	III
Tuberous xanthomas	II, III
Atherosclerosis	II, III > IV

  - Clinical types
    - Tuberous xanthoma
      - Pink-yellow papules or nodules over joints (particularly elbows and knees)

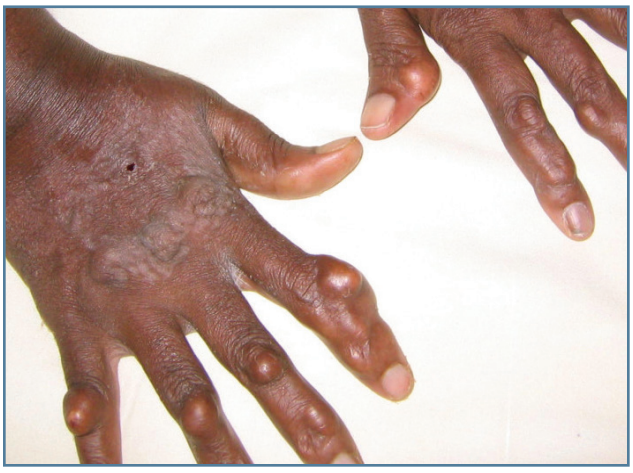


Figure 2.1.50 Tuberous xanthomas.

- Types II, III, and IV associated with biliary cirrhosis

- Tendinous xanthoma
  - Papules or nodules over tendons; Achilles most common site
  - Types II, III
- Eruptive xanthoma
  - Small yellow/orange/red papules appearing in crops over entire body
    - Extensors, buttocks most common
  - Significantly elevated triglycerides
  - Types I, III, IV, and V
  - Diabetes, obesity, pancreatitis, chronic renal failure, hypothyroidism, estrogen therapy, corticosteroids, isotretinoin, acitretin
- Plane xanthoma
  - Yellow or tan thin papules spread diffusely over large areas
  - Eyelids, neck, trunk, shoulders, axillae most common
  - Multiple associations
    - Biliary cirrhosis, biliary atresia, myeloma, HDL deficiency, monoclonal gammopathy, lymphoma, leukemia, serum lipoprotein deficiency, xanthomas following erythroderma, RA, acquired C1 esterase deficiency
    - Types II, III
  - **Intertriginous plane xanthomas of antecubital fossa or finger web spaces pathognomonic for homozygous Apo B-100 mutation (type II)**
- Palmar xanthoma **(xanthoma striatum palmare)**
  - Nodules and irregular plaques on palms and flexural surfaces of fingers
    - Type III
- Xanthelasma
  - Most common type of xanthoma
  - Eyelids, 2-30 mm in length

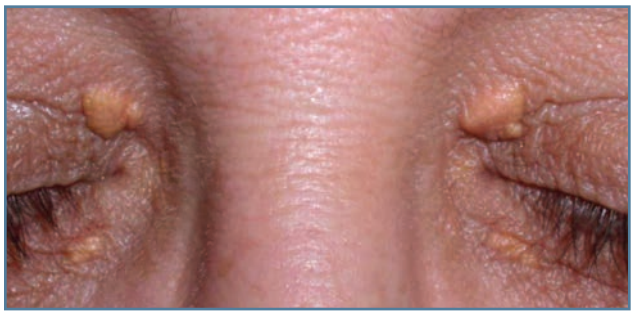


Figure 2.1.51 Xanthelasma.

  - Frequent symmetry
  - Usually present without any other disease, but may occur concomitantly with other xanthomas; can occur in types II and III, particularly
  - Common among women with hepatic or biliary disorders, also seen in myxedema, diabetes, and phytosterolemia
  - Best treated with surgical excision
- Verruciform xanthomas
  - Larger wart-like pink-yellow plaques
  - Anogenital and periorificial sites
  - No hyperlipidemia
  - Associated with lymphedema, epidermolysis bullosa, graft-versus-host disease (GVHD), CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) syndrome
  - **Large verruciform xanthomata**

Cutaneous T-Cell Lymphoma (CTCL); Mycosis Fungoides (MF)

- Clinical types
  - Patch and plaque stage
    - Thin scaly patches, sometimes pruritic

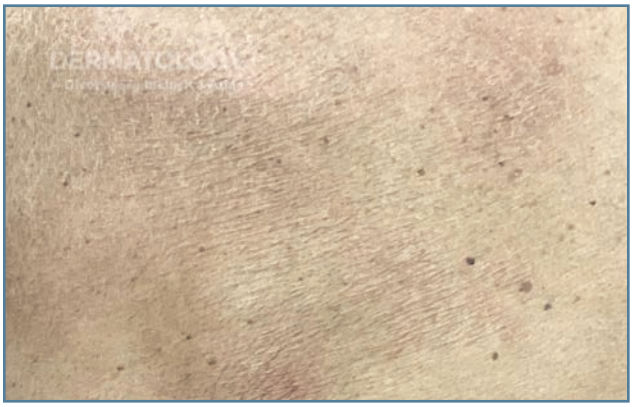


Figure 2.1.52 Cutaneous T-cell lymphoma.

    - Predilection for photoprotected sites
    - Patch stage can last for months to years before progressing
  - Plaque stage
    - Infiltrated red-brown, scaling plaques that enlarge into annular/polycyclic/horseshoe-shaped lesions
  - Tumor stage
    - Nodules that ulcerate
    - Predilection for face and body folds

- May occur in preexisting plaques and patches of CTCL
- Infiltrate denser than plaque stage, and extends to subcutaneous fat
- Epidermotropism is not a prominent feature, and grenz zone may appear

- Hypopigmented MF
  - Darker-skinned patients
  - Patients respond to therapy by regaining pigment
- Pigmented purpuric
  - Capillaritis
- Granulomatous CTCL and slack skin
  - Primarily in females
  - Large regions of slack skin accompanied by fibrotic bands
  - Axillae and groin
- Pagetoid reticulosis (Woringer-Kolopp disease or acral MF)
  - Typically presents as a solitary plaque (localized)
  - Long duration, slow growing
  - Hyperplastic epidermis with large atypical pagetoid single or nested cells only in the epidermis
- Folliculotropic MF
  - Predilection for head and neck
  - **Infiltrated plaques on eyebrow with alopecia characteristic feature**
- Alopecia mucinosa
  - Grouped follicular papules or red, raised, boggy, occasionally nodular plaques
  - Alopecia may be presenting sign
  - Mucin in outer root sheath
- Erythrodermic MF
  - *De novo* or as a progression from preexisting CTCL lesions, especially Sézary syndrome
  - May lead to leonine facies
  - Alopecia, ectropion, nail dystrophy, ankle edema

- Diagnosis
  - Diagnosis made by biopsy
    - Multiple biopsies at 3-month intervals may be needed
    - Any patient with chronic, refractory dermatosis (allergic contact dermatitis [ACD], atopic dermatitis [AD], psoriasis, pityriasis rubra pilaris [PRP]) should be biopsied to rule out CTCL
    - Clonality assists in diagnosis, but is not pathognomonic
  - Peripheral blood
    - Malignant clonal T cell populations recirculate from skin to lymph nodes, and then to blood, even in patch stage disease, $CD4^+/CD7^-$
    - Elevated CD4/CD8 ratio indicates disease expansion into blood
    - Flow cytometry must be a component in the staging process (CD4/CD8), CD3, CD45RO
    - Memory cell marker CD45RO is elevated often in cases of peripheral blood involvement by CTCL
  - Sézary cells
    - Hyperchromatic and hyperconvoluted nuclei
    - Represent an activated T cell
    - Can be seen in inflammatory dermatoses, and in Dilantin (phenytoin) hypersensitivity syndrome
    - 100 cells counted to assess percentage, and >5% associated with poor prognosis
- Prognosis
  - Involvement of 10% or less with patch disease: Median survival, 12 years
  - Tumors, erythroderma, or node involvement: Median survival, 2-3 years
  - Sézary syndrome: Median survival, 2-3 years
- Treatment
  - Skin-targeted therapies
    - Nitrogen mustard (bis-chloroethylnitrosourea, BCNU); mechlorethamine
      - Hypersensitivity, primary irritation, secondary cutaneous malignancies, hypo- and hyperpigmentation
      - Daily whole-body application required until remission, after which frequent maintenance therapy used
    - Radiotherapy
      - Whole body irradiation induces complete remission in >80%
      - Most relapses occur within first year after cessation of treatment
      - Alopecia, atrophy of sweat glands and skin, radiodermatitis, and edema; fractionating dose reduces side effects
      - Squamous cell carcinoma (SCC) incidence increased
  - Photochemotherapy
    - **UVB and NBUVB** = patch stage only → complete response in 75%
    - **PUVA**
    - **Extracorporeal photochemotherapy**
      - Induces remission even in tumor stages; erythroderma

- Photoinactivation of a portion of the patient's lymphocyte compartment with 8-methoxypsoralen + UVA, followed by reinfusion
- Requires 4-12 months for response

- Interferon-α and -γ
  - 10-27% complete response within 6 months, using monotherapy
  - 3 million units 3 times per week, and can be increased to 20 million units per day as tolerated
  - Maintenance dose of 1 million units daily
- DAB-IL-2 toxin/denileukin diftitox
  - **Diphtheria toxin fused to interleukin (IL)-2, binding to receptor, killing cells**
  - Infiltrates must contain high levels of IL-2 receptor—positive cells
- Systemic high-dose chemotherapy
  - Palliative
  - Glucocorticoids, Adriamycin, CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], and prednisone) therapy

Cutaneous B Cell Lymphoma

- Epidemiology
  - About 25% of primary cutaneous lymphoma
- Clinical features
  - Primary cutaneous marginal zone lymphoma
    - Localized papules or plaques
  - Primary cutaneous follicular center lymphoma
    - Localized papules or plaques on the head (esp. scalp) or trunk
  - Primary cutaneous diffuse large B cell lymphoma, leg type
    - Localized papules or plaques on the lower leg
    - More common in females
  - EBV-positive mucocutaneous ulcer
    - Immunosuppressed
    - Self-limited with indolent course

Mastocytosis

- Etiology and pathogenesis
  - Mast cell hyperplasia in the bone marrow, liver, spleen, lymph nodes, GI tract, and skin
  - Originate from pluripotent ($CD34^+$) bone marrow cells → circulate through blood → mature into fully granulated cells
  - Mutations in *c-kit* **(CD117) = type III receptor tyrosine kinase** → associated with enhanced receptor function
  - Increased production of mast cell mediators
    - Preformed mediators = histamine, heparin, tryptase/chymase, neutrophil and eosinophil chemotactic factors
    - Newly formed mediators = prostaglandin D_2 (PGD_2), leukotrienes ($LT\text{-}C_4$, $LT\text{-}D_4$, $LT\text{-}E_4$), platelet-activating factor (all from the arachidonic acid pathway)
    - Cytokines = TNF-α, IL-4, IL-5, IL-6, IL-8, IL-13
- Clinical features
  - Features are due to excess production of mast cell—dependent mediators
  - Pruritus, flushing, urtication, abdominal pain, nausea, vomiting, diarrhea, bone pain, vascular instability, headache, and neuropsychiatric difficulties
  - Mast cell stimuli: Alcohol, anticholinergics (e.g., scopolamine), *Hymenoptera* stings, acetylsalicylic acid (ASA), NSAIDs, heat, friction, exercise, narcotics, iodinated contrast, antibiotics, systemic anesthetics
  - Major types of mastocytosis
    - *Urticaria pigmentosa*
      - Most common skin manifestation in children and adults
      - 90% of those with indolent mastocytosis
      - Small, yellow-tan to reddish-brown macules or slightly raised papules

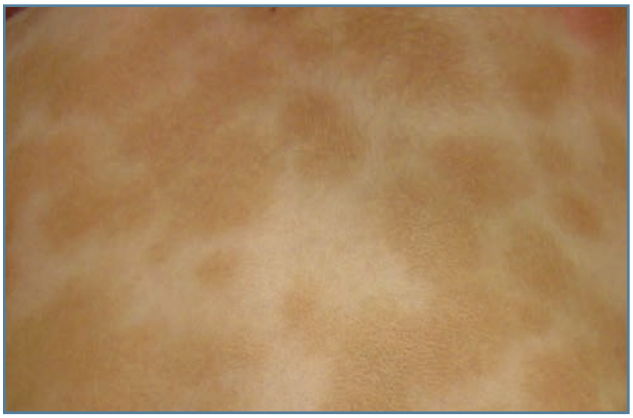


Figure 2.1.53 Urticaria pigmentosa.

      - Darier's sign: Trauma/rubbing of lesions causes urtication and erythema
      - Associated with pruritus exacerbated by changes in temperature, friction on skin, ingestion of hot beverages or spicy foods, ethanol, and certain drugs

- Diffuse cutaneous mastocytosis
  - Diffuse mast cell infiltration without discrete lesions
  - Usually occurs before age 3
  - Entire skin involved
  - Skin normal to yellow-brown and thickened
- Solitary mastocytomas
  - Rare
  - May be present at birth, usually resolves by age 10
- Bullous mastocytosis
  - Bullous eruptions with hemorrhage
  - Neonates
  - Blisters may erupt spontaneously
- Telangiectasia macularis eruptiva perstans
  - <1% of patients
  - Tan-to-brown macules with subtle Darier's sign
  - Telangiectasias
  - Exclusively in adults

- Systemic features
  - Gastrointestinal
    - Gastric hypersecretion secondary to elevated histamine → gastritis with peptic ulcer disease
    - Diarrhea and abdominal pain
    - Malabsorption
    - LFT results abnormal in half of patients; elevated alkaline phosphatase
  - Splenomegaly
    - 50% of patients
    - Mast cell infiltrates with fibrosis
    - Extramedullary hematopoiesis
  - Skeletal
    - Osteosclerosis and osteosclerosis/osteoporosis
    - Skull, spine, pelvis most common
    - Pathologic fractures may occur
  - Bone marrow
    - Anemia, leukopenia, thrombocytopenia and eosinophilia may occur
    - **MEL lesions: M**ast cells, **E**osinophils, and **L**ymphocytes (differentiates mastocytosis from myeloproliferative and myelodysplastic diseases that could have increased mast cells)
  - Neuropsychiatric
    - Headaches
    - Decreased attention span and memory impairment
    - Irritability
  - Mast cell leukemia
    - Rarest form and has most fulminant behavior; peripheral blood shows >10% immature mast cells

- Work-up
  - Skin exam: Gross and microscopic
  - Complete blood count (CBC) with manual differential
    - If eosinophilia, screen for *FIP1L1-PDGFRA* fusion gene (**responds to imatinib**)
  - Serum tryptase level
  - 24-hour urine
    - Histamine normal, but metabolite **1,4-methylimidazole acetic acid (MeImAA) often elevated**
    - 5-Hydroxyindoleacetic acid (5-HIAA) and urinary metanephrines to rule out carcinoid tumor or pheochromocytoma
  - Bone marrow biopsy
- Treatment
  - H_1 blockers reduce pruritus, flushing, tachycardia
  - H_2 blockers or cromolyn sodium for GI complaints
  - Topical steroids under occlusion (lesions recur after stopping)
  - Epinephrine for vascular collapse
  - Ketotifen fumarate and azelastine to stabilize mast cells
  - Epinephrine for vascular collapse (patients should be prepared to self-administer)
  - PUVA (with methoxsalen) relieves pruritus and whealing after 1-2 months, but recurs after 3-6 months
  - Radiotherapy for bone pain
  - Imatinib if *FIP1L1-PDGFRA* gene mutation
- Survival
  - 50% of children with urticaria pigmentosa (UP) resolve by adulthood
  - Adults with UP usually progress gradually to systemic disease and rarely develop hematologic disease
  - Diffuse cutaneous mastocytosis is usually associated with indolent systemic disease
  - Mast cell leukemia: Survival less than 6 months
  - Lymphadenopathic mastocytosis with eosinophilia: 2-4 years without therapy

PERFORATING DISORDERS

Elastosis Perforans Serpiginosa

- Pathogenesis
  - Altered elastic fibers in dermis and concomitant alterations of collagen fibers
  - Elastic fibers act as a foreign body and are eliminated through transepidermal channels

MNEMONIC

Dx for Diseases with EPS
MAD PORES

Marfan
Acrogeria
Down's

Penicillamine
Osteogenesis imperfecta
Rothmund-Thomson
Ehlers-Danlos
Scleroderma

- Clinical
  - 2nd decade of life
  - Lateral neck, upper extremities most common

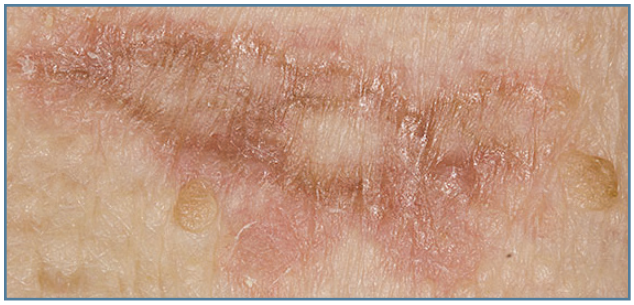


Figure 2.1.54 Elastosis perforans serpiginosa.

  - 2- to 5-mm keratotic papules, often in serpiginous or annular pattern
  - Regression leaves atrophic, wrinkled, and hypopigmented scars
  - Patients with Down's syndrome, heritable connective tissue disorders (Ehlers-Danlos type IV, osteogenesis imperfecta, Marfan's syndrome, Rothmund-Thomson, scleroderma, and acrogeria), penicillamine
- Treatment
  - Cryotherapy
  - Avoid electrocautery, dermabrasion, and surgery

Reactive Perforating Collagenosis

- Pathogenesis
  - Lesions likely precipitated by minor trauma altering collagen in the dermal papillae
  - No associated metabolic disorders
- Clinical features
  - Starts in infancy
  - 5- to 8-mm keratotic papules that occur at sites of trauma 3-4 weeks after trauma; resolve after 6-8 weeks
  - Arms and hands, sites of trauma most common sites
- Treatment
  - No consistently successful therapy
  - Maybe phototherapy
- **Acquired perforating dermatosis (Kyrle's disease)**
  - **Necrotic material (collagen > elastic fibers)**
  - Adults
  - Legs or generalized (often follicular-based)
  - Associations
    - Diabetes mellitus, pruritus of renal failure (10% of dialysis patients)

ERYTHEMAS

Urticaria

- Clinical features
  - Transient pruritic pink or pale papules or plaques of varying sizes

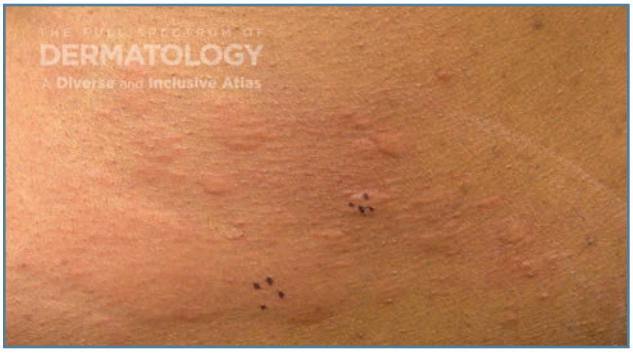


Figure 2.1.55 Urticaria.

  - Individual lesions last < 24 hours
  - Acute (< 6 weeks) vs chronic (>6 weeks)
    - Association: Autoimmune thyroid disease or other autoimmune conditions
  - Physical urticaria
    - Due to mechanical stimuli
      - Dermographism

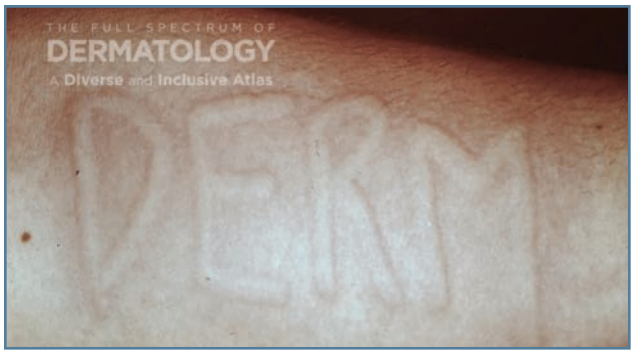


Figure 2.1.56 Dermatographism.

  - Delayed pressure urticaria
  - Vibratory angioedema
- Due to temperature changes and stress
  - Cholinergic urticaria
  - Adrenergic urticaria
  - Cold contact urticaria
  - Exercised-induced urticaria/anaphylaxis
- Solar urticaria
- Aquagenic urticaria

- Pathogenesis
  - Mast cell degranulations with release of proinflammatory mediators such as histamine, resulting in vasodilation and increased permeability
  - Idiopathic most common
  - Immunologic
    - Autoimmune
    - IgE-dependent (allergic)
    - Immune complex–related
    - Complement and kinin-dependent
  - Nonimmunologic
    - Direct mast cell–releasing agents
    - Vasoactive stimuli
    - Medication or dietary pseudoallergen
    - Angiotensin-converting enzyme inhibitor
- Treatment
  - Avoidance of triggers if identified
  - First-line therapies:
    - H_1 blockers
      - Sedating antihistamine (chlorpheniramine, hydroxyzine, diphenhydramine, doxepin)
      - Nonsedating antihistamine (cetirizine, loratadine, desloratadine, fexofenadine, levocetirizine)
    - H_2 blockers (cimetidine, ranitidine)
    - Omalizumab
  - Second-line therapies
    - Nifedipine, doxepin, colchicine, dapsone
  - Third-line therapies
    - Cyclosporine
    - Mycophenolate mofetil
    - Methotrexate
    - NBUVB

Angioedema

- Edema in deeper dermis or subcutaneous or submucosal tissue
- May affect lips, rarely bowel
- Type I
  - Occurs in setting of lymphoproliferative disease (low-grade lymphoma, chronic lymphocytic leukemia [CLL], monoclonal gammopathy of undetermined significance, systemic amyloidosis) or rheumatologic illness, where idiotype/anti-idiotype immune complexes consume available C1q, and functionally and quantitatively lower the amounts of C1 esterase inhibitor
  - Can also occur in setting of autoimmunity directed against the C1 esterase protein
  - Important point: In both the inherited and acquired forms, levels of C2 and C4 are decreased because of the uncontrolled actions of C1s

TIP

Inherited (Quincke's edema) (normal C1q levels)

- Detected in the first or second decade of life
- Autosomal dominant pattern of inheritance
- Serum C1q normal in inherited form
- Defect in synthesis and/or function of C1 esterase inhibitor
- Type I: Low amounts of normal C1 esterase inhibitor
- Type II: Normal amounts of dysfunctional C1 esterase inhibitor

Acquired (low C1q)

- Affects adults or elderly with no family history
- Serum C1q decreased in acquired form

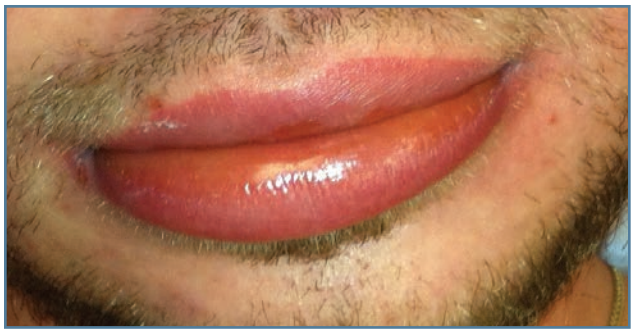


Figure 2.1.57 Angioedema involving the lips.

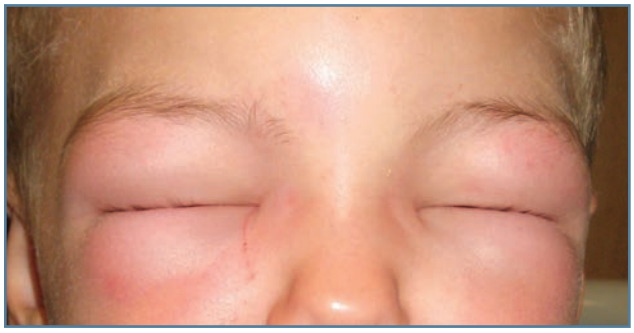


Figure 2.1.58 Angioedema.

- Clinical features
  - Swelling of head, neck, and extremities
  - Abdominal symptoms
  - Upper airway symptoms
  - Recurrent symptoms, with intervening time of weeks to months
- Treatment
  - Androgen therapy: Danazol or stanozolol → bring about dramatic decreases in frequency and severity of attacks
  - Glucocorticoids, but tapering results in relapse of symptoms
  - Therapy for underlying disease
  - Pretreatment with androgens prior to surgical procedures
- Diagnosis
  - Screen with C3 and C4 levels → C4 low, C3 normal in angioedema
  - C1q level low in acquired, but normal in hereditary

Gyrate Erythemas

- Erythema marginatum
  - Cutaneous signs of early rheumatic fever

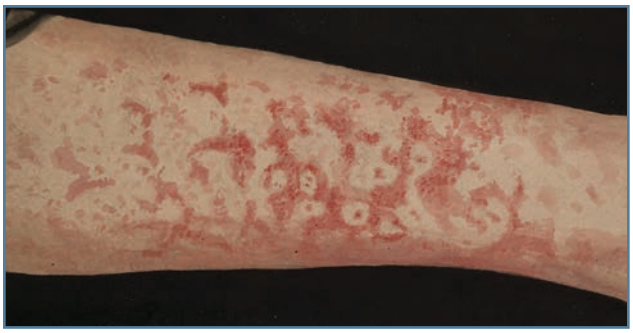


Figure 2.1.59 Erythema marginatum.

  - Spreading evanescent patchy erythema that migrates peripherally, often polycyclic
  - Appearing for a few hours or days on the trunk or proximal extremities
- Erythema migrans
  - Cutaneous manifestation of Lyme disease
  - Expansion of redness around the site of initial tick bite
  - Central area may clear, leaving ring of erythema

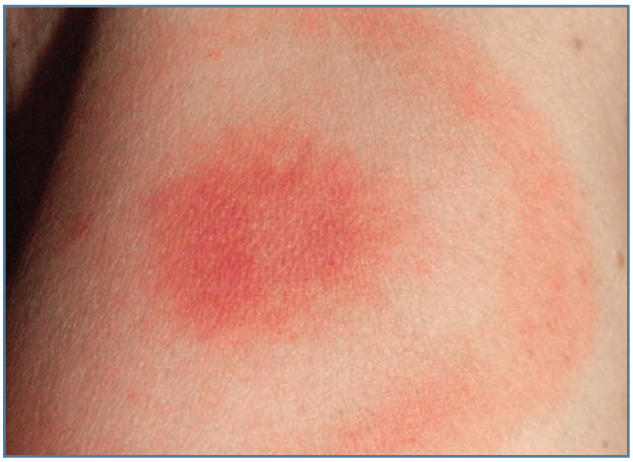


Figure 2.1.60 Erythema migrans.

- Erythema gyratum repens
  - Concentric, undulating wavy bands of elevated erythema with trailing scale, typically involves the entire body
  - Migrate up to 1 cm/day
  - Needs malignancy work-up, lung carcinoma is the most common
  - See Figure 2.1.7 Erythema Annulare Centrifugum (EAC)

2.2 Infectious Diseases of the Skin

BACTERIAL INFECTIONS

Actinomycetoma

- Causative organisms: Aerobic filamentous bacteria including *Nocardia brasiliensis, Actinomadura madurae, A. pelletieri,* and *Streptomyces somaliensis*
- Characteristic features: Chronic, slowly progressive subcutaneous infection characterized by tumefaction, draining sinuses, and an exudate containing grains
- Most commonly involves the foot
- Source of infection is **exogenous,** e.g., soil
- Treatment: Amikacin or streptomycin in addition to either dapsone or trimethoprim-sulfamethoxazole (TMP-SMX)

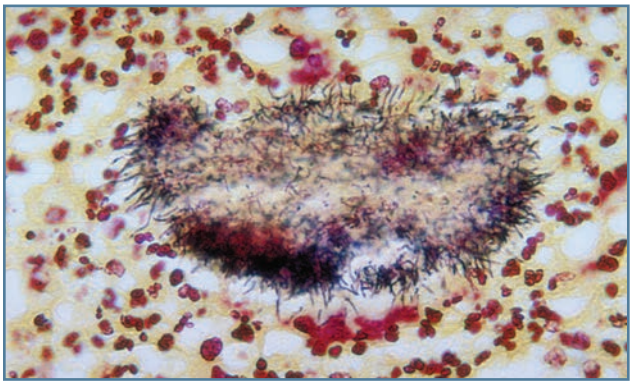


Figure 2.2.1 Actinomycetoma.

Actinomycosis

- Causative organism: *Actinomyces israelii* (an anaerobic gram-positive rod), part of normal oral, gastrointestinal/genital flora
- Characteristic features: Chronic suppurative nodules and sinus tracts with an exudate containing **"sulfur granules"**
- Most commonly involves the cervicofacial region, especially near mandible—"lumpy jaw." (Can also involve the abdomen and thoracic region)
- Source of infection is **endogenous,** e.g., oral flora
- Risk factors: Poor oral hygiene, penetrating foreign bodies, and dental procedures
- Male:female = 3:1
- Treatment: Ampicillin or penicillin G (clindamycin, doxycycline, erythromycin in patients with a penicillin allergy); 2 weeks to 12 months of treatment depending on severity
- Histology: Central basophilic "sulfur granules" with eosinophilic periphery and surrounding granulomatous inflammation (infiltrate is neutrophilic in early lesions)

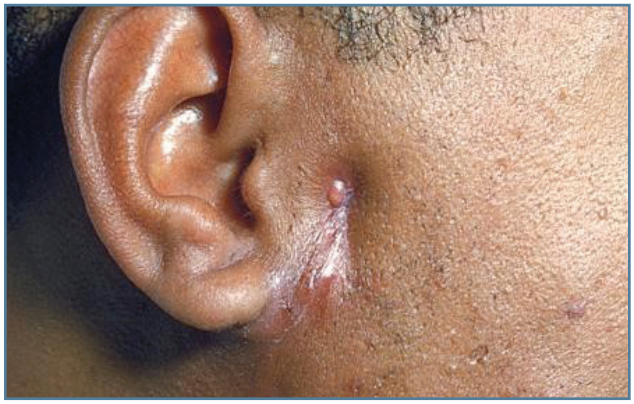


Figure 2.2.2 Actinomycosis.

Anthrax

- Causative organism: *Bacillus anthracis,* a gram-positive spore-forming rod
- Primarily caused by contact with infected wild or domestic animals, or their products (e.g., wool, goat hair, animal hides, bones, etc.)
- Three clinical forms
  - Inhalational (also known as woolsorter's disease)
  - Gastrointestinal
  - Cutaneous (most common [~95% of cases] and least severe form)
- Painless necrotic ulcer, with possible surrounding vesicles ("malignant pustule")
- Virulence depends on three components
  - Edema factor (EF)
  - Lethal factor (LF)
  - Protective antigen (PA)
  - ***Edema toxin* (EF + PA): Causes tissue edema**
  - ***Lethal toxin* (LF + PA): Causes shock and death via TNF-α and IL-1β**
- Treatment
  - Quinolones, doxycycline (alternatives: Penicillin, clindamycin, amoxicillin)
  - 7-10 days cutaneous, 60+ days systemic
  - **Antibiotics do not alter the course of skin findings;** rather, they reduce the severity of systemic illness
  - Surgery is contraindicated as it can spread infection

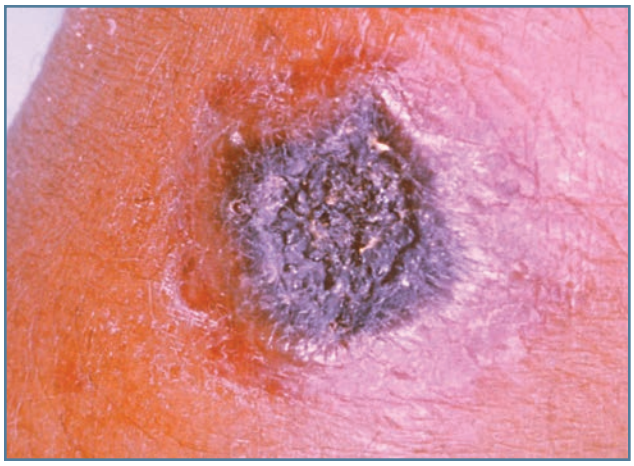


Figure 2.2.3 Anthrax.

Bartonellosis

- Infections caused by aerobic, gram-negative bacilli of the genus *Bartonella*
- Multiple different species produce a variety of cutaneous diseases

Blistering Distal Dactylitis

- Causative organism: Group A *Streptococcus* (group A strep) or *Staphylococcus aureus* (staph)
- Darkening of skin days before blister formation
- Volar fat pad of finger > toe
- Most common in children
- Treatment: Drainage and 10-day oral antibiotics with staph coverage

TABLE 2.2.1 BARTONELLA DISEASE SPECTRUM

Disease	Clinical Features	Bartonella Species	Vector	Treatment
Cat-scratch disease	Papule at inoculation site and lymphadenopathy	*B. henselae*	Cat flea—*Ctenocephalides felis* (humans infected by cat bite or scratch)	Spontaneous resolution in mild cases, azithromycin if needed Doxycycline + rifampin for severe cases
Bacillary angiomatosis	Vascular-appearing papules or nodules that can mimic pyogenic granulomas	*B. henselae* *B. quintana*	Unknown	Doxycycline or erythromycin (mild) plus gentamicin (severe)
Trench fever	Relapsing fever with nonpruritic macular eruption	*B. quintana*	Human body louse—*Pediculus humanus corporis*	Doxycycline, erythromycin
Oroya fever (Carrion's disease—acute, severe)	Fever/malaise with hemolysis and immunodeficiency with secondary infections	*B. bacilliformis*	Sand fly—*Lutzomyia verrucarum*	Chloramphenicol (because of frequent superinfection with *Salmonella*) + β-lactam Quinolone in those > 6 years old, nonpregnant
Verruga peruana (Carrion's disease—chronic, mild)	Erythematous papules and nodules with bleeding/ulceration	*B. bacilliformis*	Sand fly—*Lutzomyia verrucarum*	Azithromycin

Borreliosis

TABLE 2.2.2 BORRELIOSIS

	Borrelia Species	Vector	Clinical Features	Treatment
Lyme Disease	*B. burgdorferi* (in USA)	*Ixodes dammini (scapularis)* (northeast USA), *Ixodes pacificus* (western USA), *Ixodes ricinus* (Europe)	• Erythema migrans • Acrodermatitis chronica atrophicans	Doxycycline 100 mg orally, twice daily, for 14-21 days (pregnancy, children < 9: Amoxicillin)
Relapsing Fever: Louse-Borne (Africa, South America)	*B. recurrentis*	Human body louse *(Pediculus humanus)*	• Paroxysmal fevers (2 episodes) • Headache • Lymphocytoma • Myalgias • Erythematous or petechial macules on trunk and extremities	Doxycycline 100 mg orally × 1 dose
Relapsing Fever: Tick-Borne (Western USA)	*B. duttonii* *B. hermsii*	Soft-bodied ticks *(Ornithodoros)*	Same as louse-borne	Doxycycline 100 mg orally, twice daily, for 7 days

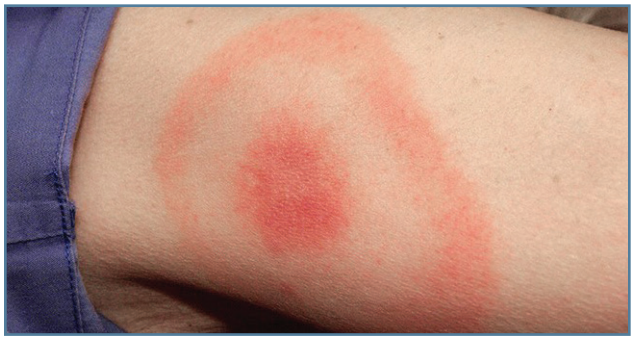


Figure 2.2.4 Borreliosis (lyme).

Botryomycosis

- Causative organisms: *S. aureus* (most common), *Pseudomonas aeruginosa, Escherichia coli, Proteus,* and other species
- Characteristic features: Chronic or subacute suppurative nodules or plaques, sinuses and fistula tracts draining purulent fluid and/or yellow granules; can involve bone
- Granular bodies on light microscopy of drainage
- Histopathology: Bacterial "grains" with basophilic center and eosinophilic periphery
- Risk factors: Immunosuppression, diabetes, trauma, alcoholism
- Treatment: Debridement and antibiotic depending on causative organism

Cellulitis

- Causative organism: Group A strep or *S. aureus* (most common in children), may be polymicrobial
- Inflammation in deep dermis and subcutaneous tissue
- Location
  - Kids—head and neck
  - Adults—lower extremities
- Treatment: 10-day course for uncomplicated infection. Consider hospitalization for systemic symptoms and facial involvement

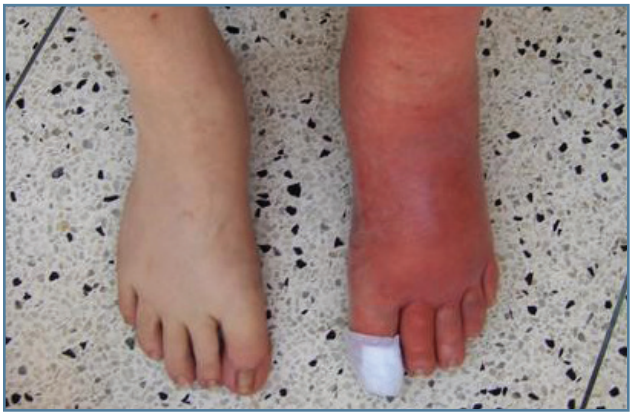


Figure 2.2.5 Cellulitis.

Ecthyma

- Causative organism: *Streptococcus pyogenes*/group A strep
- Shallow ulcer, typically with eschar, and heals with scarring

Ecthyma Gangrenosum

- Causative organism: *Pseudomonas aeruginosa*
- "Gunmetal gray," infarcts with surrounding erythema on the extremities or anogenital area in immunocompromised patients
  - Dissemination from septicemia, not direct innoculation
- Treatment: Intravenous antipseudomonal antibiotics

Erysipelas

- Causative organism: Primarily group A strep
- Sharply demarcated plaque with nonpitting edema; affects dermis and has lymphatic involvement
  - "Step off" sign
- Most common site is lower legs **although "classic" location is face**
- Systemic symptoms

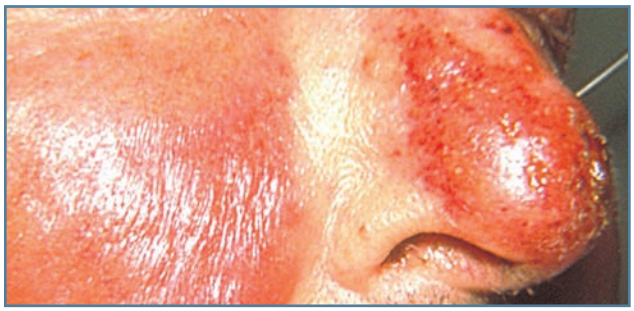


Figure 2.2.6 Erysipelas.

Erysipeloid

- Causative organism: *Erysipelothrix rhusiopathiae*—a gram-positive rod
- Typically occurs in handlers of contaminated raw fish or meat (e.g., fishermen, butchers)
- Characteristic features: Tender, well-demarcated, violaceous lesion with raised margins and central clearing, typically on the hand or finger; classic presentation involves the finger webs but spares the terminal phalanges
- Generalized form can have systemic symptoms
- Treatment: Penicillin

Folliculitis

- Causative organism: *S. aureus* is most common
  - Can be gram negative in acne patients on longer term antibiotics
    - Isotretinoin treatment of choice
- Sycosis barbae: Deep folliculitis
- Treatment: Antibiotic wash (chlorhexidine and bleach/hypochlorous acid). Topical mupirocin or clindamycin 7-10 days. Consider nasal mupirocin and antibiotic wash for temporary decolonization
- For larger area or recurrent: Oral β-lactam antibiotics, tetracycline, or macrolides
- *Pseudomonas* folliculitis can resolve spontaneously but consider ciprofloxacin

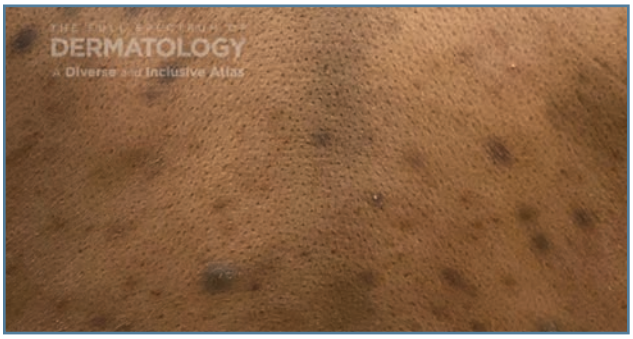


Figure 2.2.7 Folliculitis.

Glanders

- Causative organism: *Burkholderia mallei*
- Disease caused by contact with infected horses
- Characteristic features: Ulcerated nodule with possible sporotrichoid pattern and lymphadenopathy
- Treatment: Imipenem or doxycycline

Impetigo

- Causative organism: Both bullous and nonbullous (70% of cases) are most commonly *S. aureus*, then group A β-hemolytic strep. When *S. pyogenes,* can lead to acute glomerulonephritis (not affected by treatment)
- Most common skin infection in children
- Bullous impetigo: ETA/ETB, *S. aureus* group II phage type 71
  - Toxin target: Desmoglein 1 **(DSG1)**
- Treatment: Mupirocin if limited, oral or IV could be needed for systemic symptoms or large area. Consider resistance patterns

Figure 2.2.8 Impetigo.

Meningococcemia

- Causative organism: *Neisseria meningitidis* (a gram-negative diplococcus)
- Affects young children and patients with **complement C5-C9 deficiencies** or asplenia
- Characteristic features: Petechiae that often progress to large ecchymotic or necrotic areas on trunk and extremities; fever, chills, meningitis, hypotension
- Treatment: IV penicillin or ceftriaxone

Necrotizing Fasciitis

- Causative organism: Most common is group A strep, can be polymicrobial (can also be fungal)
- Rapid progression of subcutaneous fat necrosis
- Disproportionate pain or lack of pain
- Fournier gangrene (in groin) often polymicrobial
- Treatment: Antibiotics based on culture. Hyperbaric oxygen and IV immunoglobulin may have some benefit

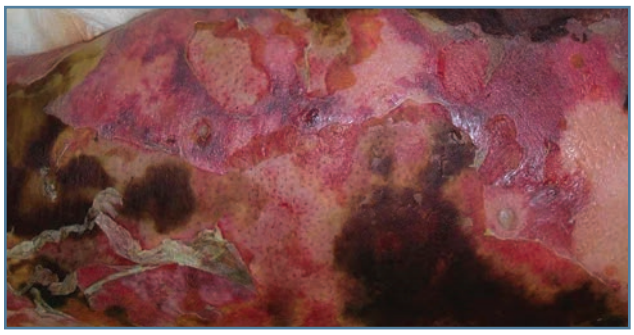


Figure 2.2.9 Necrotizing fasciitis.

Paronychia

- Causative organism: Acute paronychia most commonly due to *S. aureus* or *Strep. pyogenes*
- Follows minor trauma to the nail
- If chronic, consider *Candida*. If recurrent, consider herpes simplex virus (HSV)
- Treatment: Drain abscess and administer oral antibiotic or antiviral

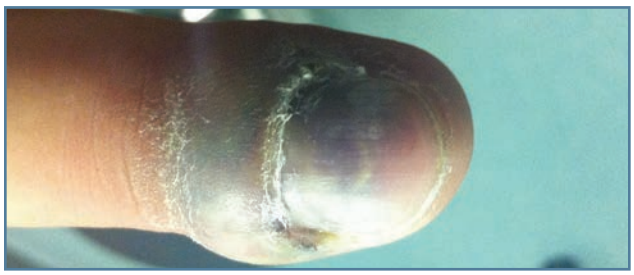


Figure 2.2.10 Paronychia.

Perianal Strep

- Causative organism: Group A strep (perianal dermatitis can also be from staph, intertrigo, or allergic contact dermatitis)
- Sharply demarcated tender erythematous plaque in perianal region, most common in children

Pitted Keratolysis

- Causative organism: *Kytococcus sedentarius* most common
  - Woods lamp exam negative
- Characteristic features: Shallow 1- to 3-mm pits on plantar surface of feet; malodor and hyperhidrosis are common
- Treatment: Topical erythromycin, clindamycin, or benzoyl peroxide. Consider aluminum chloride

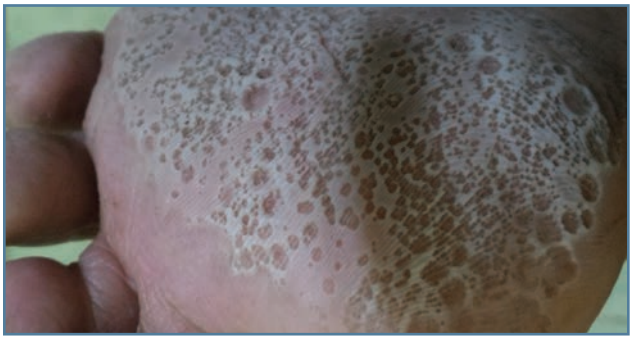


Figure 2.2.11 Pitted keratolysis.

Purpura Fulminans

- Causative organism: Any overwhelming systemic infection with disseminated intravascular coagulation (DIC). Usually group A strep, *Neisseria meningitidis,* methicillin-resistant *Staphylococcus aureus* (MRSA)
- Hemorrhagic infarction of the skin caused by DIC
- Symmetric, large ecchymotic areas with irregular ("geographic") borders on extremities, ears, and nose, most commonly
- Associated with **protein C deficiency**
- Treatment: Treat DIC, surgical treatment as needed, organism-specific antibiotic treatment

Rat Bite Fever

- Causative organism: *Streptobacillus moniliformis*
- Infection acquired from rodents or contaminated food
- Characteristic features: Fever, migratory polyarthritis, rash (acral erythematous macules or papules, which can become generalized)
- Treatment: Penicillin

Rhinoscleroma

- Causative organism: *Klebsiella pneumoniae* subsp. *rhinoscleromatis*
- Characteristic features: Progressive hypertrophic plaques on external nares
- Mikulicz cells on histopathology (foamy macrophages containing bacilli)
- Treatment: Tetracycline and surgical treatment, ciprofloxacin and rifampin as well

Figure 2.2.12 Rhinoscleroma.

Scarlet Fever

- Causative organism: Group A strep
- Pyrogenic exotoxins types A, B, and C
- Children 2-10 years of age, from tonsillitis or pharyngitis
- Exanthem: Diffuse erythematous eruptions on neck, chest, and intertriginous areas 12-48 hours after sore throat, then generalized with "sandpaper texture," linear petechial patches in axillae and antecubital fossae, cheeks flushed with circumoral pallor, palatal petechiae. Desquamation 1 week later
- Enanthem: Exudative pharyngitis, strawberry tongue
- Complications: Rheumatic fever, acute glomerulonephritis, and other systemic issues

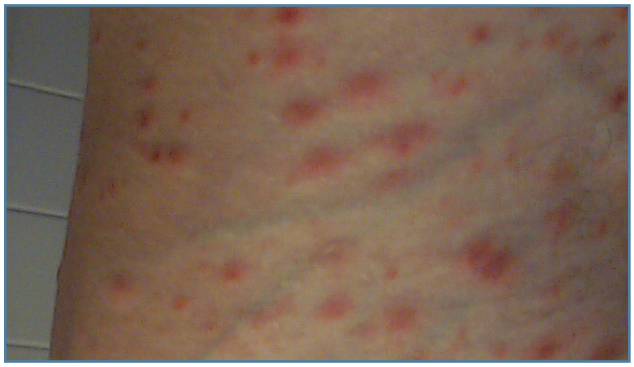


Figure 2.2.13 Scarlet fever.

Staph Scalded Skin Syndrome

- Causative organism: *S. aureus* (group 2 phage type 71)
- Hematogenous dissemination of exfoliative toxins
- Cleavage in granular layer (stratum granulosum)
- Infants/children, male > female
- Focus is nasopharynx and conjunctiva in children and pneumonia in adults
- Starts head and intertriginous, may have fever/malaise, nonscarring
- **No organisms seen on Gram stain on pathology.** Culture mostly negative (can be positive in adults). Culture of blisters negative
- Slide latex agglutination, double immunodiffusion or ELISA can identify toxins
- Treatment: Oral β-lactamase × 1 week or more for mild cases and hospitalization with parenteral antibiotics for severe cases

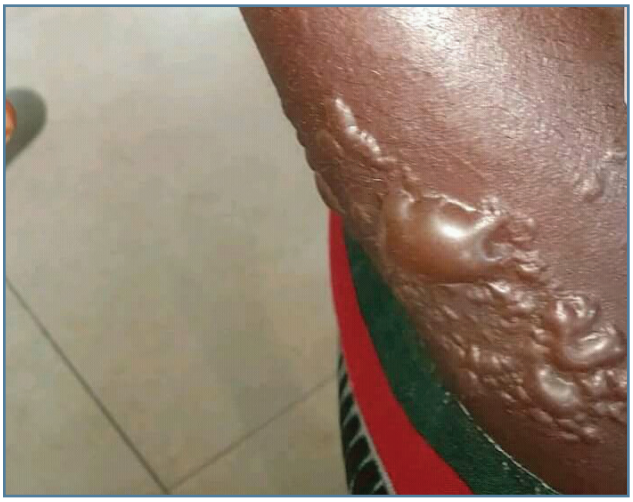


Figure 2.2.14 Staph scalded skin syndrome.

TIP

ETA chromosomal encoded
ETB plasmid encoded
Serine proteases that bind and cleave desmoglein 1

Toxic Shock Syndrome

- Causative organism: *S. aureus* and strep
  - Staph causes more skin symptoms than strep
  - **Strep more likely to have positive blood culture and localized soft tissue infection and higher mortality**
- Exotoxin/TSST-1 binds MHC class II and V_β of T-cell receptors in non-antigen-specific manner, "cytokine storm"
- Rapid high fever, myalgias, vomiting/diarrhea with rapid hypotensive shock

- Exanthem: Erythema or scarlatiniform, trunk to extremities. Erythema of palms/soles, strawberry tongue, hyperemia of conjunctiva. Desquamation 1-2 weeks after
- Treatment: Treat hypotension. Remove possible source of infection. β-Lactamase-resistant antibiotics. Clindamycin (suppress protein) and IV immunoglobulin may help neutralize toxin
- **Neonatal TSS-like exanthematous disease is mild version due to immature T cells in newborns**

Trichomycosis Axillaris

- Causative organism: *Corynebacterium tenuis*
- Characteristic features: Yellowish brown concretions on axillary hair shafts
- Treatment: Shaving; benzoyl peroxide gel; topical erythromycin

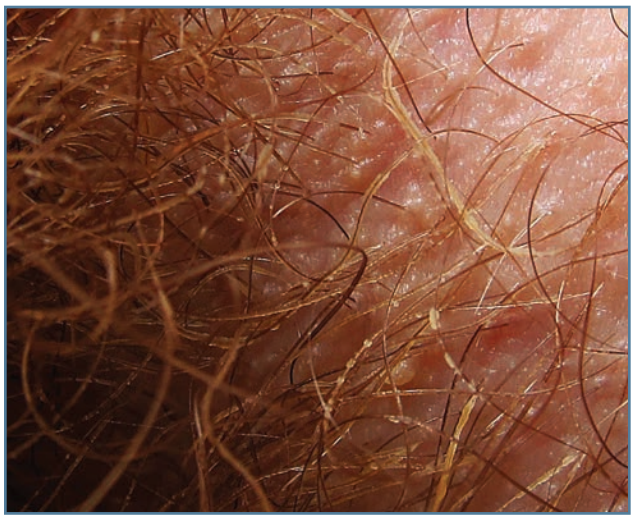


Figure 2.2.15 Trichomycosis axillaris.

Tularemia

- Causative organism: *Francisella tularensis*
- Most commonly caused by contact with infected rabbits (e.g., hunters) or tick bite
- **Ulceroglandular form is the most common**—chancre-like ulcer with raised borders and regional lymphadenopathy; typically on finger or hand
- Other forms: Glandular, chancriform, oculoglandular, typhoidal, pulmonary, oropharyngeal, *vibrio*, and meningeal
- Treatment: Streptomycin

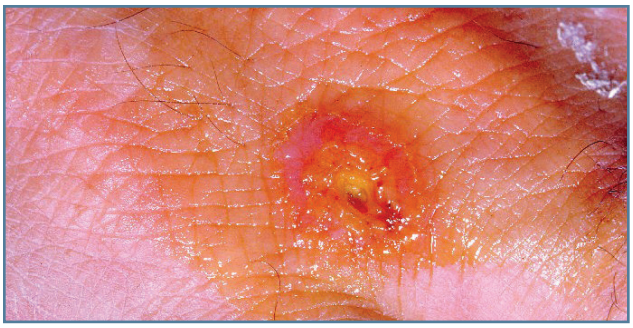


Figure 2.2.16 Tularemia.

MYCOBACTERIAL INFECTIONS

Leprosy

- Causative organism: *Mycobacterium leprae* and *Mycobacterium lepromatosis*
  - Obligate intracellular acid-fast rod
  - Requires cooler temperatures to grow
  - Affects macrophages and Schwann cells
- Characteristic features
  - Transmitted from human to human most likely via airborne droplets. Armadillos are heavily infected and are a source in the USA. Can live outside the body for short periods
  - Granulomatous inflammation around peripheral nerves
  - Sensation changes, muscle atrophy, contractures, decreased sweating, dry eyes and nasal mucosa, madarosis, saddle nose, gynecomastia
  - Spectrum of disease based on cell-mediated immune response (see Table 2.2.3)
  - The polar forms of leprosy, tuberculoid (TT) and lepromatous (LL), do not evolve into any other form throughout the course of the disease
  - Indeterminate leprosy: Usually a solitary lesion; no sensory loss; can progress into lepromatous, tuberculoid, or borderline leprosy

Figure 2.2.17 Leprosy.

- Treatment (WHO recommendations)
  - Paucibacillary:
    - Dapsone 100 mg (oral, daily) for 6 months
    - Rifampin 600 mg (oral, monthly) for 6 months
  - Multibacillary:
    - Dapsone 100 mg (oral, daily) for 12 months
    - Clofazimine 50 mg (oral, daily) or 300 mg monthly for 12 months
    - Rifampin 600 mg (oral, monthly) for 12 months

TABLE 2.2.3 LEPROSY DISEASE SPECTRUM

TT	BT	BB	BL	LL
Th1 cytokine profile: IFN-γ, IL-2 Paucibacillary Few bacilli Lepromin test result positive				Th2 cytokine profile: IL-4, IL-10 Multibacillary Many bacilli Lepromin test result negative
≤5 lesions	Few lesions, asymmetric	Many lesions, asymmetric	Numerous lesions, likely symmetric	Generalized and symmetrical distribution

- Type 1 reaction
  - Affects all forms other than indeterminate, most common in borderline
  - **Enhanced cell-mediated immunity, Th1**
  - **Inflammation of established skin lesions, neuritis**
  - Treatment: Prednisone
- Type 2 reaction: Erythema nodosum leprosum
  - Affects BL/LL > BB
  - **Humoral immunity, Th2**
  - Bright pink, painful nodules arising in normal-appearing skin
  - Systemic symptoms: Fever, malaise, arthralgias, orchitis, hepatosplenomegaly, glomerulonephritis
  - Typically occurs after initiation of therapy but may be much later
  - Treatment: Thalidomide
- Lucio phenomenon
  - Necrotizing cutaneous small-vessel vasculitis

Tuberculosis

TABLE 2.2.4 TUBERCULOSIS OF THE SKIN

Tuberculosis Verrucosa Cutis	Tuberculous Chancre	Scrofuloderma	Tuberculosis Cutis Orificialis	Lupus Vulgaris	Tuberculous Gumma	Miliary Tuberculosis
Exogenous reinfection	Primary exogenous inoculation	Contiguous spread from underlying infection	Autoinoculation from underlying advanced visceral tuberculosis	Hematogenous, lymphatic, or contiguous spread from distant site	Hematogenous spread	Hematogenous spread
Sensitized host with strong immunity	Nonsensitized host	Sensitized host with low immunity	Sensitized host with diminishing immunity	Sensitized host with high immunity	Immunosuppressed host	Low-immunity host
Paucibacillary	Pauci- or multibacillary	Pauci- or multibacillary	Multibacillary	Paucibacillary	Multibacillary	Multibacillary
Most common cutaneous form Slowly growing verrucous plaques with irregular borders Typically on hand	Painless red-brown papule that ulcerates Tuberculous primary complex: Regional lymphadenopathy, 3-8 weeks postinfection	Subcutaneous nodules with purulent or caseous drainage May develop sinuses and ulcers with granulating bases Occurs most commonly over cervical lymph nodes	Papule that forms punched-out ulcers with undermined edges On mucocutaneous junctions of mouth, genitalia	Brownish-red annular plaque with central scarring "Apple-jelly" color on diascopy Head/neck involvement in 90% of cases	Subcutaneous abscesses May form fistulas and ulcers Typically on trunk, head, or extremities	Disseminated erythematous papules with vesicles/umbilication Heal with scarring From fulminant tuberculosis of the lung or meninges

Mycobacterium Fortuitum Complex

- *M. fortuitum, M. chelonae, M. abscessus*
- **"Rapid growers"**
- Found in soil, water, and animals
- Infections occur after exposure to contaminated surgical instruments, trauma, contaminated tattoo ink or medications, or in immunocompromised hosts
- Typically presents with single or multiple erythematous subcutaneous nodules on an extremity—sometimes sporotrichoid
- Systemic involvement can also occur
- Treatment: Surgical drainage/debridement followed by course of antimicrobial therapy (amikacin, clarithromycin, ciprofloxacin, imipenem, and others)

Mycobacterium Marinum Infection

- *M. marinum*—swimming pool/aquarium granuloma
- Begins as small papule at site of inoculation and evolves into a nodule or granulomatous plaque, often with a verrucous surface
- Sporotrichoid spread can occur
- Treatment: Minocycline or clarithromycin

VIRAL INFECTIONS

TABLE 2.2.5 DNA VIRUSES

Virus Group	Major Examples
Herpesvirus	Herpes simplex virus (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV)
Hepadnavirus	Hepatitis B virus
Adenovirus	Numerous serotypes
Papillomavirus	Human papillomavirus (HPV)
Parvovirus	Human parvovirus B19
Poxvirus	Molluscum contagiosum virus, smallpox virus, orf virus, milker's nodule virus

TABLE 2.2.6 RNA VIRUSES

Virus Group	Major Examples
Paramyxovirus	Measles virus, mumps virus
Togavirus	Rubella virus
Rhabdovirus	Rabies virus
Retrovirus	HIV, HTLV

TABLE 2.2.6 RNA VIRUSES CONTINUED

Virus Group	Major Examples
Picornavirus	Enterovirus: Coxsackievirus (hand, foot, and mouth disease)
Flavivirus	Hepatitis C virus (HCV), dengue virus, yellow fever virus, West Nile virus

Human Herpesvirus

TABLE 2.2.7 HUMAN HERPESVIRUS TYPES

Abbreviation	Name
HHV-1	Herpes simplex virus
HHV-2	Herpes simplex virus
HHV-3	Varicella-zoster virus
HHV-4	Epstein-Barr virus, DRESS (drug reaction with eosinophilia and systemic symptoms)
HHV-5	Cytomegalovirus, DRESS
HHV-6	Roseola, pityriasis rosea, DRESS
HHV-7	Roseola, pityriasis rosea, DRESS
HHV-8	Kaposi's sarcoma, Castleman disease

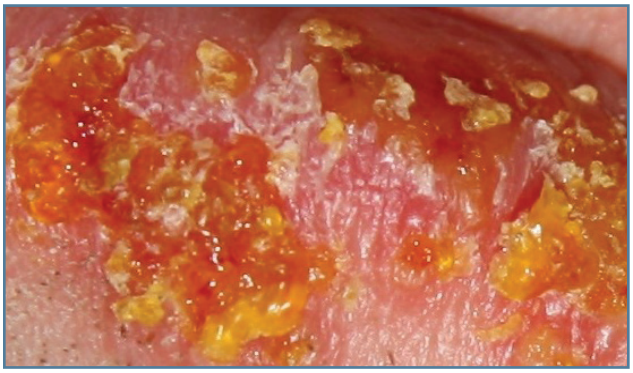


Figure 2.2.18 Herpes.

Herpes Simplex Virus (HHV-1, HHV-2)

- Virus replicates at the site of infection and then travels retrograde to the dorsal root ganglia
- Incubation time 3-7 days. Lymphadenopathy and systemic symptoms may precede skin findings in primary infection, but majority are asymptomatic
- HSV-1
  - HSV-1 more common on the oral area and HSV-2 on genital area, but both can present in either area

- Oral HSV-1 becomes recurrent in 20-40% of cases
- Genital HSV-1 is less likely to be recurrent compared with genital HSV-2
- HSV-1 is the most common cause of: Eczema herpeticum, herpetic whitlow, herpes gladiatorum, herpes folliculitis, ocular HSV in children or adults, herpes encephalitis

- HSV-2
  - HSV-2 tends to be eventually symptomatic in 50% of carriers
  - HSV-2 may increase risk of transmission of HIV
  - HSV-2 is the most common cause of ocular HSV in newborns
- Neonatal herpes simplex
  - Clinical spectrum ranges from localized skin lesions to multisystemic infection with encephalitis, hepatitis, pneumonia, and coagulopathy
  - Systemic risk is highest in those who acquire HSV as a primary infection around the time of delivery
  - Use of **scalp electrodes** may increase risk of transmission
  - In utero infections rare and associated with fetal anomalies—microcephaly, encephalitis, intracranial calcifications
- Treatment
  - Acyclovir, famciclovir, valacyclovir
  - **For acyclovir-resistant HSV (most commonly due to thymidine kinase-deficient strains of HSV): Foscarnet and cidofovir**

Varicella-Zoster Virus (HHV-3)

- Distinguishing features (compared with smallpox)
  - Absent or mild prodrome
  - Lesions begin on face and spread to trunk, relative sparing of distal extremities
  - "Dew drops on a rose petal"—superficial vesicle with erythematous halo
  - Lesions in different stages of evolution
  - Rapid evolution (<24 hours) of lesions from macule-papule-vesicle-crust
- Varicella in pregnancy
  - First 20 weeks of gestation: Congenital varicella syndrome—hypoplastic limbs, ocular and CNS abnormalities
  - **5 days before and 2 days after delivery: Neonatal varicella—neonate develops varicella at 5 to 10 days of age because of inadequate transplacental delivery of maternal anti-varicella antibodies; treat with varicella zoster immunoglobulin (VZIG) + IV acyclovir**
- Ramsay Hunt syndrome: VZV infection of **geniculate ganglion** of facial nerve. May cause facial paralysis, tinnitus or other auditory and oral symptoms. Clinical clue: Vesicles on external ear and ear canal
- Hutchinson's sign: Increased (50%) risk of ocular involvement with lesion on nasal tip, dorsal nose, or nasal root (**nasociliary** branch of ophthalmic nerve)

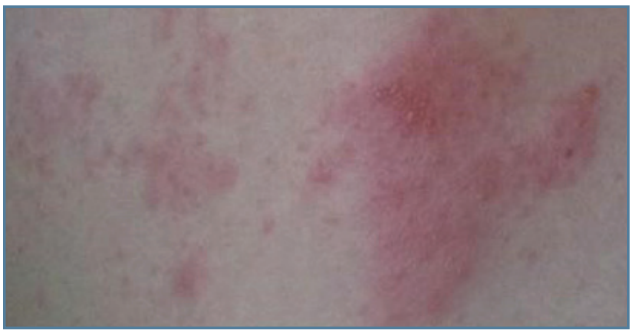


Figure 2.2.19 Varicella-zoster virus.

Epstein-Barr Virus (HHV-4)

- Infects **B lymphocytes**
- Associated with numerous disorders including infectious mononucleosis, oral hairy leukoplakia, hydroa vacciniforme, Gianotti-Crosti syndrome, nonsexual genital ulcers, and lymphoproliferative disorders (Burkitt lymphoma—Africa; nasopharyngeal carcinoma—Asia)
- Primary infection tends to be asymptomatic in children, but 50% of young adults develop mononucleosis
- Skin eruption can have different morphologies: Urticarial, erythema multiforme, petechial, genital ulcers
- Infectious mononucleosis
  - Incubation 1-2 months
  - Can have morbilliform eruption after treatment with ampicillin
  - Splenic rupture after trauma and other systemic complications (hepatitis, anemia, glomerulonephritis, etc.)

Cytomegalovirus (HHV-5)

- Skin eruption is rare, multiple morphologies
  - Petechial, urticarial, erythema nodosum
  - Extramedullary hematopoiesis ("blueberry muffin") in congenital infection
  - Can also have morbilliform eruption after treatment with ampicillin
- Most common congenital viral infection (TORCH)
  - **#1 infectious cause of deafness and intellectual disability in USA**

Roseola Infantum (Exanthem Subitum, Sixth Disease) (HHV-6, HHV-7)

- Most commonly affects infants and toddlers; **reactivation in immunosuppressed patients**
- High fever (can lead to febrile seizures) that resolves days later when sudden asymptomatic **pink macules** and papules with white halos develop on trunk/extremities
- Enanthem of red papules on soft palate **(Nagayama's spots)**
- Periorbital edema is common

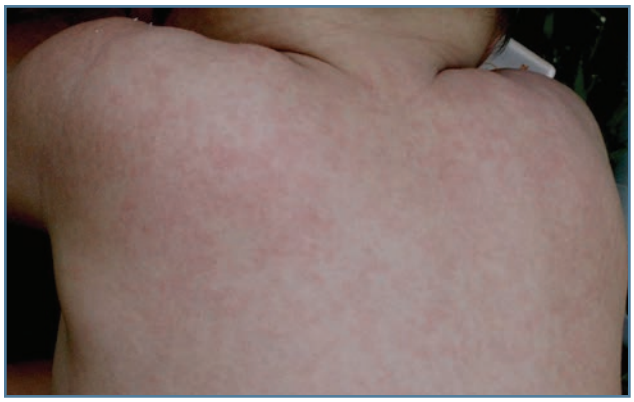


Figure 2.2.20 Exanthem subitem.

Kaposi's Sarcoma (HHV-8)

- Subtypes
  - Mediterranean: Older men, lower legs, slowly progressive
  - African: Men and young children, range of clinical presentation from indolent to aggressive
  - AIDS-related/immunosuppression-associated: More widespread, including systemic

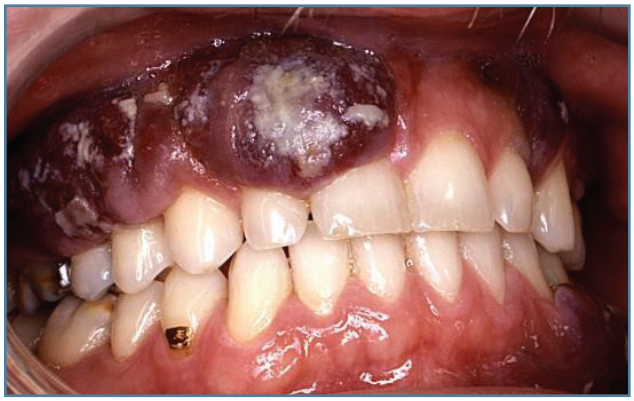


Figure 2.2.21 Kaposi's sarcoma.

Human Papillomavirus

- Nonenveloped double-stranded DNA virus
- Genome encodes "E" (early) and "L" (late) proteins
- E proteins (E1-E8): Participate in viral DNA replication. Several E proteins, including E6 and E7, are cancer promoting
- L proteins (L1 and L2): Structural proteins that form the virion (the outer shell of the virus)
- **Epidermodysplasia verruciformis (genodermatosis) and impaired cellular immunity predisposes to HPV**

TABLE 2.2.8 HUMAN PAPILLOMAVIRUS TYPES

HPV Type	Type of Wart
1, 2, 27, 57	Common, palmoplantar
3, 10	Flat
7	Butcher's
6, 11	Condyloma acuminata, Buschke-Lowenstein, conjunctival papillomas, recurrent respiratory papillomatosis
16, 18, 31, 33-35	High-risk anogenital/cervical; bowenoid papulosis
13, 32	Heck's disease
3, 5, 8	Epidermodysplasia verruciformis
5, 8	Epidermodysplasia verruciformis—squamous cell carcinoma

Cutaneous Signs of COVID-19

Chilblain-like Eruptions on Fingers and Toes

- "Covid finger and toes" are more common in younger patients and those with mild disease
- No association with cold exposure
- Clinical findings
  - Erythematous violaceous papules, macules, vesicles, bullae on feet/toes > hands/fingers
  - Lesions can be asymptomatic, pruritic or painful.
  - Usually asymmetrically distributed
  - Lesions are self-limited and typically disappear after 2 weeks

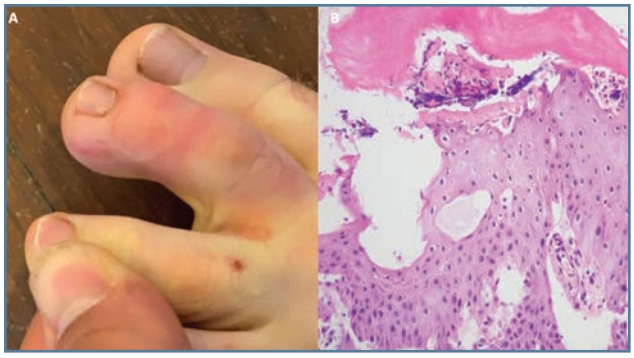


Figure 2.2.22 Chilblain-like eruptions on toes.

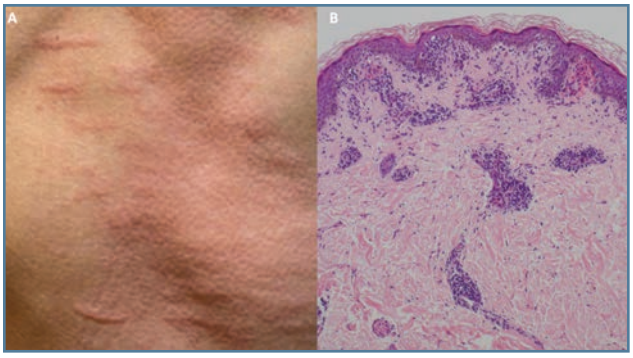


Figure 2.2.23 Urticarial rash due to COVID-19.

Acro-Ischemia

- This signifies severe disease. Severe COVID-19 can lead to a hypercoagulable state and disseminated intravascular coagulation
- Clinical findings
  - Acro-ischemia with finger and toe cyanosis
  - Cutaneous bullae
  - Livedoid/necrotic lesions
  - Dry gangrene

Petechial/Purpuric Rash

- This appears to be a symptom of milder COVID-19 disease
- Clinical findings
  - Purpura and petechiae in a symmetric periflexural distribution sparing palmoplantar skin and mucosa
- Histopathology shows a perivascular lymphocytic infiltrate with abundant red cell extravasation

Vesicular Rash

- Clinical findings
  - Pruritic, small monomorphic vesicles (chickenpox-like) with surrounding erythema distributed on the trunk

Urticarial Rash

- Seen in the early phase of infection. Urticaria may be the first sign of COVID-19
- Clinical findings
  - Pruritic, erythematous wheals on face/upper body > lower body

Erythema Multiforme-like Rash

- Erythema multiforme-like lesions seen in children and adults
- Associated with a mild COVID-19 course.
- Clinical findings
  - Annular erythemato-violaceous patches with a dusky center coalescing into large patches. Typically spares palms and soles (unlike erythema multiforme)

Pityriasis Rosea-like Eruptions

- Clinical findings
  - Erythematous scaly, annular/oval papules and plaques that is preceded with a herald annular plaque with trailing scale

Leucocytoclastic Vasculitis

- Clinical findings
  - Purple palpable papules more common on the legs and lower trunk

Oral Mucosa Lesions

- Painful ulcers and blisters in the oral cavity (desquamative gingivitis)

Other Viral Infections

Hand, Foot, and Mouth Disease

- Coxsackievirus A16/A10 (A16 atypical) or enterovirus 71
- Oral-oral and fecal-oral modes of transmission
- Erythematous papules with grayish vesicle and surrounding red areola are characteristic cutaneous lesions
- Onychomadesis following resolution

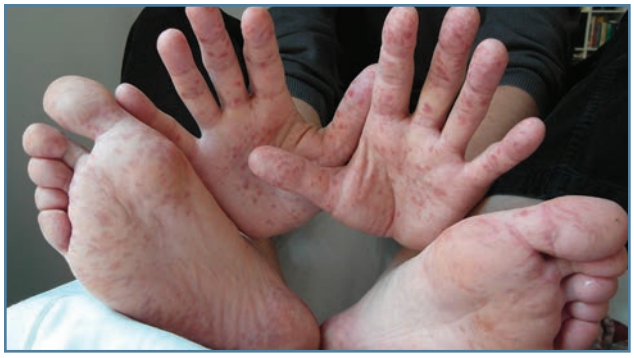


Figure 2.2.24 Coxsackievirus.

Herpangina

- Group A and B coxsackievirus and echovirus
- Fever, headache, cervical lymphadenopathy, and petechiae
- Gray-white papulovesicles in oral mucosa that ulcerate (commonly present on tonsillar fauces, palate)

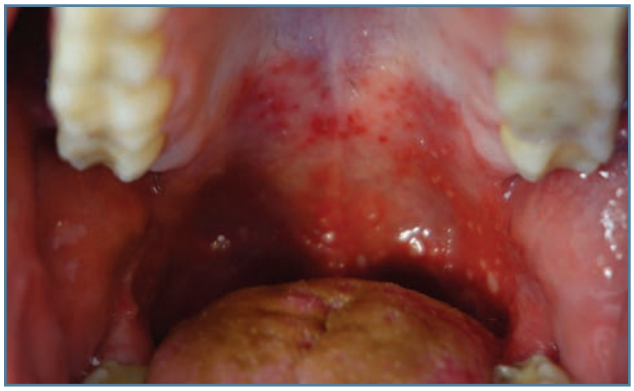


Figure 2.2.25 Herpangina.

Measles

- Caused by measles virus, an RNA paramyxovirus
- Respiratory droplet spread, incubation time 10-14 days
- High fever, "3 C's:" Cough, coryza (rhinitis), conjunctivitis
- Erythematous macules and papules begin on face and then generalize
- Koplik spots—gray-white papules on buccal mucosa
- Complications: Otitis, pneumonia, encephalitis, myocarditis
- Subacute sclerosing panencephalitis
- Delayed neurodegenerative disorder; can occur many years later; seizures, personality changes, coma, death
- Treatment: **Vitamin A can reduce morbidity**

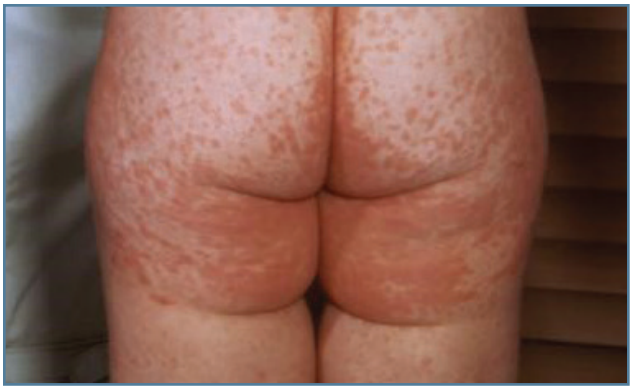


Figure 2.2.26 Measles.

Milker's Nodule

- Caused by paravaccinia virus, a poxvirus of the genus *Parapoxvirus*
- Transmitted to humans from infected cows
- Typically presents as a single 1-cm erythematous nodule on the finger or forearm, but multiple possible
- Self-limited

Molluscum Contagiosum

- Caused by molluscum contagiosum virus (MCV), a poxvirus
- HIV patients usually have diagnosis of AIDS and T-cell count < 100
- Treatment: None (self-limited). If symptomatic, destructive therapies or topical immunomodulatory therapies. Imiquimod does not seem to work alone

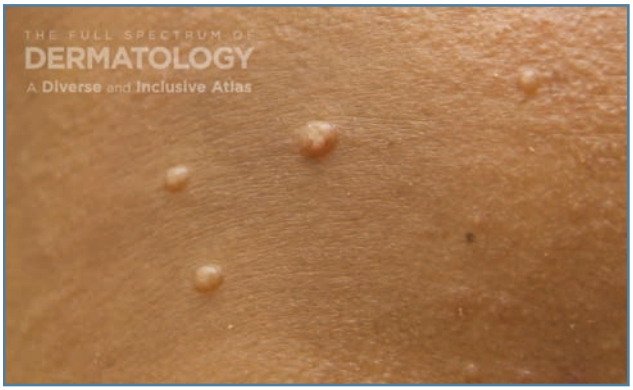


Figure 2.2.27 Molluscum contagiosum.

Orf

- Caused by orf virus (OV), a poxvirus of the genus *Parapoxvirus*
- Endemic in sheep, goats, and reindeer, presenting as nodules on the face and udders
- Most common in shepherds, farmers, and veterinarians
- Typically presents as a papule/nodule on the dorsal index finger

- Six stages, each lasting 6 days
  1. Papular—red papule
  2. Target—nodule with erythematous center, white middle ring, and erythematous halo
  3. Acute—red, weeping nodule
  4. Regenerative—crust with black dots on surface of nodule
  5. Papillomatous—small papillomas
  6. Regressive—lesion crusts, flattens, and ultimately resolves

Parvovirus B19

- Single-stranded DNA virus
- Tropism for erythroid progenitor cells; "P antigen" (globoside) on cells binds virus. Can cause aplastic crisis in susceptible individuals
- Children: Erythema infectiosum (fifth disease) —"slapped cheek" appearance, then lacy rash
- Adults: Acute arthropathy with fever and adenopathy; acral, flexural, petechial rash
- Papular purpuric **"gloves and socks" syndrome (PPGS):** Erythema, petechiae, and edema on hands and feet along with fever and oral erosions (can also be coxsackievirus, HHV-6, EBV)
- In erythema infectiosum, onset of the rash coincides with IgG antibody formation; hence, patients are noncontagious when rash develops
- However, patients with PPGS are contagious when rash is present

Figure 2.2.28 Parvovirus B19.

TIP

Pregnancy: Hydrops fetalis, spontaneous abortion (highest risk in first half of pregnancy)

Rubella

- RNA togavirus
- Erythematous macules and papules begin on face—rash then spreads to trunk in 24 hours (disappearing as it spreads) with lymphadenopathy
- Congenital infection: **Most common if acquired in first 16 weeks**
  - Cataracts, deafness, congenital heart defect, and CNS abnormalities

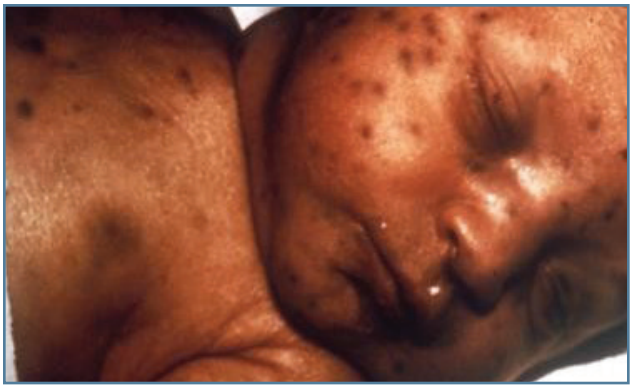


Figure 2.2.29 Rubella.

MNEMONIC

TORCH Syndrome
Toxoplasmosis
Other (syphilis, bacterial sepsis)
Rubella
CMV
HSV

SEXUALLY TRANSMITTED INFECTIONS

Syphilis

- Causative organism: *Treponema pallidum* (a spirochete)
- Clinical features
  - Primary Chancre—ulcer with raised, indurated borders, lymphadenopathy
    - Occurs 10 days to 3 months after exposure. Lasts 3-12 weeks
  - Secondary Variable involvement of skin and mucous membranes
    - Widespread cutaneous eruptions, ham-colored macules on the palms and soles, mucous patches, condylomata lata, split papules, "moth-eaten" alopecia
    - Lasts 1-3 months
- Latent
  - Early (<1 year)
  - Late (>1 year)
- Tertiary
  - Late benign—no cardiovascular or CNS involvement; gummas

- Cardiovascular syphilis
- Neurosyphilis

- Congenital
  - Early (<2 years of age)
    - Low birth weight
    - Bone disease ("saw-tooth" appearance of metaphysis). Painful
    - Rhinitis ("snuffles")
    - Rhagades (Parrot's lines)
    - Lymphadenopathy (epitrochlear)
    - Neurosyphilis
  - Late (>2 years of age)
    - **Hutchinson's triad**
      - Hutchinson's teeth (widely spaced, peg-shaped upper incisors)
      - Eighth nerve deafness
      - Interstitial keratitis
    - Mulberry molars
    - High-arched palate
    - Saddle nose
    - Saber shins
    - Clutton's joints (nontender, bilateral swelling of knees)
    - Higoumenakis' sign (unilateral enlargement of medial clavicle)
    - Retinitis
    - Gummas—nose and palate
    - Dactylitis

TIP

Hutchinson's Triad

1. Hutchinson's teeth
2. Hutchinson's nerve deafness
3. Interstitial keratitis

- Serology
  - Nontreponemal (cardiolipin antibodies)
    - VDRL: **Reactive 4-5 weeks after infection;** often reverts to nonreactive during late latent stage. Nonreactive after treatment
    - RPR: Similar features as VDRL
    - Causes of false positive nontreponemal test results
      - Other spirochete infection (leptospirosis, Lyme disease, relapsing fever, rat bite fever, yaws/pinta)
      - Pregnancy
      - Viral infections (CMV, HIV, infectious mononucleosis)
      - Autoimmune diseases (antiphospholipid syndrome, systemic lupus erythematosus [SLE])
      - Malaria
      - Lepromatous leprosy
      - Drug abuse
  - Treponemal (antibodies to surface proteins of *T. pallidum*)
    - Fluorescent treponemal antibody absorption (FTA-ABS) test
      - Positive by 3rd week of infection. Remains positive after treatment
      - The most sensitive serologic test in primary syphilis
    - MHA-TP: Similar serologic features as FTA-ABS, except less sensitive during primary syphilis
    - Enzyme-linked immunosorbent assay (ELISA) (IgM) EIA
      - First to become reactive, less sensitive in late disease because of reduction in IgM production
      - 100% specificity

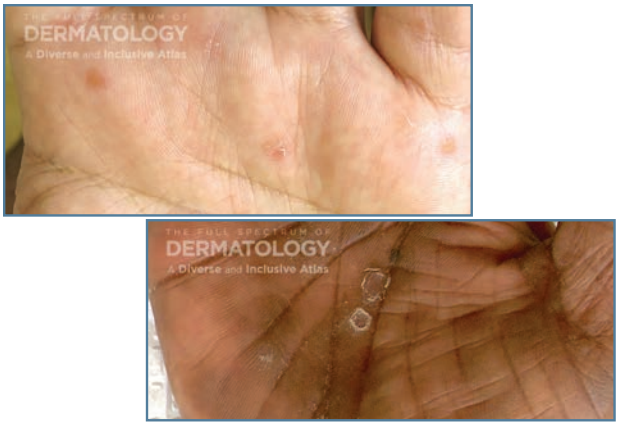


Figure 2.2.30 Syphilis.

- Treatment
  - Primary and secondary (without end-organ involvement)
    - Early latent
      - Benzathine penicillin G, 2.4 million units IM × 1 dose
      - Penicillin allergy: Doxycycline 100 mg orally, twice daily, for 2 weeks
    - Indeterminate or late latent and tertiary (without neurosyphilis)
      - Benzathine penicillin G, 2.4 million units × 3 doses, 1 week apart
      - Penicillin allergy: Doxycycline 100 mg orally, twice daily, for 28 days

TABLE 2.2.9 SEXUALLY TRANSMITTED INFECTIONS

	Gonococcemia	Chancroid	Granuloma Inguinale	Lymphogranuloma Venereum
Causative organism	*Neisseria gonorrhoeae*	*Haemophilus ducreyi*	*Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*)	*Chlamydia trachomatis* *L1, L2, L3*
Clinical features	Sparsely distributed hemorrhagic vesiculopustules with erythematous bases on palms, soles, and over **joints** Fever, chills, arthralgias, malaise Recurrent cases may be associated with complement deficiencies (especially C5-C8)	Soft, painful/tender chancre with ragged edges **"School of fish"** on Gram or Giemsa stain	Primary lesion: Papule, subcutaneous nodule (pseudobubo), or ulcer Four clinical forms: (1) Ulcerovegetative (most common), (2) nodular, (3) hypertrophic, and (4) cicatricial **Donovan bodies** ("safety-pin"-shaped intracytoplasmic inclusions in macrophages) seen on microscopy	Painless, soft erosion that heals spontaneously Secondary inguinal adenopathy with fluctuant, tender nodes above and below Poupart's ligament—**"groove sign"** (can be bilateral) Serologic diagnosis by complement fixation test
Treatment	Ceftriaxone IV	Azithromycin Ceftriaxone Ciprofloxacin Erythromycin	TMP-SMX Doxycycline Erythromycin Ciprofloxacin	Doxycycline

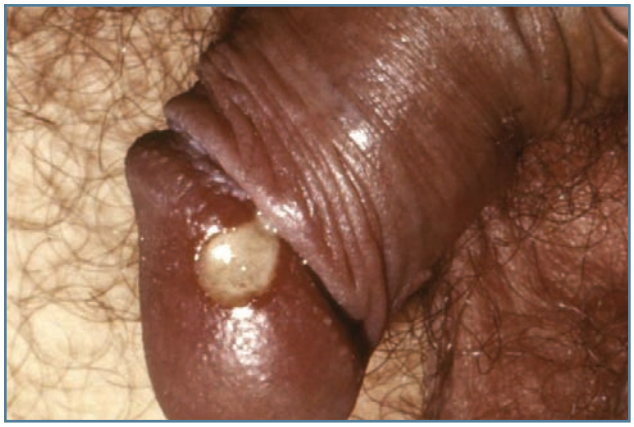


Figure 2.2.31 Chancroid.

- Neurosyphilis and ocular syphilis
  - Aqueous penicillin G, 3-4 million units IV every 4 hours × 10-14 days
  - Penicillin allergy: Ceftriaxone 2 g IM/IV for 10-14 days
- Complications of treatment: Jarisch-Herxheimer reaction (fever, lymphadenopathy, flare of skin lesions, elevated white count) is caused by the release of inflammatory cytokines, particularly TNFα, due to phagocytosis of spirochetes following antibiotic administration

NONVENEREAL TREPONEMATOSES

Pinta

- Central/South America
- *Treponema carateum*
- Primary macules on the lower extremities enlarge into plaques
- Secondary "pintids" start as small scaly papules that enlarge into psoriasiform plaques
- Tertiary pinta has depigmented vitiligo-like lesions (not infectious)

Yaws

- Africa, Asia, and Central/South America
- *Treponema pallidum pertenue*
- Primary painless papule, "mother yaw," that ulcerates and then heals spontaneously. Mostly lower extremities in children
- Secondary "daughter yaws" are smaller lesions that develop afterward in a larger distribution
- Final stage forms abscesses and necrosis and can affect bones and lead to "saber shins" and other deformities

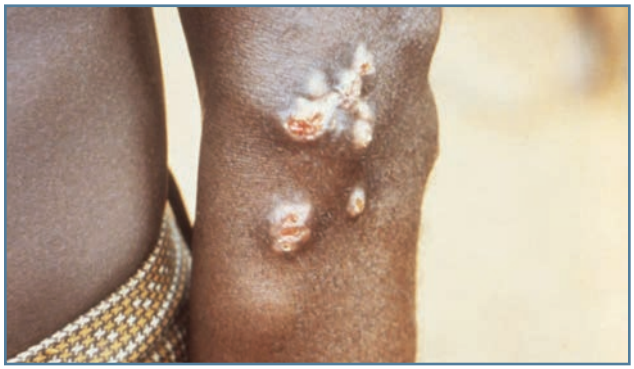


Figure 2.2.32 Yaws.

Endemic Syphilis/Bejel

- Africa, Southeast Asia, and Arabian Peninsula
- *Treponema pallidum endemicum*
- Primary lesion often goes unnoticed
- Secondary lesions similar to venereal syphilis
- Tertiary stage leads to gumma formation and can be disfiguring to facial structures

Leptospirosis

- *Leptospira*
- From contact with infected animals or contaminated water
- Majority of cases are milder "anicteric" form; about 10% are more severe "icteric" form
- Initial stage has fevers and myalgias
- Second phase is "immune" phase that can have a cutaneous eruption, widespread or limited to shins, cause progress to meningitis; pulmonary, renal, and hepatic involvement; and uveitis
- Most cases are self-limited, but antibiotics can help (azithromycin)

Treatment

- Penicillin is treatment option for all of the above. Azithromycin in penicillin allergy or for ease of use

PARASITIC INFECTIONS

Protozoa

Leishmaniasis

- Obligate intracellular parasites
- Cutaneous
  - Middle East, South America > Mediterranean, sub-Saharan Africa, Central Asia, India. South-central Texas is only endemic area in USA
  - Old World: ***Leishmania major*** and ***L. tropica*** > ***L. infantum, L. aethiopica***
  - New World: ***L. mexicana*** complex **(mexicana, amazonensis, venezuelensis)** and ***L. braziliensis*** complex *(braziliensis, guyanensis, pananensis, peruviana)*
    - Diffuse cutaneous: *L. amazonensis*
- Mucocutaneous
  - Central and South America most common
  - ***L. braziliensis complex***
- Visceral
  - Africa and Asia most common
  - ***L. donovani, L. infantum (Europe), L. infantum chagasi*** (Central and South America)
- Vector: Sand flies
  - ***Phlebotomus*** (Old World)
  - ***Lutzomyia*** (New World)
- Diagnosis
  - Culture in **Novy-MacNeal-Nicolle (NNN) medium**
  - Histopathology: Amastigotes identified in histiocyte cytoplasm as oval bodies with nucleus and kinetoplast (after staining with Giemsa)
  - Montenegro skin test or Leishman reaction (positive in cutaneous/mucocutaneous infection over 3-month duration, does not signify current infection, negative in diffuse cutaneous infection)
  - PCR for species identification
- Treatment
  - Pentavalent antimony (sodium stibogluconate) for cutaneous and mucocutaneous
  - Amphotericin B for visceral disease

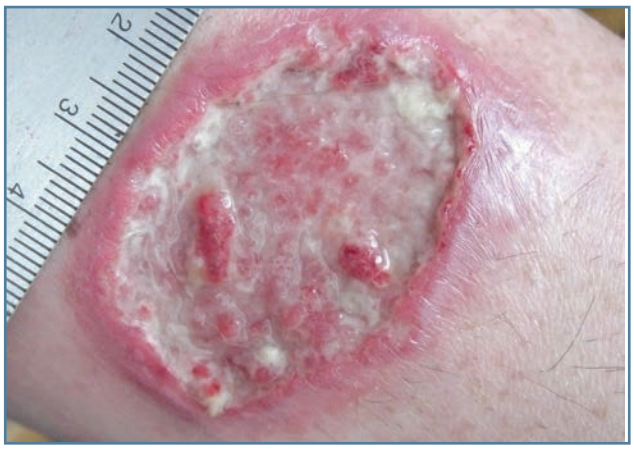


Figure 2.2.33 Cutaneous leishmaniasis.

Trypanosomiasis

TABLE 2.2.10 TRYPANOSOMIASIS

Disease	Causative Organism	Vector	Characteristic Clinical	Treatment
African trypanosomiasis	*Trypanosoma brucei gambiense* (West Africa)	Tsetse fly (*Glossina* spp.)	**Winterbottom's** sign: Posterior cervical	Pentamidine
	T. brucei rhodesiense (East Africa)			Suramin
American trypanosomiasis (Chagas' disease)	*T. cruzi* (Central and South America)	Reduviid bug (*Reduviidae* spp.)	**Romaña's** sign: Eyelid edema at site of inoculation Parinaud sign: Preauricular lymphadenopathy	Benznidazole Nifurtimox

Amoebas

- Single-celled eukaryotes that move by pseudopods
- *Entamoeba histolytica* usually affects gastrointestinal tract but spreads to perianal skin by direct extension or to abdominal skin via fistula
  - Treatment: Metronidazole
- *Balamuthia mandrillaris,* a free-living amoeba; it causes a rare, usually fatal encephalitis in immunocompetent hosts. Slowly expanding painless plaque on face > extremity can present month before CNS involvement

Worms

Cutaneous Larva Migrans

- Causative organism: Larvae of hookworms from dogs and cats (*Ancylostoma braziliense* or *Bunostomum phlebotomum*)
- Tortuous pruritic track moving slowly, 2 mm-2 cm per day (compared with larva currens, ~5 -10 cm/hour)
- Lacks collagenase, unable to penetrate basement membrane
- Treatment: Albendazole

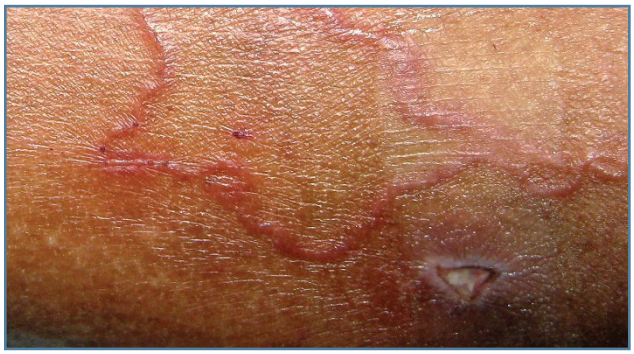


Figure 2.2.34 Cutaneous larva migrans.

Dracunculiasis

- Causative organism: *Dracunculus medinensis*
- Vector: Cyclops copepods (aquatic arthropods), which are ingested by humans after drinking copepod-infested water
- Characteristic feature: The worm can be found emerging from the skin, most often on the lower extremity
- Prevent by filtering water
- Treatment: Extraction, thiabendazole or metronidazole

Filariasis

- Clinical features: Lymphedema/elephantiasis
- Causative organisms: *Wuchereria bancrofti* (majority) > *Brugia malayi, Brugia timori*
- Vectors: Infection spread by mosquitoes belonging to genera *Aedes, Anopheles, Culex,* and *Mansonia*
- Treatment: Diethylcarbamazine

Loiasis

- Causative organism: *Loa loa*
- Vector: Mango flies or deerflies of genus *Chrysops*
- Characteristic feature: **Calabar swellings.** Adult worm migrating across conjunctivae ("eye worm")
- Treatment: Diethylcarbamazine

Onchocerciasis

- Causative organism: *Onchocerca volvulus*
- Vector: Blackflies of genus *Simulium*
- Characteristic features: Pruritic papules, depigmented macules/patches ("leopard skin"), onchocercal nodules (over bony prominences). Ocular involvement may lead to blindness

- Treatment: Ivermectin
- Mazzotti reaction: Potentially life-threatening fever, urticaria, lymphadenopathy, and hypotension, classically after treatment of onchocerciasis with diethylcarbamazine or ivermectin

Figure 2.2.35 Onchocerciasis.

Strongyloidiasis

- Causative organism: *Strongyloides stercoralis*
- Mode of infection: Penetration of larvae through skin or mucous membranes, usually from contact with contaminated soil. Transmission through oral-anal intercourse and autoinfection also occurs
- Characteristic features
  - Cutaneous strongyloidiasis (larva currens, ground itch): Serpiginous urticarial plaques on buttocks, groin, or trunk that migrate up to 5-10 cm/hour
  - Disseminated strongyloidiasis: "Thumbprint" purpura on periumbilical skin and widespread petechiae on trunk/proximal extremities. High mortality
- Treatment: Ivermectin (first-line therapy); albendazole or thiabendazole

RICKETTSIAL DISEASES

- Caused by obligate intracellular gram-negative coccobacilli
- Transmitted by arthropod vectors
- Treatment: Tetracyclines (doxycycline preferred)
- Treatment in pregnancy: Rifampin (non-life-threatening case of human granulocytic anaplasmosis or human monocytic ehrlichiosis), azithromycin (scrub typhus), chloramphenicol (non-life-threatening case of Rocky Mountain spotted fever)

Figure 2.2.36 Rocky Mountain spotted fever.

TABLE 2.2.11 RICKETTSIAL DISEASES

Disease	Causative Organism	Vector	Target Cells
Rocky Mountain spotted fever	*Rickettsia rickettsii*	1. Western USA—*Dermacentor andersoni* (tick) 2. Eastern USA—*Dermacentor variabilis* (tick) 3. Southwest USA—*Rhipicephalus sanguineus* (tick)	Endothelium
Rickettsialpox	*R. akari*	*Liponyssoides sanguineus* (mite of the house mouse)	Endothelium
Epidemic typhus	*R. prowazekii*	*Pediculus humanus corporis* (human body louse)	Endothelium
Endemic typhus	*R. typhi*	*Xenopsylla cheopis* (rat flea)	Endothelium
Scrub typhus	*Orientia tsutsugamushi*	Chiggers (trombiculid mite larvae)	Endothelium
Q fever	*Coxiella burnetii*	Inhalation of animal birth fluids > tick	Macrophages
Ehrlichiosis			
Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*	*Amblyomma americanum, Dermacentor variabilis* (ticks)	*Ehrlichia*—monocytes or neutrophils
Human granulocytic anaplasmosis	*Anaplasma phagocytophilum*	*Ixodes scapularis, Ixodes pacificus, Ixodes ricinus, Ixodes persulcatus* (ticks)	*Anaplasma*—neutrophils

OPPORTUNISTIC ORGANISMS

Opportunistic organisms are often found in immunosuppressed patients:

- *Aspergillus* sp.
- *Candida albicans*
- *Clostridium difficile*
- *Coccidioides immitis*
- *Cryptococcus neoformans*
- *Cryptosporidium*
- Cytomegalovirus
- *Histoplasma capsulatum*
- *JC polyomavirus*
- HHV-8 (Kaposi's sarcoma)
- *Legionella pneumophila* (Legionnaires' disease)
- *Microsporidium*
- *Mycobacterium avium complex*
- *Mycobacterium tuberculosis*
- *Pneumocystis jirovecii*
- *Pseudomonas aeruginosa*
- *Salmonella*
- *Toxoplasma gondii*

TABLE 2.2.12 INFECTIOUS DISEASES OF THE SKIN - RANDOM FACTS AND SUMMARY

Disease	Organism
Actinomycetoma	***Nocardia brasiliensis, Actinomadura madurae, A. pelletieri, and Streptomyces somaliensis***
Actinomycosis	***Actinomyces israelii***
Anthrax	***Bacillus anthracis***
Cat-scratch disease	***Bartonella henselae***
Bacillary angiomatosis	*B. henselae, B. quintana*
Trench fever	***B. quintana***
Oroya fever	***B. bacilliformis***
Verruga peruana	***B. bacilliformis***
Blistering distal dactylitis	Group A strep or *Staphylococcus aureus*
Lyme disease	*Borrelia burgdorferi*
Relapsing fever: Louse-borne	*B. recurrentis*
Relapsing fever: Tick-borne	*B. duttonii* *B. hermsii*

TABLE 2.2.12 INFECTIOUS DISEASES OF THE SKIN - RANDOM FACTS AND SUMMARY CONTINUED

Disease	Organism
Botryomycosis	*S. aureus* (most common), *Pseudomonas aeruginosa, Escherichia coli*
Cellulitis	Group A strep or *S. aureus* (most common in children)
Ecthyma	*Streptococcus pyogenes*/ group A strep
Ecthyma gangrenosum	*Pseudomonas aeruginosa*
Erysipeloid	*Erysipelothrix rhusiopathiae*
Folliculitis	*S. aureus* is most common
Glanders	*Burkholderia mallei*
Impetigo	Most commonly *S. aureus*, then group A β-hemolytic strep
Meningococcemia	*Neisseria meningitidis*
Necrotizing fasciitis	Most common is group A strep
Paronychia	*S. aureus* or *Strep. pyogenes*
Pitted keratolysis	*Kytococcus sedentarius*
Perianal strep	Group A strep
Purpura fulminans	Group A strep, *Neisseria meningitidis*, MRSA
Rat bite fever	*Streptobacillus moniliformis*
Rhinoscleroma	*Klebsiella pneumoniae* subsp. *rhinoscleromatis*
Scarlet fever	Group A strep
Staph scalded skin syndrome	*S. aureus*
Toxic shock syndrome	*S. aureus* and strep
Erysipelas	Primarily group A strep
Trichomycosis axillaris	*Corynebacterium tenuis*
Tularemia	*Francisella tularensis*
Leprosy	*Mycobacterium leprae* and *M. lepromatosis*
Tuberculosis	*Mycobacterium tuberculosis*

TABLE 2.2.12 INFECTIOUS DISEASES OF THE SKIN - RANDOM FACTS AND SUMMARY CONTINUED

Disease	Organism
Mycobacterium fortuitum complex	*Mycobacterium fortuitum, M. chelonae, M. abscessus*
Aquarium granuloma	*Mycobacterium marinum*
Herpes	Herpes simplex virus (HHV-1, HHV-2)
Varicella-zoster (shingles)	Varicella-zoster virus (HHV-3)
Infectious mononucleosis, oral hairy leukoplakia, non-sexual genital ulcers, NK/T cell lymphomas, nasopharyngeal carcinoma (lethal midline granuloma), hydroa vacciniforme, lymphomatoid granulomatosis, Kikuchi's syndrome (histiocytic necrotizing lymphadenitis)	HHV-4
Cytomegalovirus Infection	HHV-5
Exanthem subitum	HHV-6/7
Kaposi's sarcoma	HHV-8
Human papillomavirus	HPV (many types)
Hand, foot, and mouth disease	Coxsackievirus A16/A10
Herpangina	Group A and B coxsackievirus and echovirus
Measles	Measles virus, a paramyxovirus
Milker's nodule	Paravaccinia virus, genus *Parapoxvirus*
Molluscum contagiosum	Molluscum contagiosum virus, a poxvirus
Orf	Orf virus, genus *Parapoxvirus*
Erythema infectiosum	Parvovirus B19
Rubella	Togavirus
Gonococcemia	*Neisseria gonorrhoeae*
Chancroid	*Haemophilus ducreyi*

TABLE 2.2.12 INFECTIOUS DISEASES OF THE SKIN - RANDOM FACTS AND SUMMARY CONTINUED

Disease	Organism
Granuloma inguinale	*Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*
Lymphogranuloma venereum	*Chlamydia trachomatis*
Syphilis	*Treponema pallidum*
Pinta	*Treponema carateum*
Yaws	*Treponema pallidum pertenue*
Endemic syphilis/bejel	*Treponema pallidum endemicum*
Leptospirosis	*Leptospira*
Leishmaniasis	*Leishmania major, L. tropica, L. infantum, L aethiopica, L. mexicana, L. braziliensis*
African trypanosomiasis	*Trypanosoma brucei gambiense, T. brucei rhodesiense*
Chagas' disease	*Trypanosoma cruzi*
Cutaneous larva migrans	*Ancylostoma braziliense or Bunostomum phlebotomum*
Dracunculiasis	*Dracunculus medinensis*
Loiasis	*Loa loa*
Onchocerciasis	*Onchocerca volvulus*
Strongyloidiasis	*Strongyloides stercoralis*
Rocky Mountain spotted fever	*Rickettsia rickettsii*
Rickettsialpox	*Rickettsia akari*
Epidemic typhus	*Rickettsia prowazekii*
Endemic typhus	*Rickettsia typhi*
Scrub typhus	*Orientia tsutsugamushi*
Q fever	*Coxiella burnetii*
Human monocytic ehrlichiosis	*Ehrlichia chaffeensis*
Human granulocytic anaplasmosis	*Anaplasma phagocytophilum*

FUNGAL INFECTIONS

Superficial Mycoses

- Pityrosporum Disease
  - Tinea versicolor (pityriasis versicolor)
    - Caused by *Malassezia* spp.
      - ***Malassezia globosa*** is major implicated species. Less commonly due to *M. furfur, M. restricta, M. sympodialis, M. obtusa, M. slooffiae*
    - More common in summer months (warm, humid environments)
    - Favors oily areas (predilection for chest, abdomen, back, neck, pubis, and intertriginous areas)
    - Clinical findings
      - Multiple hyperpigmented, hypopigmented, or light pink scaly macules coalescing into patches/thin plaques favoring seborrheic areas

Figure 2.2.37 Pityriasis versicolor.

      - Hypopigmentation from production of azelaic acid (a dicarboxylic acid), which inhibits tyrosinase
    - Diagnosis
      - Yellow-green fluorescence under Wood's lamp
      - Skin scraping and KOH shows short, thick fungal hyphae and large number of spores (**"spaghetti and meatballs"**)
      - Hematoxylin-eosin (H&E): Thick basket-weave stratum corneum with hyphae and spores. Dark holes in superficial stratum corneum
      - Culture requires olive oil overlay
    - Treatment
      - Topical antifungals (shampoos, creams, lotions)
        - Imidazoles, triazoles, zinc pyrithione, ciclo pirox, selenium sulfide
      - Systemic antifungals (e.g., fluconazole)
        - Oral griseofulvin and **terbinafine NOT effective**
  - *Pityrosporum* folliculitis
    - Caused by *Malassezia* spp. (*M. furfur, M. globosa*)
    - More common in young women and in the immunosuppressed (e.g., transplant recipients)
    - Clinical findings: Small monomorphic, pruritic papules and pustules on the upper back, arms, neck, or face
    - Diagnosis
      - Yellow-green fluorescence under Wood's lamp
      - Pityrosporum **yeast** in smears or biopsies
    - Treatment: Oral antifungals (fluconazole), selenium sulfide
- Piedra
  - Fungal nodules on hair shafts
  - Black piedra
    - Caused by *Piedraia hortae,* found in soil in tropics
    - Clinical findings: Asymptomatic brown-black, firm, adherent nodules on hair shafts
    - Diagnosis: KOH shows dematiaceous (black) fungi
    - Treatment: Shaving, oral and topical terbinafine, ketoconazole shampoo
  - White piedra
    - Caused by *Trichosporon beigelii, T. inkin, T. ovoides*
    - More common in temperate climates
    - Clinical findings: Nonadherent, soft white/beige/light brown slimy nodules or sheath coating hair shafts
    - Diagnosis: KOH shows nondematiaceous fungi
    - Treatment: Shaving, oral itraconazole, topical antifungals
    - ***Trichosporon asahii* can cause disseminated disease in the immunosuppressed**

Figure 2.2.38 White piedra.

- Tinea Nigra
  - Caused by ***Hortaea werneckii***
  - Clinical findings: Brown/black macules on palms > soles

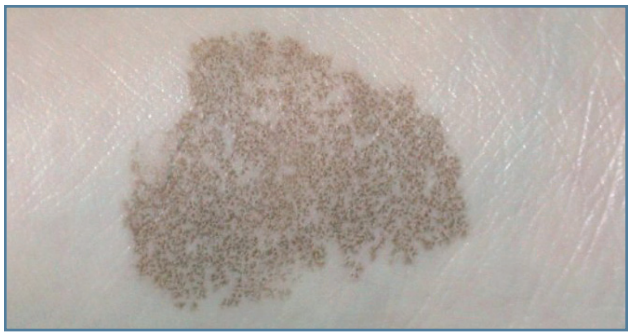


Figure 2.2.39 Tinea nigra.

- Diagnosis: Brown/golden hyphae seen on KOH. **Pigment confined to stratum corneum** (can be easily scraped off)
- Treatment: Topical azoles, terbinafine, skin scraping. Griseofulvin ineffective

The Dermatophytes

- Introduction
  - Infections of keratinized tissue (stratum corneum, hair, nails) by the dermatophyte genera: *Trichophyton, Microsporum,* and *Epidermophyton*. Rarely, invasive dermatophytosis can occur in the immunosuppressed
- Tinea Capitis

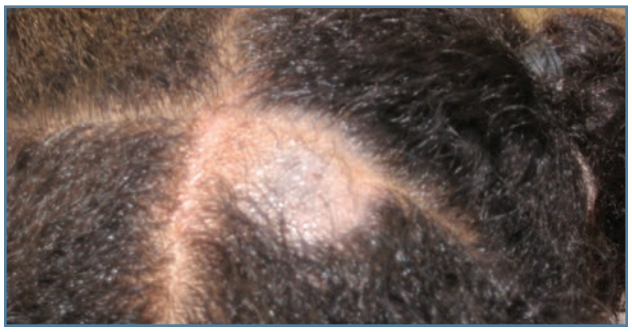


Figure 2.2.40 Tinea capitis.

  - Most common cause in USA is *Trichophyton tonsurans* (**To**nsurans = **To**p of the head); Microsporum canis most common cause worldwide
  - Pet exposure associated with *M. canis* (**Canis** with **Cani**nes)
  - More common in children
  - Endothrix (spores within the hair shaft): Black dot tinea capitis
    - Do not fluoresce with Wood's light
    - *T. tonsurans, T. violaceum, T. schoenleinii*
  - Ectothrix (spores on the outside of the hair shaft)
    - Fluoresce under Wood's light, due to **pteridine** production
    - *Microsporum canis, M. audouinii, M. distortum, M. ferrugineum, M. gypseum, Trichophyton schoenleinii*

MNEMONIC

Endothrix: "TV's in the House"
*T. **t**onsurans, T. **v**iolaceum, T. **s**choenleinii*

MNEMONIC

Ectothrix: "Cats And Dogs Fight and Growl Sometimes"
*M. **c**anis, M. **a**udouinii, M. **d**istortum, M. **f**errugineum, M. **g**ypseum, T. **s**choenleiniii*

  - Kerion
    - Boggy, purulent plaques with abscess formation
    - Can lead to lymphadenopathy, fever, pain, scarring alopecia
    - Caused by *Trichophyton tonsurans, T. rubrum, Microsporum canis, T. mentagrophytes, T. verrucosum*
    - Add prednisone to antifungal therapy to decrease risk of scarring
  - Favus
    - Caused by ***T. schoenleinii*** > *T. violaceum* and *M. gypseum*
    - Thick yellow crusts of hyphae and skin debris (called scutula) form around loose, wiry hairs. Scarring alopecia
    - Hyphae and air spaces in hair shaft with blue-white fluorescence
  - Treatment
    - Oral griseofulvin, terbinafine
    - Selenium sulfide shampoo and ketoconazole shampoo can be used in conjunction with systemic antifungals
- Tinea Barbae (Tinea Sycosis)
  - More common in postpubertal males in beard area or neck
  - Inflammatory type with nodular plaques and kerion-like swelling due to *T. mentagrophytes* or *T. verrucosum*
  - Superficial type with pustular folliculitis due to *T. violaceum* or *T. rubrum*
  - Abscess formation with *M. canis*
  - Verrucous granulomatosis due to *Epidermophyton floccosum*
  - Treatment: Oral antifungals

- Tinea Faciei
  - *Trichophyton rubrum, T. mentagrophytes, T. concentricum, Microsporum canis*
  - More common in women and children; upper lip/chin
  - Treatment: Oral antifungals if folliculitis present. If no folliculitis, topical antifungals
- Tinea Corporis
  - Caused by ***Trichophyton rubrum*** > *T. mentagrophytes, Microsporum canis*
  - Clinical findings: Annular, sharply circumscribed, erythematous plaques with advancing scaling edge and central clearing. Often with peripheral pustules

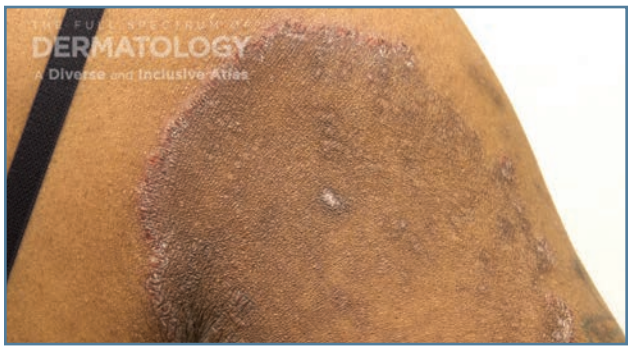


Figure 2.2.41 Tinea corporis.

  - Tinea imbricata
    - Caused by ***T. concentricum,*** most commonly in equatorial South Pacific
    - Presents as scaling concentric annular rings

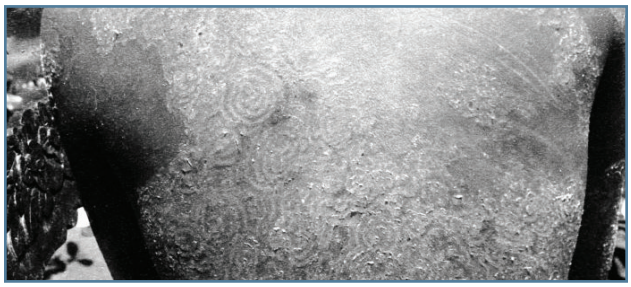


Figure 2.2.42 Tinea imbricata.

  - Tinea incognito
    - Nonscaly
    - Often a result of treating tinea with topical steroids
  - Majocchi granuloma (fungal folliculitis)
    - Caused most often by *T. rubrum* or *T. mentagrophytes* infecting hairs
    - Often seen in areas of shaving or skin occlusion, or when topical steroids have been used
    - Clinical findings: Perifollicular pustules and annular, crusty boggy granuloma
- Tinea Cruris
  - *T. rubrum* most common cause
  - **Scrotum is rarely involved** (think *Candida* if scrotum involved)
  - Often associated with tinea pedis
  - Treatment: Reduction of perspiration, loose clothing, topical powders
- Tinea Manuum
  - *T. rubrum* most common cause
  - Two feet-one hand syndrome: Unilateral tinea manum/unguium with moccasin type tinea pedis
- Tinea Pedis
  - Moccasin type: *E. floccosum, T. rubrum*
  - Interdigital type: *E. floccosum, T. mentagrophytes*
  - **Vesicular type: *T. mentagrophytes***

Figure 2.2.43 Tinea pedis.

- Onychomycosis (Tinea Unguium)
  - Most commonly due to *T. rubrum* > *T. mentagrophytes* > *E. floccosum*
  - Distal subungual onychomycosis
    - Most common pattern
    - *T. rubrum*
  - White superficial onychomycosis (leukonychia trichophytica)
  - Caused mainly by ***T. mentagrophytes*** **(*T. rubrum* in HIV+ patients)**
  - Proximal subungual onychomycosis
    - *T. rubrum* and *T. megninii*
    - AIDS-defining infection
  - Oral terbinafine (6 weeks for fingernail involvement, 12 weeks for toenails)
  - Efinaconazole
    - Low molecular weight for nail penetration
    - Low keratin binding profile
    - Unique vehicle
      - Non-lacquer —no buildup or debridement required
      - Allows penetration of nail
      - Clear, low surface tension solution
  - Once daily x 48 weeks
  - Tavaborole

- Boron-based compound
- Low molecular weight
- Highly water soluble
- Broad-spectrum antifungal activity
- New target: Cytoplasmic aminoacyl-transfer RNA (tRNA) synthetases
- Retains antifungal activity in the presence of keratin
- Once daily x 48 weeks

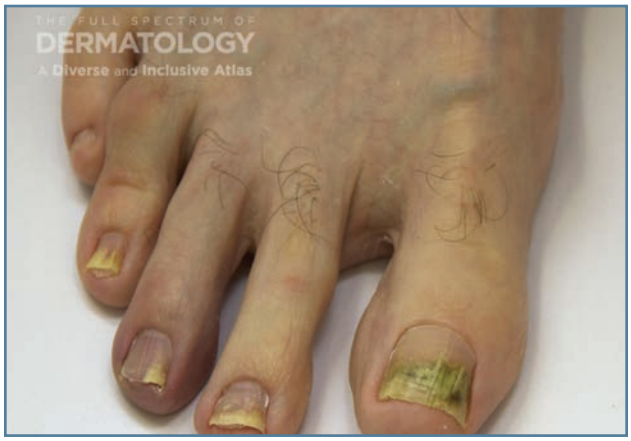


Figure 2.2.44 Onychomycosis.

Candidiasis

- Mucocutaneous Candidiasis
  - *Candida albicans* most common species (50-60%), C. glabrata (15-20%)
  - Oral candidiasis (thrush)
    - Clinical findings: Gray, white membranous plaques on oral mucous membranes
    - Risk factors: Dry mouth (saliva inhibits growth of *Candida*), broad-spectrum antibiotics
    - Treatment: Oral nystatin suspension, azoles
  - Perlèche/angular cheilitis
    - Maceration/fissuring of oral commissures
  - Candidal vulvovaginitis
    - Pruritus, burning sensation, and discharge
    - Treat with topical azoles or one dose of fluconazole
  - Candidal intertrigo
    - Superficial white pustules or pink papules often adjacent to patches (satellite lesions)
  - Diaper candidiasis
    - Can lead to granuloma gluteale infantum
  - Congenital cutaneous candidiasis
    - Risk factors include premature rupture of membranes and *C. albicans* infection in birth canal
    - Lesions widespread (oral cavity and diaper area usually spared)
    - Can lead to systemic involvement
  - Erosio interdigitalis blastomycetica
    - Clinical findings: Maceration of third web space, between the third and fourth fingers
  - Chronic mucocutaneous candidiasis
    - Chronic infection with onset at young age
    - Risk factors include primary immunodeficiencies with deficient cellular immunity, mutations in **interleukin-17 receptor**
  - Median rhomboid glossitis
    - Oral candidiasis
    - Occurs on midline of tongue anterior to circumvallate papillae

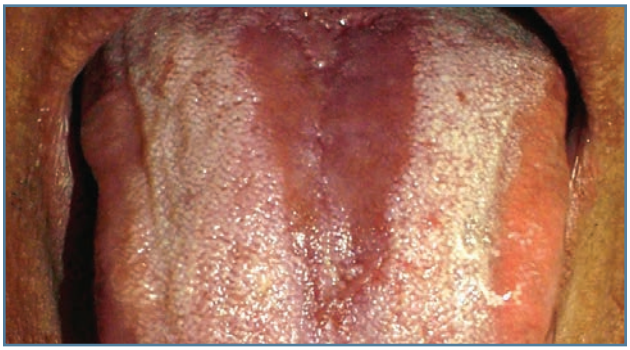


Figure 2.2.45 Median rhomboid glossitis.

  - Candidal paronychia
    - Chronic; common in diabetics
    - Clinical findings: Erythema and swelling of proximal and lateral nail folds, resulting in a bulbous appearance of nail folds
  - Candida onychomycosis
    - Destruction of nail and massive nail bed hyperkeratosis. Fingernails > toenails
- Systemic Candidiasis
  - Most commonly caused by *C. albicans*
  - *Candida tropicalis* most likely to produce cutaneous lesions
  - Risk factors include those with malignancy (e.g., leukemia/lymphoma), immunosuppression (e.g., HIV, transplant recipients), patients with indwelling IV catheters, IV drug use
  - Pathology shows budding yeast and pseudohyphae

Subcutaneous Mycosis

- Sporotrichosis
  - Caused by ***Sporothrix schenckii,*** a dimorphic fungus found in soil
  - Results from direct inoculation by a thorn (or other decaying plant matter), cat's claw, or other penetrating injury
  - **Gardeners, florists, or animal handlers at higher risk**

- **Cats are common source in Brazil**

- Clinical findings
  - Early findings may be a solitary nodule that may heal. Over a few weeks, nodules develop along the draining lymphatics (**regional lymphangitic sporotrichosis** most common type)
  - **Fixed cutaneous sporotrichosis** in 20% with solitary nodule without regional lymphangitis. Due to prior exposure
    - May present as localized rosacea-like lesions on face
  - **Disseminated sporotrichosis** is least common form, seen in the immunocompromised
- Pathology
  - **Cigar-shaped** budding yeasts
  - **Asteroid body** (central yeast cell surrounded by eosinophilic spicules)
- Treatment
  - Itraconazole for cutaneous and lymphocutaneous involvement
  - Potassium iodide effective for cutaneous forms
  - Heat compresses in conjunction with antifungal (*S. schenckii* intolerant to high temperatures)

- Mycetoma (Madura Foot; Maduromycosis)
  - Direct inoculation from soil in tropical and subtropical locations
  - Actinomycetoma
    - Caused by filamentous bacteria (*Nocardia, Actinomadura, Streptomyces*)
  - Eumycetoma: True fungi
    - Caused by *Madurella* spp. and *Pseudallescheria*
  - Botryomycosis: True bacteria
    - *Staphylococcus aureus* most common cause
  - Clinical findings
    - Involves **foot > hand.** Starts as asymptomatic painless papule. Then develops into surrounding soft tissue swelling and purulent draining sinuses with granules
      - **Triad of tumefaction, sinuses, and granules**
  - Treatment
    - Surgical excision or antifungals (e.g., voriconazole, itraconazole) for eumycetoma
    - Antibiotics (e.g., penicillin, sulfa) for actinomycetoma

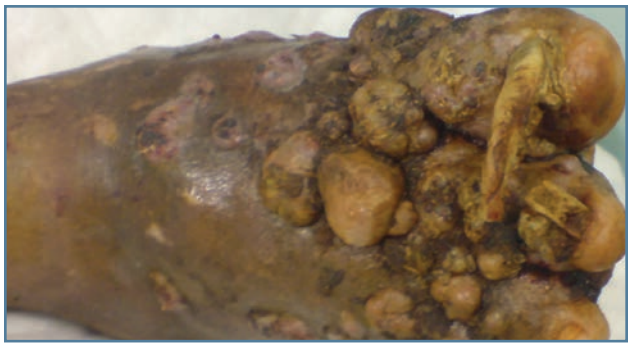


Figure 2.2.46 Madura foot.

- Chromoblastomycosis
  - Most commonly caused by ***Fonsecaea pedrosoi***
  - Results from direct inoculation and affects lower extremity more commonly than upper extremity
  - Clinical findings
    - Begins as small pink papule that spreads through direct extension
    - Chronic lesions have verrucous or nodular borders with central scarring/atrophy
  - Pathology
    - Dark brown, thick-walled ovoid spheres in clusters or chains referred to as sclerotic bodies (Medlar bodies, **"copper pennies"**)
  - Treatment
    - Excision, heat, cryotherapy, itraconazole, terbinafine, amphotericin B, CO_2 laser
- Lobomycosis (Keloidal Blastomycosis, Lacaziosis)
  - Most cases in Central and South America
  - Associated with **dolphins**
  - Caused by ***Lacazia loboi***
  - Clinical findings
    - Keloidal nodules common on the **ears,** face, and arms
  - Pathology
    - Single or multiple budding thick-walled cells that appear attached by a bridge
      - **Brass knuckles**/chain of coins/string of pearls
  - Treatment
    - Excision or cryosurgery (antifungals ineffective)

Systemic Mycoses

- Histoplasmosis
  - Caused by ***Histoplasma capsulatum*** var. *capsulatum,* a soil saprophyte frequently found in **bat** and bird feces
  - Endemic in the central USA along the Mississippi River basin

- Caused by inhalation of airborne spores or direct cutaneous inoculation
- Primary pulmonary histoplasmosis is usually benign and self-limited, presenting as fever, night sweats, malaise, or cough. May present with **erythema nodosum**
- Progressive disseminated histoplasmosis in the immunocompromised
  - Ulcerations and granulomas of oronasopharynx
  - Skin lesions show umbilicated nodules, papules, and plaques

Figure 2.2.47 Histoplasmosis.

  - Molluscum contagiosum mimic
- Primary cutaneous histoplasmosis is rare and characterized by a chancre-type lesion and lymphadenopathy
- African histoplasmosis
  - Caused by *Histoplasma capsulatum* var. *duboisii*
  - Mucocutaneous, subcutaneous, bone lesions
- Pathology
  - **Intracellular** yeast cells with rim of clearing (pseudocapsule) in histiocytes
    - **H**isto with a **H**alo
  - Looks similar to leishmaniasis, but the yeast cells in histiocytes lack a kinetoplast and are distributed evenly throughout the cytoplasm. In leishmaniasis, the amastigotes line up at the periphery of the cell
  - At room temperature produces **pear-shaped** microconidia
- Diagnosis
  - Urinary ELISA, PCR
- Treatment
  - None in immunocompetent primary disease (self-limited)
  - Amphotericin B in severely ill and immunocompromised; itraconazole, voriconazole
  - HIV^+ patients need lifelong prophylaxis with itraconazole

- Blastomycosis (North American blastomycosis, Gilchrist's disease, blastomycetic dermatitis)
  - Caused by ***Blastomyces dermatitidis***
  - Organisms prevalent in the **southeastern USA,** Ohio and Mississippi River basins (especially beaver lodges)
  - Most skin involvement a result of dissemination from primary pulmonary disease
  - Only deep fungal infection that can cause primary cutaneous infection
  - Clinical findings
    - Chronic pulmonary disease mimics pneumonia and can disseminate to skin, bone (ribs and vertebrae)
    - Cutaneous findings are chronic and show verrucous nodules, sinuses, and pustules along the advancing edge. Form white scars as they spread peripherally. Heals with cribriform scarring
  - Pathology
    - **Broad-based budding** and thick, doubled contoured walls
  - Treatment
    - Itraconazole, amphotericin B (for severe disease), fluconazole, voriconazole
- Coccidioidomycosis (coccidioidal granuloma, valley fever, San Joaquin valley fever)
  - Caused by ***Coccidioides immitis***
  - Endemic in southwestern USA, Central and South America
  - Results from disturbed soil (e.g., earthquakes, construction)
  - Clinical findings
    - Primary pulmonary coccidioidomycosis
      - Inhalation of *C. immitis* followed by incubation period of days to weeks resembling flulike illness in 50% (50% asymptomatic)
      - Can lead to skin manifestations (erythema nodosum is a favorable prognostic sign)
    - Disseminated coccidioidomycosis (coccidioidal granuloma) occurs in less than 1% of infections
      - Presents as verrucous nodules, pink papules; umbilicated papules mimic molluscum contagiosum in AIDS patients
    - Primary cutaneous coccidioidomycosis
      - Rare. Indurated nodules that may ulcerate
  - Diagnosis
    - Highly infectious; culture of deep fungi should NOT be done in office, must be done in specialized lab
  - Pathology
    - Endospore-containing spherules much smaller and more uniform than those found in rhinosporidiosis
  - Treatment
    - Fluconazole, itraconazole, amphotericin B
- Paracoccidioidomycosis (South American blastomycosis)
  - Caused by *Paracoccidioides brasiliensis,* endemic to Central/South America

- Clinical findings
  - Mucocutaneous type
    - Intraoral and perioral lesions
    - **Gingival** lesions most common. Progresses to involve tongue, lips, and adjacent tissue leading to destruction of nose, lips, face
  - Primary cutaneous with direct skin inoculation leading to verrucous papules, plaques, ulceration
  - Disseminated disease with painful, ulcerative, verrucous mucocutaneous lesions and cervical **lymphadenopathy**
- Pathology: **Mariner's wheel**
- Treatment
  - Itraconazole is treatment of choice
  - Trimethoprim-sulfamethoxazole, amphotericin B

Opportunistic Infections

- Introduction
  - Predisposing factors include neutropenia, HIV infection, immunocompromised state
- Aspergillosis
  - Caused by ***Aspergillus fumigatus, A. flavus,*** and *A. niger*
  - Neutropenia is a key risk factor for invasive aspergillosis
  - Colonizes eschar in third-degree burns
  - Clinical findings
    - Otomycosis
      - Malignant otitis externa if diabetic or immunosuppressed
      - Often found concurrently with *Pseudomonas aeruginosa*
    - Primary cutaneous aspergillosis
      - Most occur at the site of IV cannulas in immunosuppressed patients
      - Can present with necrotic ulcers and hemorrhagic bullae
    - Secondary cutaneous aspergillosis
      - Primary lung infection with dissemination to skin
  - Pathology
    - **45-degree** dichotomous branching of hyaline septate hyphae on silver or periodic acid—Schiff (PAS) staining
  - Treatment
    - Voriconazole treatment of choice for invasive aspergillosis
    - Amphotericin B, caspofungin, itraconazole
- Mucormycosis (Zygomycosis)
  - Most commonly caused by ***Rhizopus, Absidia, Mucor***
    - Ubiquitous molds common in the soil, decaying plants/animals, or in the air
  - Clinical forms of mucormycosis
    - Rhinocerebral: Associated with diabetes or immunocompromised state (e.g., leukemia patients)
    - Pulmonary: Inhalation leads to respiratory or sinus infection
    - Cutaneous: Can be from contiguous spread or dissemination
      - Can present with subtle unilateral facial swelling and slight erythema, progressing to large areas of necrosis with thick hemorrhagic crust
    - Gastrointestinal: In malnourished patients
    - Disseminated: In neutropenic patients. Hematogenous spread from lungs
  - Histopathology
    - Nonseptate broad ribbon-like hyphae with **90-degree branching**

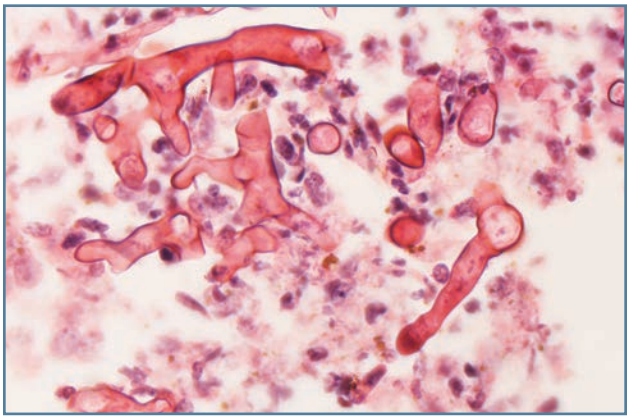


Figure 2.2.48 Mucormycosis.

  - Treatment: Debridement, amphotericin B
- Cryptococcosis
  - Caused by ***Cryptococcus neoformans*** and ***Cryptococcus gattii,*** often found in **pigeon** droppings
  - Risk factors include immunocompromised state (e.g., AIDS), exposure to soil or pigeon droppings
  - Clinical findings
    - Primary pulmonary cryptococcosis
      - Infection remains localized to lungs in 90% of patients

- Disseminated cryptococcosis in 10% of cases
  - Has affinity for CNS (mycotic meningitis) and skin
  - Cutaneous cryptococcosis presents with swelling, abscesses, molluscum contagiosum—like lesions; ulcers most commonly on head/neck
- Histopathology

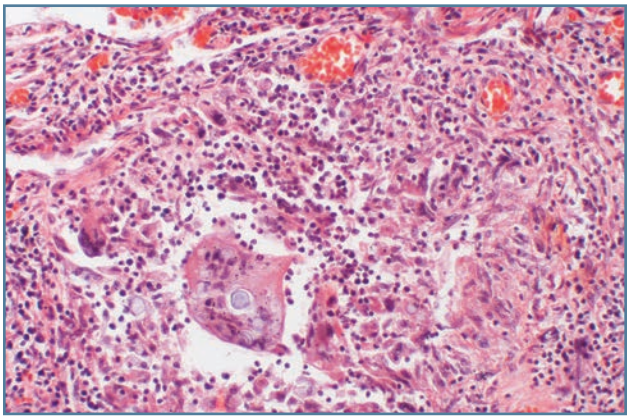


Figure 2.2.49 Cryptococcosis.

  - **Gelatinous pattern** with many organisms, necrosis, little inflammation
  - **Granulomatous pattern** with fewer organisms, little necrosis, granulomas
  - PAS stains central yeast forms
  - **Mucicarmine,** Alcian blue, or **India ink**
- Treatment
  - Amphotericin B, fluconazole, voriconazole

- Penicilliosis (Hyalohyphomycosis)
  - Commonly caused by ***Penicillium marneffei***
    - Infection is an indicator of HIV disease
    - Endemic in Southeast Asia, China
    - **Bamboo rat reservoir**
  - Cutaneous findings
    - Molluscum contagiosum—like lesions, necrotic nodules, acneiform lesions on forehead, arms, and trunk; mucosal ulceration
  - Histopathology
    - Similar appearance to histoplasmosis. Intracellular and extracellular oval to round yeast. Stains well with PAS and GMS (Gomori methenamine-silver stain), not H&E
- Phaeohyphomycosis
  - Dematiaceous fungi with **brown/black hyphae** found in plants and soil
  - Broad spectrum of disease ranging from superficial infection (e.g., tinea nigra) to deep involvement
  - Often disseminated to other organs *(Bipolaris spicifera* is the most common cause of disseminated disease)
  - Organisms appear in tissue as dark yeast-like cells, pseudohyphae or hyphae
  - Need culture for identification of organism
- Pneumocystosis
  - ***Pneumocystis jirovecii*** has features of both protozoa and fungi
  - Opportunistic infection occurs primarily as pulmonary infection in HIV patients
  - Cutaneous involvement is rare
    - Most common on external ear. Presents as erythematous/skin-colored, nontender papules/nodules
  - Treatment: Trimethoprim-sulfamethoxazole
- Geotrichosis
  - Caused by ***Geotrichum candidum,*** a yeast-like fungus found in milk, fruit, soil
    - Used for maturing of cheese
  - In the immunocompromised, can cause disseminated mucocutaneous disease
  - Treat with nystatin

TIP

DDX molluscum contagiosum—like lesions on the face in the setting of immunosuppression: cryptococcosis, histoplasmosis, coccidioidomycosis, penicilliosis

2.3 Bullous and Vesicular Dermatosis

OVERVIEW AND WORKUP

A blister is formed when the skin's structural connections are weakened or destroyed.

Three main causes:

- Autoimmune (most common): Autoantibody binds to a molecule that is integral to holding the skin together
- Mutation: Absence of or loss of function of an adhesion molecule
- Toxins: Formed by bacteria or viral infections

Blistering diseases are classified by disease-causing mechanism and then further by where in the skin the blister formation occurs.

Diagnostic workup is different for autoimmune and genetic blistering diseases. Here are the common methods used:

Histopathology

- Half blister and half normal skin placed in formalin
- Detects level of split

Immunofluorescence Microscopy

- Perilesional skin placed in Michel's/Zeus transport fluid
- Detects deposition of immunoglobulins and complement factors in the skin

Indirect Immunofluorescence

- Blood drawn from patient
- Detects autoantibodies to skin components by using various substrates, such as human skin, rat bladder, and monkey esophagus

Immunomapping

- Biopsy from the patient is labeled with various antibodies that are components of the basement membrane
- Detects the level of blister formation
- Mostly used for congenital blistering diseases (preferably done on newly induced blister)

Electron Microscopy and Immune Transmission Electron Microscopy

- Used mostly for congenital blistering disease
- Detects the level of blister formation

ELISA (Enzyme-Linked Immunosorbent Assay)

- An assay performed on patient's blood
- Measures autoantibody titers

Genetic Mutation Analysis

- Congenital blistering disorders

Figure 2.3.1 Negative direct immunofluorescence testing. There is background fluorescence, but no specific deposition.

Figure 2.3.2 Indirect immunofluorescence testing: Pemphigus vulgaris. The antibodies present in the patient's serum (tagged with a fluorescent antibody against IgG) deposit intercellularly within the monkey esophagus substrate.

Figure 2.3.3 Direct immunofluorescence testing: Pemphigus vulgaris. The patient's skin has intercellular IgG deposition detected by a tagged fluorescent antibody against IgG.

TIP

Immunofluorescence Patterns

- Bullous pemphigoid—linear C3/IgG (epidermal and/or dermal side of split skin)
- Pemphigoid gestationis—linear C3/IgG
- Epidermolysis bullosa acquisita—linear IgG + others (dermal side of split skin)
- Bullous lupus erythematosus—linear or discontinuous IgG + others (dermal side of salt-split skin)
- Porphyria cutanea tarda—multiple Igs, complement, and/or fibrin at dermal-epidermal junction or around vessels
- Mucous membrane pemphigoid—linear C3/IgG, sometimes IgA
- Pemphigus—intercellular IgG/C3
- Dermatitis herpetiformis—granular or fibrillar IgA
- Linear IgA disease—linear IgA
- Chronic bullous disease of childhood (CBDC)—linear IgA

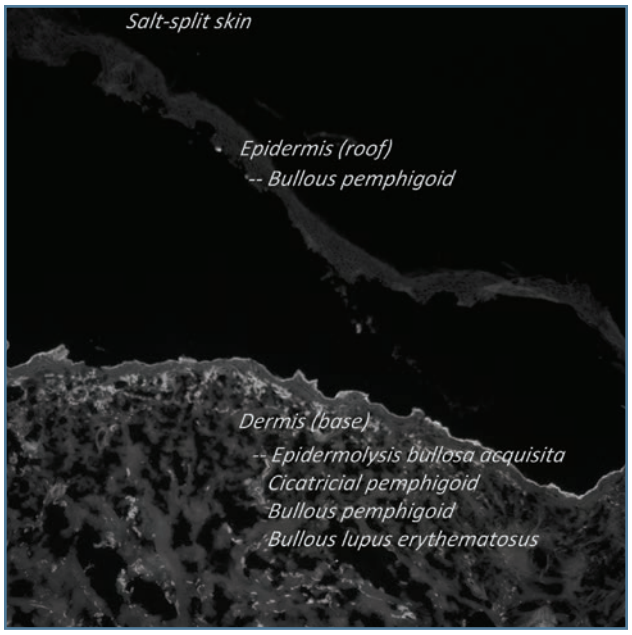


Figure 2.3.4 Salt split skin diagram.

BASEMENT MEMBRANE AND MOLECULES

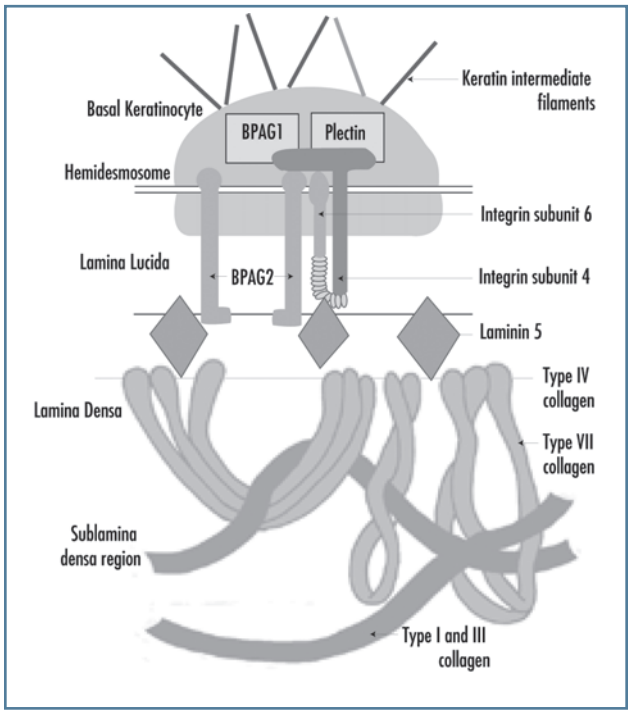


Figure 2.3.5 Basement membrane and molecules.

TABLE 2.3.1 LOCATION OF SPLIT AND SAMPLE DISORDERS

Location of Split	Disease Examples
Subcorneal	Pemphigus foliaceus Pemphigus erythematosus Staphylococcal scalded skin syndrome Bullous impetigo
Suprabasilar	Pemphigus vulgaris
At/within basal layer	Bullous pemphigoid Epidermolysis bullosa simplex
Below basal keratinocytes	Bullous pemphigoid Linear IgA disease Cicatricial/mucous membrane pemphigoid Porphyria cutanea tarda Bullous lupus erythematosus Epidermolysis bullosa acquisita Dermatitis herpetiformis

Armadillo Family

- Plaque proteins that function in adhesion
- Includes β-catenin (plakoglobin can substitute for β-catenin) in adherens junctions
- Plakoglobin and plakophilins in desmosomes

TABLE 2.3.2 DISORDERS ASSOCIATED WITH ARMADILLO PROTEINS

Mutations: Armadillo	Disorder
β-Catenin	Some pilomatricomas Colorectal carcinoma
Plakoglobin	Naxos disease
Plakophilin 1	Ectodermal dysplasia with skin fragility
Antigenic: Armadillo	**Disorder**
Plakoglobin	Coprecipitates with desmogleins in pemphigus foliaceus, pemphigus vulgaris, and paraneoplastic pemphigus

Cadherin Family

- Calcium-dependent adhesion molecules
- Classic: E-cadherin, N-cadherin, P-cadherin
- Desmosomal type (has homology to classic cadherins): Desmoglein 1, desmoglein 3, desmocollins
- In adherens junctions and desmosomes

TABLE 2.3.3 DISORDERS ASSOCIATED WITH CADHERIN PROTEINS

Mutations: Cadherin	Disorder
Desmoglein 1	Striate palmoplantar keratoderma (PPK) type 1
E-cadherin	Gastric cancer
Antigenic: Cadherin	**Disorder**
Desmoglein 1	Pemphigus foliaceus Staphylococcal scalded skin syndrome (toxin mediated)
Desmogleins 1/3	Mucocutaneous pemphigus vulgaris
Desmoglein 3	Mucosal pemphigus vulgaris
Desmocollin	IgA pemphigus

Enzymes

- Transglutaminase 1: Mutated in autosomal recessive congenital ichthyosis (lamellar ichthyosis)
- Transglutaminase 3: Antigen for dermatitis herpetiformis

Integrins

- Found between cell membranes and basement membrane in focal contacts and hemidesmosomes

TABLE 2.3.4 DISORDERS ASSOCIATED WITH INTEGRINS

Mutations: Integrin	Disorder
$\alpha_6\beta_4$-Integrin	Junctional epidermolysis bullosa (JEB) with pyloric atresia
Antigenic: Integrin	**Disorder**
β_4-Integrin	Ocular cicatricial pemphigoid

Intermediate Filaments

- Found within a variety of cells, many different types
  - Type I = acidic keratins 9-20, chromosome 17
  - Type II = basic keratins 1-8, chromosome 12
  - Type III = vimentin, glial fibrillary acidic protein (GFAP), desmin, peripherin
  - Type IV = neurofilaments
  - Type V = nuclear lamins
  - Type VI = nestin

TABLE 2.3.5 DISORDERS ASSOCIATED WITH KERATINS

Mutations: Keratin	Disorder
Keratin 1	Ichthyosis hystrix
Keratins 1/10	Epidermolytic ichthyosis Epidermal nevi with EHK
Keratins 1/16	Nonepidermolytic PPK
Keratin 2e	Ichthyosis bullosa of Siemens
Keratins 3/12	Corneal dystrophy of Meesmann
Keratins 4/13	White sponge nevus of Cannon
Keratins 5/14	Epidermolysis bullosa simplex variants
Keratins 6a/16	Pachyonychia congenita
Keratins 6b/17	Pachyonychia congenita
Keratin 9	Epidermolytic PPK
Lamin A	Progeria

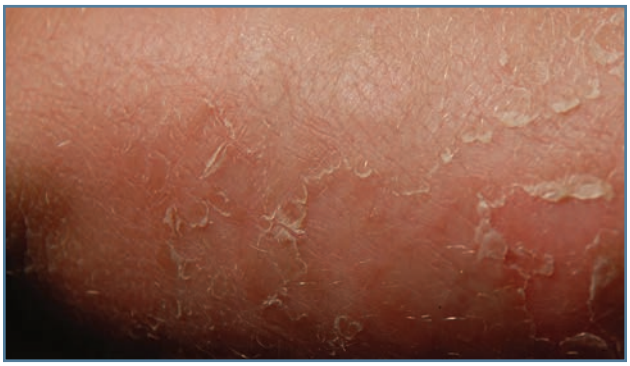


Figure 2.3.6 Lower leg of 12-month-old with ichthyosis bullosa of Siemens.

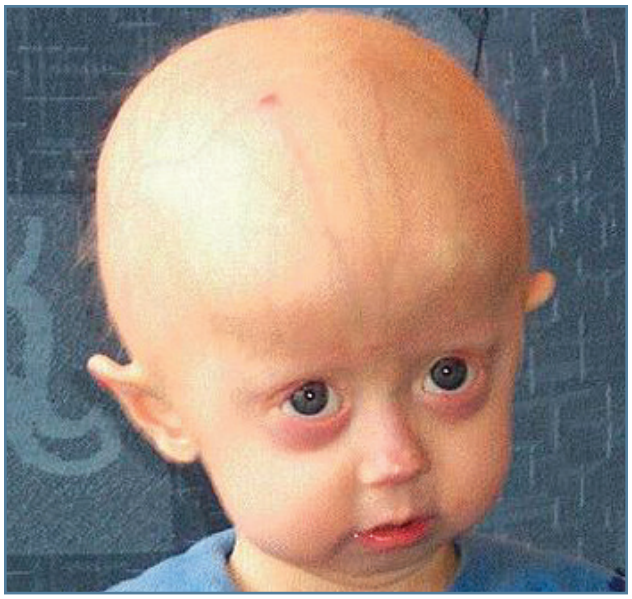


Figure 2.3.7 Progeria.

Plakins

- Plaque proteins that function in adhesion
  - Desmoplakins I and II, envoplakin, periplakin in desmosomes
  - Bullous pemphigoid antigen 1 (BPAg1), plectin in hemidesmosomes

TABLE 2.3.6 DISORDERS ASSOCIATED WITH PLAKINS

Mutations: Plakin	Disorder
Desmoplakin	Carvajal syndrome (striate PPK with woolly hair type II) Arrhythmogenic right ventricular cardiomyopathy Lethal acantholytic epidermolysis bullosa
Plectin	Epidermolysis bullosa simplex with muscular dystrophy
Antigenic: Plakin	**Disorder**
Desmoplakin Envoplakin Periplakin BPAg1	Paraneoplastic pemphigus
Desmoplakins I and II	Stevens-Johnson syndrome
BPAg1 and BPAg2	Bullous pemphigoid

Adherens Junction

- Mediates quick, weak cell:cell adhesion
- Contains E-cadherin, P-cadherin, α- and β-catenin, vinculin, and radixin; also plakoglobin, like desmosomes
- Important in cell signaling; anchors actin at interface of two cell membranes

Desmosome

- Mediates slow, strong cell:cell adhesion
- Contains desmosomal cadherins (desmoglein, desmocollin), desmocalmin (keratocalmin), desmoyokin, band 6 protein, plakophilin; contains plakoglobin, like adherens junctions
- Anchors keratin intermediate filaments at interface of two cell membranes

Focal Contact

- Contains integrins, vinculin
- Anchors actin at interface of cell membrane/basement membrane

Gap Junction

- Contains connexins (connexins assemble to form connexons)
- Allows for communication between cells

TABLE 2.3.7 DISORDERS ASSOCIATED WITH CONNEXINS

Mutations: Connexins	Disorder
26	Vohwinkel syndrome Keratitis-ichthyosis-deafness (KID) syndrome Palmoplantar keratoderma (PPK) with deafness
30	Hidrotic ectodermal dysplasia
30.3, 31	Erythrokeratodermia variabilis

Hemidesmosome—Anchoring Filaments

- Within the basal cell: BPAg1, plectin
- Cell membrane spanners: $\alpha_6\beta_4$-Integrin, bullous pemphigoid antigen 2 (BPAg2 = type XVII collagen)
- Within the lamina lucida: Anchoring filaments, laminin 5
- Anchors keratin intermediate filaments at cell membrane/basement membrane interface

TABLE 2.3.8 DISORDERS ASSOCIATED WITH PROTEINS OF THE HEMIDESMOSOME

Mutations: Protein	Disorder
BPAg2	JEB, non-Herlitz type
Laminin V	JEB, Herlitz type
Plectin	Epidermolysis bullosa simplex with muscular dystrophy
$\alpha_6\beta_4$-Integrin	Junctional epidermolysis bullosa with pyloric atresia
Antigenic: Protein	**Disorder**
BPAg1 and BPAg2-NC16A	Bullous pemphigoid
BPAg2 97-kDa antigen	Lichen planus pemphigoides Linear IgA disease
BPAg2-NC16A	Herpes gestationis
BPAg2-C-terminal domain	Mucous membrane pemphigoid
Laminin 5	Mucous membrane pemphigoid
β_4-Integrin	Ocular cicatricial pemphigoid

Lamina Densa

- Contains entactin (nidogen) in a complex with collagen IV and laminin and heparan sulfate

Tight Junction

- Contains occludins and claudins
- Important for an intact skin barrier (found in granular layer)

INTRAEPIDERMAL AUTOIMMUNE DISEASES

Pemphigus Foliaceus (PF)

- Clinical
  - Flaccid, superficial bullae that rupture easily (can look like impetigo), often confined to seborrheic areas (e.g., face, scalp, and upper trunk) or localized/generalized exfoliation with crusting and malodor
  - **Highest expression of desmoglein 1 (DSG1) on chest/upper back**
  - Nikolsky sign positive, mucous membranes usually spared
  - Endemic in Brazil (fogo selvagem) and Tunisia
- Histology
  - Subcorneal/intragranular acantholysis with "cling ons" = acantholytic cells hanging onto the blister roof
  - Neutrophils can be present in blister cavity and can resemble impetigo histologically, so correlate with clinical features
  - Direct immunofluorescence (DIF): Intercellular IgG4 (may be more prominent in upper layers of epidermis)
  - Indirect immunofluorescence (IIF): Intercellular in 80% on guinea pig esophagus
- Antibodies
  - Against desmoglein 1
  - **Note that neonates are not usually born with PF despite the fact that maternal autoantibodies against desmoglein 1 can cross the placenta; this is thought to be because desmoglein 3 is expressed throughout the epidermis in the neonate; this is similar to the expression of desmoglein 3 in full-thickness oral epithelium, preventing oral involvement in PF**
- Drug-induced
  - Thiol drugs (captopril, penicillamine), sulfa-releasing drugs (penicillin, piroxicam, cephalosporin)
- DDx
  - Impetigo, subcorneal pustular dermatosis (Sneddon-Wilkinson disease) (neutrophils only, no acantholytic cells)
- Treatments
  - Similar to pemphigus vulgaris (see below)

Fogo Selvagem

- Clinical
  - Endemic form of pemphigus foliaceus in rural areas of Brazil
  - Increased incidence in children/young adults
  - Flaccid bullae that rapidly become superficial crusted erosions that can look like eczema or psoriasis or impetigo or seborrhea; can be vegetative or exfoliative
  - Nikolsky sign positive
- Possibly this is an infectious disease that is **transmitted by the black fly *(Simulium)***
- Histology is identical to pemphigus foliaceus
- Antibody profile is identical to pemphigus foliaceus
- Treatments: Steroids

Pemphigus Erythematosus (Senear-Usher Syndrome)

- Clinical
  - Overlap of lupus erythematosus and pemphigus foliaceus with erythematous crusts and hyperkeratotic lesions and occasional bullae on the nose/ears/cheeks/scalp and chest/extremities, sun-exposed skin
- Histology is identical to pemphigus foliaceus
  - DIF: Like pemphigus foliaceus and with linear IgG at dermoepidermal junction
  - Lupus band positive in 80%; anti-nuclear antibody (ANA) positive in 30%
- Treatments
  - Oral/topical steroids, sunscreen, immunosuppressive steroid-sparing agents

IgA Pemphigus

- Clinical
  - **Subcorneal pustular dermatosis** (SPD) type: Serpiginous pustules
  - **Intraepidermal neutrophilic** (IEN) type: Flaccid bullae that can start as vesiculopustules, lesions enlarge peripherally, causing annular "flower-like" arrangements; common sites are intertriginous; pruritus common
- Histology
  - Subcorneal or intraepidermal
  - **Neutrophils** in epidermis, no acantholysis obvious
  - DIF: 100% intercellular IgA (distinguishes SPD type from subcorneal pustular dermatosis (Sneddon-Wilkinson disease), rare C3
  - IIF: Intercellular IgA in 50%
- Antibodies
  - **Against desmocollin 1 in SPD type, desmoglein 1 or desmoglein 3 in IEN type**
- Associations
  - **IgA gammopathy**
- Treatments
  - Dapsone, acitretin, steroids

Pemphigus Vulgaris (PV)

- Clinical
  - Flaccid, thin-walled bullae, easily ruptured, erosions, crusts, heal with hyperpigmentation, desquamative gingivitis
  - Oral erosions in 60-100% (most commonly affected areas are the gingiva, soft palate, and tongue)
  - Nikolsky sign positive, blisters spread with pressure on surface of blister (Asboe-Hansen sign, bulla spread sign)
- Histology
  - Suprabasilar acantholysis with "tombstoning" of basal layer; eosinophils and neutrophils in the infiltrate
  - DIF: Intercellular epidermal IgG4 > C3 (may be more prominent in lower epidermis)
  - IF: Intercellular in 80-90% on monkey esophagus; can follow these titers to follow disease activity
- Antibodies
  - **Desmoglein 3 (mucosal) and desmogleins 1 and 3 (mucocutaneous)**
    - DSG1 spans entire epidermis and upper part of mucosal epithelium
    - DSG3 spans entire mucosal epithelium and lower part of the epidermis
- ELISA
  - Testing against DSG1 and/or DSG3 can be used to follow disease activity
- Associations
  - Various HLA markers (DR4, DR14, B15, etc.)
- Treatments
  - Steroids, rituximab (FDA-approved indication), mycophenolate mofetil, azathioprine, cyclophosphamide, intravenous immunoglobulin (IVIG)

TABLE 2.3.9 SUBSTRATES USED FOR INDIRECT IMMUNOFLUORESCENCE

IIF Substrate	Disease
Rat bladder	Paraneoplastic pemphigus
Guinea pig esophagus	Pemphigus foliaceus
Monkey esophagus	Pemphigus vulgaris

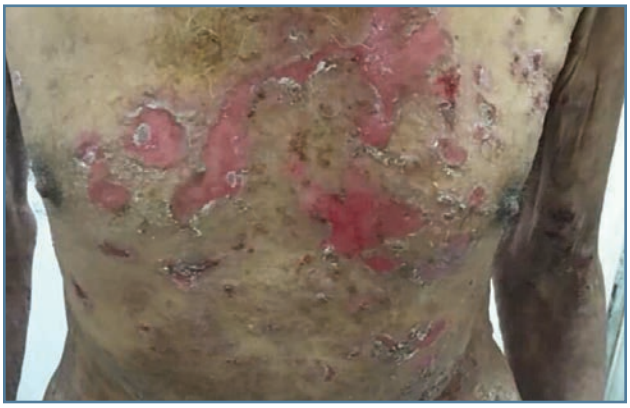


Figure 2.3.8 Pemphigus vulgaris.

Pemphigus Vegetans

- Clinical
  - Two types: Neumann type (starts and ends like PV) and Hallopeau type (begins with pustules)
  - Bullae or pustules quickly turn into vegetating malodorous plaques most commonly in body folds or on scalp
- Histology
  - Suprabasilar acantholysis can be subtle; there is marked hyperplasia and papillomatosis of the epidermis with characteristic **eosinophilic abscesses.** Acantholysis in suprabasilar and subcorneal areas
- Antibodies
  - **Against desmoglein 3, sometimes desmoglein 3 and desmocollins 1 and 2**

Drug-Induced Pemphigus

- Inducing drugs: Thiol-containing drugs (captopril, penicillamine, thiopronine), drugs with disulfide bonds (gold, pyritinol); also drugs that have the potential to release sulfur moieties (penicillins, piroxicam, cephalosporins), pyrazolone derivatives and enalapril (possibly secondary to an amide group), indomethacin, rifampin
- 75% or more like pemphigus foliaceus (especially when secondary to thiol drugs), 25% resemble pemphigus vulgaris; pemphigus vulgaris type may be increased now as nonthiol drugs are often the culprits
- DIF: 90% intercellular
- IIF: 70% intercellular

Paraneoplastic Pemphigus

- Clinical
  - Can resemble severe erythema multiforme with **terrible oral ulcerations** or pemphigus vulgaris, or occasionally bullous or cicatricial pemphigoid
  - Skin lesions can be polymorphous with erythematous papules, lichenoid lesions, targetoid lesions, flaccid or tense bullae
  - Respiratory failure can lead to death
- Histology
  - Suprabasilar acantholysis and dyskeratotic keratinocytes with basal vacuolar change
  - DIF: IgG and C3 intercellular and linear/granular at dermoepidermal junction
  - IIF: Intercellular IgG on rat bladder
- Antibodies
  - **Against plectin, desmoplakins I and II, BPAg1, envoplakin, periplakin, desmogleins 1 and 3**
- Treatments
  - Occasionally remits with treatment of the tumor

TIP

Criteria for Paraneoplastic Pemphigus: Need 3 Major or 2 Major Plus 2 Minor

- Major criteria
  - Polymorphous mucocutaneous eruption
  - Concurrent internal neoplasia
  - Characteristic serum immunoprecipitation findings
- Minor criteria
  - Positive IIF on rat bladder
  - Positive DIF
  - Acantholysis on biopsy

TIP

Associations with Paraneoplastic Pemphigus

- Malignancy, especially non-Hodgkin's lymphoma (42%)
- Chronic lymphocytic leukemia (29%)
- Castleman's (6%)
- Sarcoma (6%)
- Thymoma (6%)

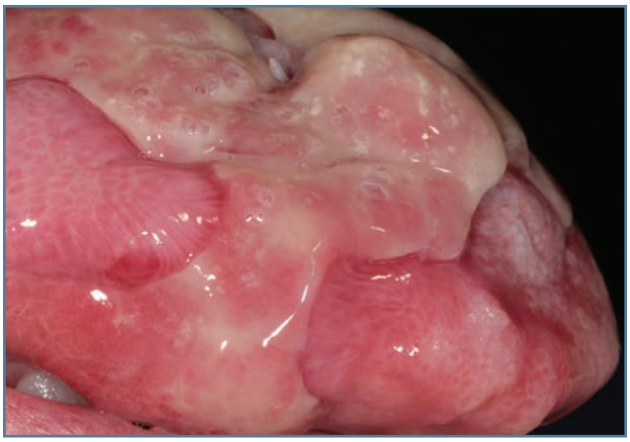


Figure 2.3.9 Paraneoplastic pemphigus.

SUBEPIDERMAL AUTOIMMUNE DISEASES

Bullous Pemphigoid (BP)

- Clinical
  - Tense bullae, noninflammatory base, rupture leads to well-demarcated denuded areas of skin
  - May also see urticarial, erythematous plaques
  - 20% have oral involvement
  - Rarely can be localized to the vulva or to a radiation site
  - **Risk factors include old age, dementia, and Parkinson's disease**
- Histology
  - Subepidermal blister with many eosinophils
  - Can have collections of **eosinophils** in dermal papillae
  - In urticarial stage of BP, eosinophilic spongiosis
  - DIF: Linear basement membrane C3 in ~95%, IgG4 in ~80%; "n-serrated pattern"
  - IF (ideal substrate: salt-split skin): Linear at basement membrane in 70%, usually stains to the **roof in salt-split skin**
- Antibodies
  - Against **BPAg1 (230 kDa), BPAg2-NC16A domain; BPAg2 (180 kDa)** is thought pathogenic
  - Neutrophil elastase and/or matrix metalloproteinase-9 cleaves BPAg2 in vitro
- Drug-induced BP
  - Classically cited inciting drug is **furosemide,** but sulfa drugs and thiol-containing drugs (captopril, penicillamine, gold thiosulfate) may be more common; others are nonsteroidal antiinflammatory drugs (NSAIDs) (ibuprofen), penicillin derivatives, cardiovascular drugs (enalapril, nadolol, practolol); psoralen plus ultraviolet A (PUVA) photochemotherapy can also lead to BP

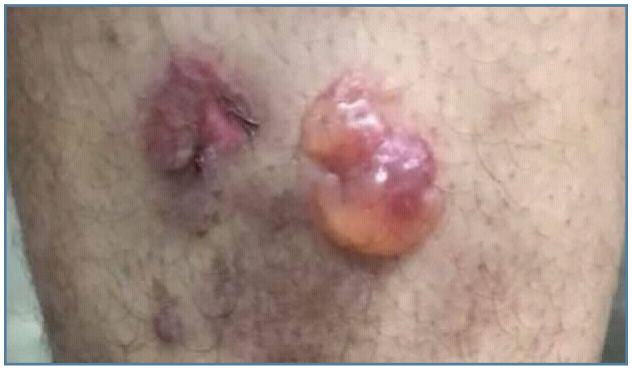


Figure 2.3.10 Drug-induced bullous pemphigoid.

- Treatments
  - Topical or oral steroids, rituximab, azathioprine, mycophenolate mofetil, nicotinamide, tetracycline
- Two other disorders can present clinically like BP but have different target autoantigens, so-called anti-p105 and anti-p200 pemphigoid
- Variants of bullous pemphigoid
  - Lichen planus pemphigoides: Overlapping features of bullous pemphigoid and lichen planus
  - Pemphigoid vegetans: Variant of BP with vegetative lesion predominantly in fold areas
  - Pemphigoid nodularis: Overlapping features of bullous pemphigoid and prurigo nodules

TIP

Autoimmune Tense Bullae Differential

- Bullous pemphigoid
- Epidermolysis bullosa acquisita
- Pemphigoid gestationis
- Linear IgA disease

Herpes Gestationis (HG) (Pemphigoid Gestationis)

- Clinical
  - 1:50,000 pregnancies; **onset in second or third trimester or postpartum period; can recur with subsequent pregnancies** or with oral contraceptive use or menstrual periods
  - Lesions are **urticarial papules/plaques around umbilicus** that progress to the abdomen and rest of body; blisters are often in a characteristic annular or polycyclic arrangement
  - Neonate: **May be premature or be small for gestational age;** <5% will have bullae
- Histology
  - Subepidermal split; is similar to BP
  - DIF: Linear C3, occasionally IgG at basement membrane
  - IIF: Often negative; 75% of patients have a circulating HG factor (an IgG antibody that fixes complement)
- Antibodies: **Against BPAg2, sometimes BPAg1**
- Associations: **Graves' disease,** rare case reports of associated choriocarcinoma, HLA-DR3 and HLA-DR4
- Treatments: Oral steroids

Mucous Membrane Pemphigoid (Cicatricial Pemphigoid [CP])

- Clinical
  - Transient vesicles that result in erosions/ulcers on the oral mucosa in about 100% of patients
  - Desquamative gingivitis
  - Conjunctiva involved in about 70% and can lead to scarring/symblepharon/blindness; skin lesions in 25% (face, neck, scalp, groin, extremities)
  - Variant: Brunsting-Perry pemphigoid
    - No mucosal involvement, blisters on patches of erythema on head/neck with scarring/scarring alopecia
    - Treatments: Topical/intralesional/oral steroids, dapsone, cyclophosphamide, azathioprine
- Histology
  - Subepithelial bullae, similar to BP
  - DIF: Linear C3, IgG, fibrinogen, occasionally IgM/IgA at basement membrane in 90%
  - IIF: Linear at basement membrane in 20%
- Antibodies
  - **Against BPAg1 and BPAg2, laminins 5 and 6, β_4-integrin, and type VII collagen**
- Drug-induced CP
  - Topical medications for glaucoma, cardiovascular drugs (practolol)

TIP

Subtypes of CP and Their Associated Autoantibodies

- Mucosal and skin lesions
- Ocular form
- Malignancy associated
- BPAg2 (distal C-terminal domain)
- β_4-Integrin
- Laminin 5 (= epiligrin, BM600, kalinin, nicein)

Dermatitis Herpetiformis (DH) (Duhring's Disease)

- Clinical
  - Severely pruritic grouped vesicles located symmetrically on extensor surfaces/occasionally scalp
  - Pruritus causes vesicles to be transient as scratching results in erosions
  - Presentation can also be nonspecific with papules, urticaria, tense bullae, or polymorphous lesions
  - Spontaneous improvement with cyclic exacerbations
  - **Iodides can worsen disease**
- Histology
  - Suprapapillary vesicles, multilocular, containing mostly **neutrophils;** papillary dermis and basement membrane zone are destroyed due to inflammatory infiltrate (no festooning), reverse festooning on the roof
  - DIF: Granular (rarely fibrillar) IgA > C3 in dermal papillae in 100%
  - IIF: Negative
- Antibodies
  - Against transglutaminase 3; ELISA testing can be ordered to check for antibodies
  - In celiac disease, there are often circulating anti-endomysial and anti-gliadin antibodies
- DDx
  - Linear IgA, DH secondary to drug, inflammatory epidermolysis bullosa acquisita (EBA), bullous systemic lupus erythematosus (SLE), BP, HG, erythema multiforme
- Associations
  - HLA-DQ2 (which is linked to the more commonly cited HLA-B8 in a common ancestral haplotype), thyroid disease (40%), small bowel lymphoma (non-Hodgkin's lymphoma), 90-100% have abnormal jejunal biopsies (similar to celiac sprue patients) but most are asymptomatic in terms of celiac disease
- Treatments
  - Gluten-free diet (gliadin is the soluble, antigenic component in gluten; gluten is found in wheat, barley, rye), dapsone, sulfapyridine, sulfasalazine

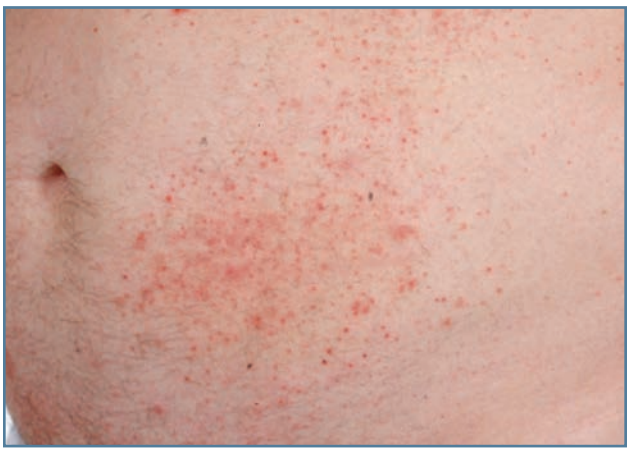


Figure 2.3.11 Dermatitis herpetiformis.

Linear IgA Disease

- Clinical
  - Can present like DH or BP with urticaria and oral/conjunctival lesions; sometimes lesions are more linear/annular/serpiginous as compared with BP ("crown of jewels" configuration); common sites are intertriginous
- Histology
  - Subepidermal blister that can look like DH with neutrophils along the dermoepidermal junction
  - DIF: Linear IgA at basement membrane in 100%
  - IIF: Linear IgA at basement membrane in 20-70%
- Antibodies
  - **Against the 97kd portion of BPAg2 (linear IgA disease antigen = LAD-1);** note that some patients originally described as having linear IgA disease with antibodies against type VII collagen may actually have had EBA
- Drug-induced
  - Commonly **vancomycin,** penicillins (PCNs), cephalosporins, captopril; also lithium, diclofenac, amiodarone, PUVA, furosemide, interleukin (IL)-2, interferon (IFN)-γ, phenytoin, atorvastatin, second-generation angiotensin-converting enzyme (ACE)-I, angiotensin receptor blockers
- Treatments
  - Dapsone, steroids, other immunosuppressants

Chronic Bullous Disease of Childhood (CBDC)

- Clinical
  - Children with blisters in circular arrangements on the groin/lower extremities **("crown of jewels")** and perioral/scalp areas; severe pruritus
- Histology
  - Subepidermal bullae with neutrophils at the dermoepidermal junction; occasional eosinophils
  - DIF: Linear IgA
  - IIF: Circulating IgA in ?50%
  - Immunoelectron mapping: IgA localizes to the lamina lucida and occasionally also to the sublamina densa
- Antibodies
  - **Against 97-kDa antigen that is a part of BPAg2**
- Treatments
  - Disease tends to resolve spontaneously, but treatments include dapsone, sulfapyridine, steroids

Epidermolysis Bullosa Acquisita (EBA)

- Clinical
  - Classically like dystrophic EB, but in adults
  - Noninflammatory trauma-induced bullae (often on hands/feet) that heal with scarring/milia, increased skin fragility
  - Oral/esophageal involvement possible (CP-like)
  - Note that the above is the classic presentation in the original reports of EBA; subsequently, BP-like presentations (inflammatory bullae, on trunk/extremities) have been described, and some feel that EBA may be a diverse group of diseases
- Histology
  - Subepidermal, classically noninflammatory (porphyria cutanea tarda [PCT]-like or dystrophic EB-like), but may be inflammatory with neutrophils (DH-like) or eosinophils (BP-like)
  - DIF: Linear IgG (sometimes IgM, IgA, C3, fibrinogen as well) at basement membrane in 100%; on base of salt-split skin (rather than roof for BP)
  - "u-serrated pattern"
  - IIF: IgG at basement membrane in 50%
- Antibodies
  - **Against type VII collagen**
  - Treatments
    - Often nonsatisfactory; consider systemic steroids, immunosuppressants (e.g., azathioprine, mycophenolate mofetil), dapsone, IVIG

TIP

Associations with EBA

- Inflammatory bowel disease
- Autoimmune disorders (SLE, rheumatoid arthritis, diabetes, Hashimoto thyroiditis)
- Amyloidosis
- Myeloma
- Lymphoma

Bullous Systemic Lupus Erythematosus

- Clinical
  - Noninflamed bullae, patient generally with history of systemic lupus erythematosus
- Histology
  - Can look like dermatitis herpetiformis
  - DIF: Linear IgG, IgM, IgA, C3, fibrinogen

- IIF: Generally negative
- Antibodies
  - **Against type VII collagen**
- Treatment
  - Dapsone, azathioprine, prednisone

HEREDITARY BULLOUS DISEASES

Epidermolysis Bullosa (EB)

- Rare genetic disorders due to defects in proteins that play a part in holding the skin together
- Clinical
  - In all types of EB, minor mechanical trauma leads to blisters, generally noninflamed, and healing is with or without scarring/milia
  - Nail dystrophy/alopecia can be present in all types (although less common in simplex type)
- Classification: There are currently four main types
  - EB simplex: Fragility and blistering confined to the epidermis
  - Junctional EB: Blister forms through the lamina lucida of the basement membrane
  - Dystrophic EB: Blister occurs below the lamina densa in the superficial dermis
  - Kindler syndrome: Blisters at multiple levels and photosensitivity
- **Subclassification: "Onion skin" approach, new since 2014**
  1. First the disease is classified into one of the four main EB types
     - Junctional
     - Simplex
     - Dystrophic
     - Kindler

     Then other information is added to classify the condition better
  2. Phenotype, severity, and distribution are described
  3. Mode of transmission, autosomal dominant or recessive
  4. Site of cleavage ultrastructurally and associated findings
  5. Protein involved
  6. Gene involved
  7. Mutation

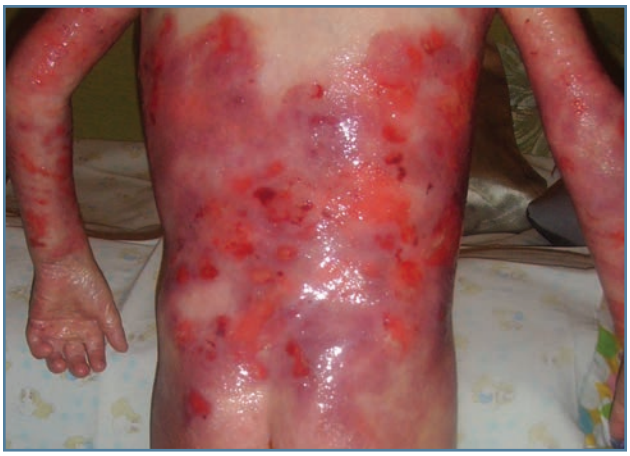


Figure 2.3.12 Epidermolysis bullosa.

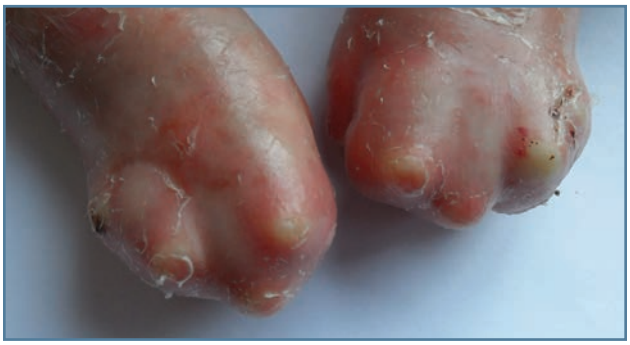


Figure 2.3.13 Mitten deformity.

TIP

EB helpful hints

- All EB simplex is autosomal dominant except for some rarer subtypes (not listed)
- Hemidesmosomal and junctional EB are autosomal recessive
- Grouped blisters are most commonly seen in generalized, severe subtype of EB simplex
- Enamel hypoplasia is more characteristic of the junctional subtypes
- Exuberant granulation tissue in perioral/axillary/neck area is most characteristic of the generalized, severe subtype of junctional EB
- Increased risk of squamous cell carcinomas in the generalized-severe type of recessive dystrophic EB

TABLE 2.3.10 EPIDERMOLYSIS BULLOSA SUBTYPES AND CAUSATIVE DEFECTS

Important Subtypes	Defects
EB simplex	Keratins 5/14 Transglutaminase 5 Plakophilin 1 Desmoplakin Plakoglobin Plectin Exophilin 5 BPAg1
Junctional EB	Laminin 332 Collagen XVII $\alpha_6\beta_4$-Integrin α_3-Integrin
Dystrophic EB	Collagen VII
Kindler	Fermitin family homolog Kindlin-1

Epidermolytic Ichthyosis (Bullous Congenital Ichthyosiform Erythroderma)

- Autosomal dominant, **defect in keratins 1/10**
- Clinical
  - Infants are often born or affected early on with blisters that resolve
  - Affected patients develop "corrugated" layered scaling that is generalized but prominent over flexural areas
- Histology
  - Epidermolytic hyperkeratosis = **characteristic pattern of degeneration of the cells of the spinous layer**

Familial Benign Pemphigus (Hailey-Hailey Disease)

- **Autosomal dominant. Mutation in *ATP2C1*,** encoding a calcium pump in the Golgi apparatus of keratinocytes
- Clinical
  - Affects neck, axillae, groin, and other intertriginous areas. Blisters that become vegetative, erosive **(stellate)** plaques that are malodorous. Usually worse in the summer. Secondary infections are common
- Histology
  - Full-thickness epidermal acantholysis forming a **dilapidated brick wall**
  - DIF and IIF: Negative
- Treatment
  - Treat secondary infection, topical/systemic steroids, cyclosporin, UVB light therapy
- Helpful hint: To see one Hailey's comet will make you just fall apart

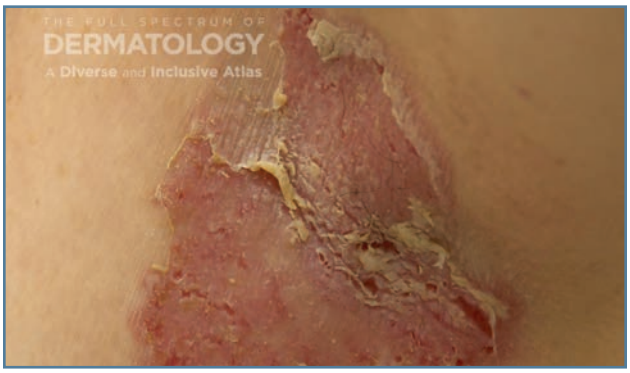


Figure 2.3.14 Hailey-Hailey disease.

Incontinentia Pigmenti

- X-linked dominant, gene mutation in NF-κB essential modulator ***(NEMO)***
- Clinical
  - Presents with different stages
    - Stage I: Vesicles/bullae (first 2 weeks of life)
    - Stage II: Become hyperkeratotic and verrucous (2-6 weeks of life)
    - Stage III: Resolving with hyperpigmentation
    - Stage IV: Sometimes hypopigmentation
  - May have abnormal teeth and/or alopecia
- Histology
  - Stage I: Spongiosis, sometimes with blister formation, with eosinophils and apoptotic keratinocytes
  - Stage II: Epidermal hyperkeratosis, acanthosis, dyskeratotic keratinocytes, melanophages, and some eosinophils
  - Stage III: Melanophages present in superficial dermis

Porphyria Cutanea Tarda (PCT)

- Clinical: Dorsal hands/scalp/face with blisters that **heal with scarring/milia, hypertrichosis,** hyperpigmentation, sclerodermoid changes. Most common porphyria
- Histology: Minimal inflammatory infiltrate, fibrin cuffing (periodic acid—Schiff [PAS]+) of vessels is type IV collagen, caterpillar bodies in epidermis, **festooning** of papillary dermis at base of blister
- DIF: Linear IgG, IgM, IgA, C3, fibrinogen at basement membrane and around vessels
- IIF: Negative
- Porphyrin profile: Urine uroporphyrin/coproporphyrin,

stool isocoproporphyrin
- Associations: Hemochromatosis (C282Y gene), hepatitis C, HIV, lupus erythematosus, hematologic malignancies
- Treatment: Phlebotomy, antimalarials

Congenital Erythropoietic Porphyria (Gunther's)

- Clinical: Severe photosensitivity that leads to mutilation if light not avoided, erythrodontia
- Treatment: Sun avoidance, bone marrow transplant

TIP

DDx of Noninflammatory Bullae

- PCT
- Pseudoporphyria
- Noninflammatory EBA
- Bullosis diabeticorum
- Suction or friction bullae
- EB
- Patient on dialysis

Porphyria, Erythropoietic Protoporphyria Type

- Clinical: Pain with sun exposure, waxy thickening of knuckles/nose, gallstones, liver failure
- Histology: Eosinophilic thickened deposits around blood vessels in upper/mid-dermis
- Treatment: β-Carotene, N-acetylcysteine

Porphyria, Variegate and Hereditary Coproporphyria

- Clinical: Skin manifestations like PCT, with acute abdominal attacks like acute intermittent porphyria

TIP

Porphyria Helpful Hints

Distinguish variegate and hereditary coproporphyria by porphyrin profile: The latter should have much more coproporphyrin in urine and stool than the former

- Variegate porphyria has a characteristic emission peak at 626 nm
- Gallstones associated with erythropoietic protoporphyria
- No porphyrins in urine in erythropoietic protoporphyria
- No skin changes in acute intermittent porphyria

TABLE 2.3.11 PORPHYRIAS AND ASSOCIATED INHERITANCE PATTERN AND ENZYMATIC DEFECT

Disease	Inheritance Pattern	Enzyme Defect
Acute intermittent porphyria	AD	Porphobilinogen deaminase
Congenital erythropoietic porphyria	AR	Uroporphyrinogen synthetase III
Porphyria cutanea tarda	AD/sporadic	Uroporphyrinogen decarboxylase
Hepato-erythropoietic porphyria	AR	Uroporphyrinogen decarboxylase
Hereditary coproporphyria	AD	Coproporphyrinogen oxidase
Variegate porphyria	AD	Protoporphyrinogen oxidase
Erythropoietic protoporphyria	AD/AR	Ferrochelatase

AD = autosomal dominant; AR = autosomal recessive.

INFLAMMATION-MEDIATED BULLOUS DISEASES

Stevens-Johnson Syndrome (SJS)

- Clinical
  - Fever, severe mucosal/conjunctival ulcerations, and occasional genitourinary/gastrointestinal (GU/GI) involvement
  - Severity can be graded (see SCORTEN [SCORe of Toxic Epidermal Necrosis] scale)
- Histology
  - Mononuclear interface dermatitis with prominent necrosis of keratinocytes
- Antibodies
  - Antibodies against desmoplakins I and II have been described
- Associations
  - HLA-B*1502 has been linked with SJS due to carbamazepine in Han Chinese

The SCORTEN scale is a severity of illness scale used to determine the severity of certain bullous conditions. Seven risk factors are used, and the total score predicts the mortality rate.

TABLE 2.3.12 SCORTEN SCALE FOR PREDICTING MORTALITY IN PATIENTS WITH STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS

Risk Factor	0	1
Age	<40	>40
Associated malignancy	No	Yes
Heart rate	<120	>120
Serum BUN	<28	>28
Detached body surface	<10	>10
Serum bicarbonate	>20	<20
Serum glucose	<252	>252

Number of Risk Factors	Mortality Rate
0-1	3.2%
2	12.1%
3	35.3%
4	58.3%
5 or more	>90%

MNEMONIC

Major Causes of Drug-induced SJS

Sulfonamides
Anticonvulsants
NSAIDs
Allopurinol

Bullous Insect Bite

- Clinical
  - May be more common in patients with **chronic lymphocytic leukemia**
  - Pruritic papules, urticarial and bullous lesions
- Histology
  - Typical findings of an insect bite (intraepidermal spongiosis with eosinophils and dermal inflammation with eosinophils), but intraepidermal spongiosis is more severe and confluent, creating bullae

Erythema Toxicum Neonatorum

- Clinical
  - Affects up to 40-50% of infants, cause unknown
  - Papules and pustules that start within 48 hours of birth, lasting 2-3 days
    - Clinically often looks like a "flea-bitten" rash
  - Affects the face/trunk/proximal extremities; spares the palms/soles
  - Scraping and Gram stain reveals **eosinophils**; germ tubes would be seen in *Candida* infection
- Histology
  - Intraepidermal blister (in hair follicle) containing eosinophils
  - Note: **Baby's skin has small hair follicles,** small eccrine glands, increased number of fibroblasts in collagen

Transient Neonatal Pustular Melanosis

- Clinical
  - Affects 4% of blacks, <1% of whites; flaccid vesiculopustules (noninflamed base) develop over 1-2 days, rupture, and leave a collarette of scale, resolving with hyperpigmented macules that last 1-2 weeks
  - Sites commonly affected are the forehead, neck
- Histology
  - Subcorneal pustules (sterile); hyperpigmented macules show increased basilar pigmentation

Subcorneal Pustular Dermatosis (Sneddon-Wilkinson Disease)

- Clinical
  - Flaccid vesicles that turn in to pustules, mostly in flexural areas
- Histology
  - Subcorneal pustules with many **neutrophils,** no "cling ons"
  - DIF: No immune deposits
- DDx
  - Pustular psoriasis, impetigo, pemphigus foliaceus, acropustulosis of infancy, IgA pemphigus
- Treatment
  - Dapsone

Acropustulosis of Infancy

- Clinical
  - Recurrent, extremely pruritic vesicular eruption (in crops) on palms/soles of infants/toddlers, need to rule out scabies; onset usually 3-6 months, disappears by age 3-4 years old
- Histology
  - Subcorneal vesicle containing **neutrophils**
- Treatment
  - Very difficult to treat; dapsone may be helpful

INFECTIOUS BLISTERING DISORDERS

Staphylococcal Scalded Skin Syndrome (Ritter's Disease)

- Clinical: Patients present with fever, skin tenderness, and erythema that leads to a generalized superficial exfoliation; generally a disease of infants or young children but occasionally adults with decreased renal function
- Histology: Separation is subcorneal
- Infectious agent is ***Staphylococcus aureus*** **group 2 phage type 71,** which produces an exfoliative toxin that cleaves desmoglein 1. Blister fluid is sterile as blister formation is mediated by a systemic toxin
  - **Culture to be taken from rectal mucosa or nares**

Bullous Impetigo

- Localized form of staphylococcal scalded skin syndrome
- Fragile bullae resembling pemphigus; easy rupture leads to annular crusted lesions
- Often secondary to infection with ***Staphylococcus aureus*** **group 2 phage types 55 and 71;** bacteria are present in blister fluid as blister formation is mediated by a local toxin

Bullous Tinea

- Most commonly on feet
- Most commonly caused by Trichophyton mentagrophytes
- Cases have been reported with positive direct immunofluorescence

Herpesvirus Infection

- Please see Viral Infections in Section 2.2 Infectious Diseases of the Skin

OTHER DISORDERS THAT CAN PRESENT WITH A BLISTER

Pseudoporphyria

- Drug-induced: NSAIDs—most commonly naproxen, nabumetone, oxaprozin, also celecoxib; tanning beds; hemodialysis; tetracycline; nalidixic acid; thiazides; furosemide; cyclosporine; etretinate; isotretinoin; amiodarone
- Urine, blood, fecal porphyrins often normal

MNEMONIC

Drug-induced PCT

Let's Really Party Hard T(w)oNight

Lasix (furosemide)
Retinoids
Pyridoxine
Hemodialysis
Thiazides
Tanning beds
NSAIDs

Bullosis Diabeticorum

- Clinical: Tense blisters on noninflamed base, generally on legs/acral, often appear suddenly
- Histology: Intra- or **subepidermal** bullae, **noninflammatory**
- DIF: Generally negative

Bullous Lichen Planus

- Thought to arise secondary to extensive interface change (and therefore bullae arise in existing lesions of lichen planus)

Lichen Planus Pemphigoides

- Some patients have features of lichen planus as well as bullous pemphigoid, and blisters arise on normal skin (not in preexisting lesions of lichen planus)
- These patients often have circulating antibodies against BPAg2
- DIF can show IgM and C3 in colloid bodies

Bullous Mastocytosis

- IgE-mediated releasers: Penicillins

TIP

Direct Histamine Releasers

- Opiates
- Succinylcholine
- *d*-Tubocurarine
- Polymyxin B
- Radiocontrast
- Vancomycin
- Thiamine

Coma Blister

- Clinical: Tense blister at pressure sites
- Histology: Intra- or subepidermal blister with **eccrine gland necrosis**
- DIF: Generally negative

Congenital Syphilis

- Unlike other forms of syphilis, congenital syphilis can present with bullae

Drug-Induced Bullae

- Any drug eruption (fixed drug, erythema multiforme, etc.) can become bullous

Edema Bullae

- Blistering secondary to edema, often on the lower extremities

Friction Blister

- Clinical: Bullae on inflamed or noninflamed base, usually soles/hands
- Histology: Generally **intraepidermal (usually within granular layer)**

Sucking Blister

- Clinical: A blister or denuded area seen in neonates, secondary to sucking the area of the blister in utero; generally seen on the hand/wrist/forearm

TABLE 2.3.13 BLISTER TYPES AND ASSOCIATED LOCATIONS OF SPLIT

Blister Type	Location of Split
Bullous impetigo	Subcorneal
Friction Suction/sucking Drug-related Coma blister	Intraepidermal or subepidermal
Diabetic bullae Lichen planus Lupus erythematosus	Generally subepidermal

2.4 Cutaneous Manifestations of Systemic Disease

VITAMIN DEFICIENCIES AND EXCESS

Essential Fatty Acid Deficiency

- Risk factors
  - Malnutrition, parenteral nutrition lacking lipid supplementation, intestinal surgery, nephrotic syndrome
- Clinical findings
  - Periorificial and flexural erosive eruption (similar to zinc and biotin deficiencies), alopecia, and dry skin
- Diagnosis
  - Decreased linoleic and arachidonic acid levels; eicosatrienoic-to-arachidonic acid ratio > 0.4

Carotenemia

- Cause: Excessive intake of foods high in β-carotene, such as carrots and yellow squash
- Risk factors
  - **Hypothyroidism, diabetes, anorexia**
- Clinical findings
  - Yellow-orange discoloration most pronounced on palmoplantar sites and central face

Lycopenemia

- Cause: High intake of red foods, including tomatoes, beets, chili beans, papaya, and guava
- Clinical findings
  - Red discoloration of skin

Marasmus

- Prolonged deficiency of both protein and calories
- Clinical findings
  - Dry and wrinkled skin, lanugo-like hair, emaciated appearance
  - **Lacks the edema/anasarca seen in kwashiorkor**

Kwashiorkor

- Protein deficiency in the setting of adequate caloric intake
- Clinical findings
  - Edema/anasarca, pot belly, desquamation of skin with "flaky paint" appearance, bands of light and dark hair ("flag sign") with light hair representing periods of malnutrition, hypopigmented hair, superimposed infections

TABLE 2.4.1 VITAMIN DEFICIENCIES AND EXCESS

Vitamin	Deficiency	Excess	Clinical Pearls
Vitamin A	Phrynoderma (keratotic follicular papules on the extensor surfaces), xerosis cutis, xerophthalmia, night blindness, keratomalacia	Alopecia, cheilitis, xerosis, desquamation, dermatitis, epistaxis, transaminitis, pain in long bones (children), skeletal hyperostosis, pseudotumor cerebri	Deficiency seen in malabsorptive states (Crohn's, celiac, cystic fibrosis, cholestatic liver disease); excess resembles systemic retinoid side effect profile
Vitamin D	Alopecia, rickets, osteomalacia	Manifestations of hypercalcemia: "renal stones, painful bones, groans (constipation), and psychiatric moans"	Check for deficiency by having 25(OH)D level determined; deficiency seen in malabsorptive states, dark skin, obese, limited sun exposure
Vitamin K	Purpura, hemorrhage		Synthesized by gut bacteria; risk factors for deficiency include malabsorptive states and medications, including antibiotics and bile acid resins

TABLE 2.4.1 VITAMIN DEFICIENCIES AND EXCESS CONTINUED

Vitamin	Deficiency	Excess	Clinical Pearls
Vitamin E		Purpura	In excess, may reduce platelet aggregation and vitamin K function
Vitamin B_1 (thiamine)	**Glossitis,** Wernicke-Korsakoff syndrome		Deficiency seen in individuals with alcohol use disorder
Vitamin B_2 (riboflavin)	**Oral-ocular-genital syndrome,** including glossitis (magenta), angular cheilitis, blepharitis, seborrheic-dermatitis-like eruption, anogenital dermatitis (papules and erosions)		Deficiency seen in alcohol use disorder
Vitamin B_3 (niacin)	Pellagra, including the "3 Ds": dermatitis, diarrhea, dementia; skin findings include a photosensitive eruption (Casal's necklace) cheilitis, glossitis, anogenital erosions	Flushing, xerosis, pruritus, acanthosis nigricans	Risk factors for deficiency include medications (INH, 5-FU, azathioprine) alcohol use disorder, carcinoid tumor, Hartnup disease (impaired absorption of tryptophan), anorexia
Vitamin B_6 (pyridoxine)	**Seborrheic dermatitis–like eruption,** glossitis, angular cheilitis, neuropathy	Photosensitivity	Highest risk for deficiency in patients with alcohol use disorder
Vitamin B_7 (biotin)	Alopecia, acrodermatitis enteropathica–like eruption, conjunctivitis		Risk factors for deficiency includes ingestion of raw egg whites, malabsorptive states, multiple carboxylase deficiency, holocarboxylase synthetase deficiency
Vitamin B_9 (folic acid)	Glossitis, hyperpigmentation (Addison's-like), megaloblastic anemia		Resembles B_{12} deficiency, but lacks neurologic findings
Vitamin B_{12} (cobalamin)	Glossitis, hyperpigmentation (Addison's-like), canities, megaloblastic anemia, neuropathy		Risk factors for deficiency include strict vegan diet, malabsorptive states, bariatric surgery, and pernicious anemia
Vitamin C	Scurvy: Hemorrhagic gingivitis, perifollicular petechiae, corkscrew hairs, epistaxis, delayed wound healing	GI upset, nephrolithiasis	Deficiency seen in alcohol use disorder
Zinc	Periorificial and acral erosive eruption; triad of dermatitis, diarrhea, depression		Can be inherited or acquired; **weaning from breast milk, which has high zinc, can unmask acrodermatitis enteropathica;** risk factors for acquired deficiency include alcohol use disorder, anorexia, vegan diet, malabsorptive states, HIV, pregnancy, and penicillamine use; **serum alkaline phosphatase is low in zinc deficiency** (zinc-dependent enzyme)

5-FU = 5-fluorouracil; 25(OH)D = 25-hydroxyvitamin D; GI = gastrointestinal; INH = isonicotinyl hydrazide (isoniazid).

ACANTHOSIS NIGRICANS

Clinical Findings

- Velvety, hyperpigmented plaques in flexural regions (particularly the posterior neck and axillae)
- Less commonly, can present on acral surfaces as hyperpigmented plaques over the knuckles (particularly in individuals of African descent) and mucosal surfaces

Associated Conditions

- Systemic diseases: Type 2 diabetes, obesity, polycystic ovarian syndrome, metabolic syndrome
- Medications: Testosterone, oral contraceptives, glucocorticoids, niacin, protease inhibitors, aripiprazole, palifermin
- Genetic syndromes: Congenital lipodystrophies, leprechaunism, Down syndrome
- Malignancy: **Adenocarcinomas** (in particular, gastric)
  - More extensive involvement with atypical sites, including mucous membranes and palmoplantar sites, where it may be seen in association with tripe palms

Treatment

- Limited evidence, but consider tretinoin + ammonium lactate or topical vitamin D analog
- For axillary involvement, consider long-pulsed alexandrite laser

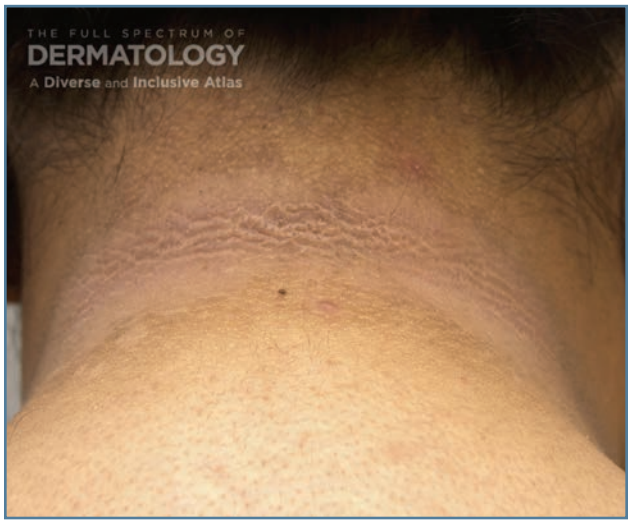


Figure 2.4.1 Acanthosis nigricans.

TIP

For patients with acanthosis nigricans (AN), consider screening for diabetes and if relevant, polycystic ovarian syndrome. For older, nonobese patients with new-onset AN, ensure that age-appropriate cancer screening is up to date and refer patient to gastroenterology for consideration of endoscopy, given the association with gastric cancer

FLUSHING DISORDERS AND CARCINOID SYNDROME

Approach to Flushing

- Step 1: Consider common causes
  - Thermoregulatory flushing
    - Fever, exercise, and hot beverages
  - Emotional blushing
  - Menopause
  - Rosacea
  - Food and beverages
    - Scombroid fish, spicy foods, monosodium glutamate, alcohol
  - Medications
    - Niacin, disulfiram, metronidazole (if taken with alcohol), calcium channel blocks, nitroglycerin, phosphodiesterase 5 inhibitors
- Step 2: Consider serious diagnoses
  - Carcinoid syndrome
    - Cause: Tumor derived from enterochromaffin cells; **appendix is the most common site,** followed by the ileum; carcinoid syndrome occurs in <4% of patients with abdominal carcinoid tumors, developing when there are hepatic metastases, a large tumor burden that overwhelms the liver's ability to degrade tumor-produced vasoactive hormones, or an atypical location in which the tumor directly accesses the systemic circulation
    - Clinical clues: **Pellagra-like rash due to consumption of tryptophan, flushing with telangiectasias,** yellow-brown or gray-brown patches on the forehead, back, and wrists, pruritus, bronchospasm, diarrhea and additional GI symptoms, valvular heart disease

- **Diagnosis: 24-hour urine 5-hydroxyindoleacetic acid (5-HIAA)**

- Systemic mastocytosis
  - Cause: Increased proliferation of mast cells (see more on mastocytosis in Section 2.1 General Dermatology)
  - Clinical clues: Symptoms of mast cell mediator release, including intermittent hypotension, tachycardia, abdominal pain, nausea, vomiting, diarrhea, and flushing
  - **Diagnosis: Serum tryptase**
- Anaphylaxis
  - Cause: Allergen, immunologic, or nonimmunologic trigger for mast cell degranulation
  - Clinical clues: Same as systemic mastocytosis, often with stridor and hives
  - **Diagnosis: Serum tryptase**
- Pheochromocytoma
  - Cause: Tumor derived from chromaffin cells, typically from the adrenal medulla
  - Clinical clues: Paroxysmal hypertension, tachycardia, headache, and flushing
  - **Diagnosis: 24-hour urine catecholamines ± plasma fractionated metanephrines**

- Step 3: Consider rare diagnoses if workup unrevealing
  - Medullary thyroid carcinoma
  - Vasoactive intestinal polypeptide (VIP) tumor (VIPoma; almost always pancreatic in origin)
  - Renal cell carcinoma
  - Neurogenic causes
    - Parkinson's, migraines, postural orthostatic tachycardia syndrome (POTS)
  - Short-gut syndrome

TIP

Menopausal flushing is caused by decreased estrogen levels, experienced by ~80% of women, and characterized by "hot flashes," which consist of intense episodes of sweating and flushing, lasting a few minutes and occurring up to 20 times per day. Treatment depends on the severity, but options include low-dose estrogen and selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and gabapentin

PRURITUS

Pathophysiology

- C fibers and A-delta fibers in the uppermost skin produce itch
- Histamine produces itch via the H1 receptor
- Other substances that produce itch: Trypsin, serotonin, bradykinin, kallidin, kallikrein, papain, substance P, and VIP
- Prostaglandins exaggerate existing itch
- Opiates have both central and peripheral itch-producing action
- Potential role of IL-31 cytokine in regulating neuroimmune pathways controlling itch

Framework for Itch

- Broadly speaking, the categories include: Dermatologic (i.e., itch caused by primary dermatologic disorder), systemic, neurologic, psychogenic, and mixed

Systemic Causes for Itch

- Chronic kidney disease
  - Unknown mechanism
  - Present in up to 80% of patients on hemodialysis (HD)
  - Often generalized (though may be worse on the back), worse at night, and may be either exacerbated during HD and/or improved right after HD
  - Treatment consists of the following: Optimizing dialysis, optimizing calcium-phosphate balance, emollients, gabapentin, narrow-band ultraviolet B (NB-UVB) therapy, kidney transplantation
- Biliary disease
  - Itch may be due to elevated bile salts
  - Generalized, but often worse on the hands and feet
  - Treatment: Correct underlying cause, warm baths, ursodeoxycholic acid (UDCA), bile acid sequestrant (cholestyramine or colestipol), rifampin, naltrexone
- Endocrine disease
  - Hyperthyroidism: Generalized pruritus (particularly in the setting of Graves' disease), treatment of thyroid disease results in improvement
  - Diabetes: Local or generalized (women may have isolated vulvar pruritus), improvement with glycemic control
- Malignancy
  - Most common associations include polycythemia vera (aquagenic pruritus) and Hodgkin lymphoma, though pruritus can be associated with other hematologic malignancies and gastric cancer

- HIV
  - May occur in the setting of an HIV-associated dermatosis (eosinophilic folliculitis) or infection (candidiasis), or be idiopathic
- Drug-induced
  - Pruritus without rash may be observed in association with chloroquine, clonidine, lithium, and gold salts
- Initial screen to evaluate generalized pruritus without rash
  - History and full review of symptoms
  - Drug history
  - Comprehensive physical exam
  - Laboratory studies, including basic metabolic panel, liver function tests, complete blood count with differential (CBC with diff), thyroid-stimulating hormone (TSH), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), and HIV screen

Neurologic Causes for Itch

- Brachioradial pruritus
  - Intermittent pruritus and/or pain on the dorsolateral forearm/elbow
  - May be caused by UV damage or cervical nerve root impingement (which can be further evaluated by a neurologist and consider of imaging)
  - Treatment is with topical capsaicin, compounded creams with amitriptyline and ketamine, and gabapentin
- Notalgia paresthetica
  - Unilateral pruritus and burning pain of the medial upper back
  - "Rippled" hyperpigmentation overlying scapula (most commonly) representing macular amyloid
  - May be due to spinal nerve entrapment
  - Treatment: Topical capsaicin, topical anesthetics, gabapentin, paravertebral nerve block

Figure 2.4.2 Notalgia paresthetica.

- Meralgia paresthetica
  - Localized numbness, paresthesias, and pruritus on the anterolateral thigh
  - Due to compression of the lateral femoral cutaneous nerve, possibly in association with obesity, pregnancy, and tight clothing
  - Treatment: Ensure there is no external pressure on the area, topical capsaicin, gabapentin, nerve block
- Reflex sympathetic dystrophy (complex regional pain syndrome)
  - Constellation of symptoms, often in a distal extremity, including burning pain, edema, sensory changes, motor limitations, vasomotor symptoms, and atrophy, which progresses through various stages following injury to a limb
  - Treatment: Physical therapy, gabapentin, tricyclic antidepressants (TCAs), and consideration of regional nerve blocks

Psychogenic Causes for Itch

- Obsessive-compulsive disorder
- Delusions of parasitosis
- Substance abuse

CUTANEOUS FEATURES AND DISORDERS OF PREGNANCY

Pemphigoid Gestationis (Herpes Gestationis)

- Due to IgG1 against the NC16A segment of bullous pemphigoid antigen 180 (BP180, or BPAg2), possibly triggered by exposure to the amniotic basement membrane zone (BMZ)
- Clinical findings
  - Urticarial papules and plaques that progress to vesicles and bullae; starts on the trunk and can spread to the face and palmoplantar sites; can involve the umbilicus (does not spare the umbilicus, as does polymorphic eruption of pregnancy)
- Diagnosis
  - Peripheral eosinophilia
  - Histology with subepidermal split with numerous eosinophils
  - Direct immunofluorescence (DIF) with linear C3 > IgG along BMZ

- Treatment
  - High-potency topical steroids; if not effective, prednisone 0.5 mg/kg, which can be tapered once blisters resolve
- Course and prognosis
  - Begins in second or third trimester; alternatively, it can begin immediately postpartum
  - Often takes weeks to months to resolve
  - Risk to fetus: **Increased risk for prematurity and small for gestational age;** may have mild blistering eruption (neonatal pemphigoid gestationis)
  - Recurs with subsequent pregnancy, oral contraceptive pills (OCPs), and menses
  - For mother, increased lifetime risk of Graves' disease; associated with HLA-DR3 and -DR4
  - Can occur in association with trophoblastic tumors (choriocarcinoma)

Polymorphic Eruption of Pregnancy

- Clinical findings
  - Papules begin in the striae and spread to trunk and extremities (spares the umbilicus and, often, the face)
- Diagnosis
  - Clinical: Laboratory study results are normal
- Treatment
  - Topical steroids, antihistamines
- Course and prognosis
  - Occurs during the third trimester or immediately postpartum
  - Resolves within a few weeks after delivery
  - No associated maternal or fetal morbidity
  - Generally does not recur
  - Increased risk in primigravadas and with maternal obesity and twin gestation

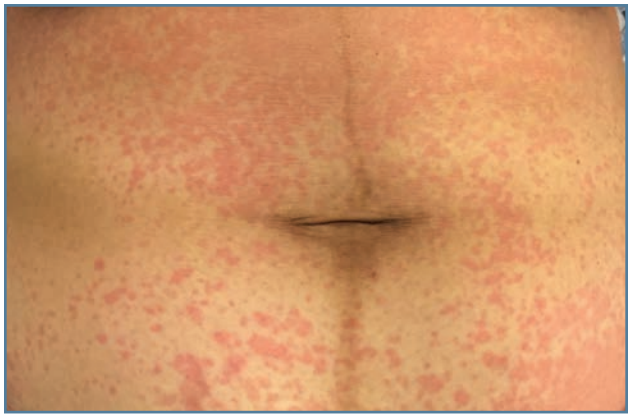


Figure 2.4.3 Polymorphic eruption of pregnancy

Atopic Eruption of Pregnancy

- Clinical features
  - Eczematous eruption, including the face, neck, and flexural region, similar to atopic distribution
- Diagnosis
  - Histology with spongiosis and perivascular inflammation
  - DIF negative
- Treatment
  - Emollients, topical steroids, antihistamines
- Course and prognosis
  - Often occurs during the first and second trimesters
  - Resolves within 2 weeks following delivery
  - No associated maternal or fetal morbidity
  - Generally recurs during subsequent pregnancies
  - Patients may have a history of atopic dermatitis

Cholestasis of Pregnancy

- Clinical findings
  - Severe pruritus without rash
  - Symptoms accentuated on palmoplantar sites and worse at night
  - Approximately 10% have jaundice
- Diagnosis
  - Increased serum bile acids (present in >90% of cases; elevation can lag behind pruritus)
  - May have elevated liver function test results
- Treatment
  - Ursodeoxycholic acid
  - Early delivery at 36 weeks
- Course and prognosis
  - Occurs during the late second or third trimester
  - Resolves within a couple of days following delivery
  - Risk to fetus: Stillbirth, premature birth, intrapartum fetal distress
  - **Maternal hemorrhage may occur due to decreased vitamin K (decreased absorption due to lack of bile acids)**
  - May recur with future pregnancies and OCPs
  - High bile acids (>40 mol/L) is predictive of poor fetal outcomes

Pustular Psoriasis of Pregnancy (Impetigo Herpetiformis)

- Clinical findings
  - Erythematous plaques studded with pustules, often starting in flexural regions and sparing the face and palmoplantar sites
  - May have onycholysis, mucosal involvement, and systemic symptoms, including fever, chills, and nausea
- Diagnosis
  - Laboratory studies may show leukocytosis, elevated ESR, and hypocalcemia
  - Culture of pustule negative
  - Histology with findings characteristic of pustular psoriasis
- Treatment
  - High-dose prednisone, typically 1-1.5 mg/kg daily
- Course and prognosis
  - Usually occurs during the third trimester, but may occur earlier and immediately postpartum
  - Resolves with delivery
  - Risk to fetus: Placental insufficiency and stillbirth
  - Recurs with future pregnancies and OCPs

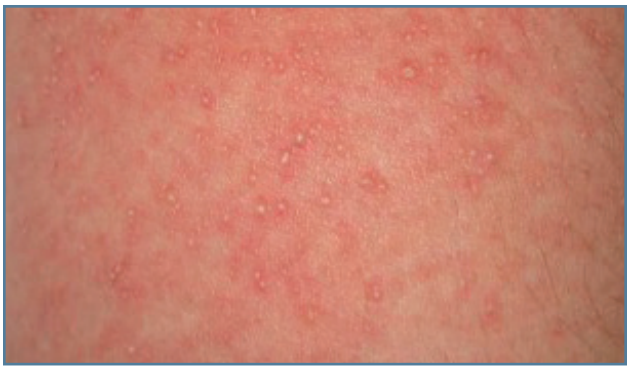


Figure 2.4.4 Pustular psoriasis of pregnancy.

Safety of Topical Steroids in the Setting of Pregnancy

- No causal associations between maternal use of topical corticosteroids and pregnancy outcomes, including assisted or cesarean delivery, birth defects, preterm delivery, fetal death, and low Apgar score
- However, maternal use of potent or very potent topical corticosteroids is associated with low birth weight, particularly when the administered dosage during pregnancy is large

PARANEOPLASTIC DERMATOSES

TABLE 2.4.2 PARANEOPLASTIC DERMATOSES

Disease	Clinical Manifestations	Associated Malignancy	Miscellaneous
Conditions Associated with Cancer in Most or All Cases			
Hypertrichosis lanuginosa acquisita	Abrupt onset of lanugo hairs (soft nonpigmented) on the face → trunk and extremities	Lung, breast, and colon carcinoma	Exclude other causes for hypertrichosis, including thyrotoxicosis and medication effect (phenytoin, cyclosporine, diazoxide). May resolve with treatment of underlying malignancy
Bazex syndrome (acrokeratosis paraneoplastica)	Erythematous/violaceous psoriasiform dermatitis affecting the ears, nose, hands, and feet. Nail dystrophy and acquired keratoderma may be found	SCC of the oropharynx, larynx, and esophagus	Skin findings usually precede the underlying malignancy. Age-appropriate cancer screening should be performed, as well as consideration of laryngoscopy and endoscopy
Erythema gyratum repens	Concentric erythematous rings with trailing scale that have a "wood grain" appearance. Present on the trunk and proximal extremities. Intensely itchy	**Lung cancer** > breast, GI, GU, and cervical	Skin findings precede the diagnosis of cancer. Symptoms improve with treatment of underlying malignancy
Sign of Leser-Trélat	Rapid increase in size and/or number of seborrheic keratoses, which may be seen in association with acanthosis nigricans, tripe palms, and generalized pruritus	Gastric or colon cancer	Occurs before or after malignancy. May improve with treatment of underlying malignancy

TABLE 2.4.2 PARANEOPLASTIC DERMATOSES CONTINUED

Disease	Clinical Manifestations	Associated Malignancy	Miscellaneous
Paraneoplastic pemphigus	Mucosal erosions and stomatitis. Skin lesions are variable and include lichenoid lesions, erythema multiforme–like lesions, and/or vesicobullous eruption. May have scarring conjunctivitis, esophageal, nasopharyngeal, and genital lesions	Non-Hodgkin's lymphoma > CLL, Castleman's disease (#1 cause in children), thymoma, and sarcoma	Treatment includes managing cancer and immunosuppression. Most patients die from complications of malignancy. Bronchiolitis obliterans can occur and lead to death
Necrolytic migratory erythema (glucagonoma syndrome)	Erythema, vesicles, and erosions in periorificial, flexural, and acral distribution. May have associated angular cheilitis, glossitis, and adult-onset diabetes	Glucagon-secreting pancreatic tumor	Diagnosis with characteristic histology (acanthosis, parakeratotic scale, epidermal pallor, and necrosis of the granular layer), elevated serum glucagon, and spiral CT. Treatment with supportive care (including octreotide), tumor resection, and chemotherapy if metastatic
Cushing's syndrome	Generalized hyperpigmentation, hirsutism, facial plethora, buffalo hump, striae, telangiectasias, and atrophy. Systemic findings include hypertension, hyperglycemia, proximal myopathy, and osteoporosis	Small-cell lung carcinoma	Diagnosis with late-night salivary cortisol, 24-hour urinary free cortisol, and dexamethasone suppression test. In the case of ectopic ACTH, cortisol cannot be suppressed
Carcinoid syndrome	Flushing, pellagra-like rash, pruritus, bronchospasm, diarrhea and additional GI symptoms, and valvular heart disease	Tumor derived from enterochromaffin (Kulchitsky) cells	Primary site appendix > ileum > rectum. Diagnosis with 24-hour urine 5-hydroxyindoleacetic acid (5-HIAA)
Conditions Associated with Cancer in Some Cases			
Acanthosis nigricans (AN)	Rapid onset of hyperpigmented, velvety plaques involving the intertriginous areas. In malignant AN, may involve atypical sites, including dorsal hands and lips, and be seen in association with tripe palms and florid oral papillomatosis	Gastric cancer > breast, ovarian, and uterine carcinoma; lymphoma; mycosis fungoides	Improves with treatment of underlying malignancy
Sweet's syndrome	Tender erythematous and edematous papules, plaques, and pustules on the face, upper trunk, and extremities. Systemic manifestations include, but are not limited to: Fever, ocular involvement, arthritis, and pulmonary infiltrates	Acute myelogenous leukemia > lymphoma, polycythemia vera	Histology with prominent edema in the superficial dermis with a dermal infiltrate rich in neutrophils; leukocytoclastic vasculitis is absent. Treatment is with prednisone and management of underlying malignancy
Dermatomyositis	Heliotrope rash, Gottron's papules, Gottron's sign, photodistributed violaceous erythema and poikiloderma (including shawl sign), cuticular overgrowth with dilated capillary loops, seborrheic-like scalp dermatitis, hyperkeratosis on the lateral aspects of the digits, calcinosis cutis, ovoid palatal patch, painful palmar papules, proximal symmetric weakness	Ovarian > gastric, pancreatic, colon, lung	**Comprehensive malignancy screening should be performed at the time of diagnosis.** Consider myositis antibody panel to further subtype disease (**TIF1γ, MDA5,** anti-Jo1, etc.). Diagnosis of malignancy typically occurs within 3 years of dermatomyositis onset. Treatment with steroids, methotrexate, and mycophenolate mofetil
Multicentric reticulohistiocytosis	Red-brown nodular lesions, most commonly located on dorsal hands and nail folds, though may also be found on the paranasal region, ears, cornea, forearms, trunk, and mucosa. Severe destructive arthritis, which may progress to arthritis mutilans in ~50% of cases	Solid organ malignancy present in ~20%	Histology with nodular infiltrate consisting of multinucleated histiocytes with granular pink-purple "ground glass" cytoplasm

TABLE 2.4.2 PARANEOPLASTIC DERMATOSES CONTINUED

Disease	Clinical Manifestations	Associated Malignancy	Miscellaneous
Cryoglobulinemia (type I)	Purpura, livedo reticularis, Raynaud's phenomenon, ulceration	Multiple myeloma, Waldenström's macroglobulinemia	Diagnosis with increased serum cryoglobulins and histology demonstrating occlusive vasculopathy with eosinophilic intravascular deposits
Primary systemic amyloidosis	Waxy papules (often on the face), periorbital pinch purpura, macroglossia, diffuse alopecia, carpal tunnel syndrome, peripheral neuropathy, cardiomyopathy	Multiple myeloma, plasma cell dyscrasia	Diagnosis is made by demonstrating amyloid deposits within tissues (eosinophilic globules in the dermis and subcutaneous tissues) and elevated monoclonal light-chain protein in the serum and/or urine
Scleromyxedema	Waxy papules arranged in a linear configuration, often appearing on the face/neck. Sclerodermoid induration, which may result in a leonine facies. Systemic involvement includes dysphagia and arthritis	**IgGλ paraproteinemia,** multiple myeloma	Increased dermal collagen, mucin, and fibroblasts
Acquired ichthyosis	Resembles ichthyosis vulgaris with fish skin—like scale involving the extensors and sparing the flexural creases	**Hodgkin's lymphoma**	Ichthyosis improves with treatment of malignancy
Erythroderma	Widespread erythema and scaling, which may be accompanied by alopecia, nail dystrophy, and ectropion	Leukemia, lymphoma, Sézary syndrome	Evaluate with histology and flow cytometry. Supportive care with topical emollients, topical steroids, antihistamines, and fluids
Necrobiotic xanthogranuloma	Yellow, indurated papules with erythema and telangiectasias, often involving the periorbital region	Multiple myeloma, lymphoproliferative disorder	Associated with IgGκ paraprotein in >80% of cases. Systemic involvement may be present involving the lungs, heart, and other organs
Granuloma annulare	Often generalized, refractory to treatment, and with a perivascular inflammatory infiltrate on pathology	Lung cancer, lymphoma	Improves with treatment of underlying cancer

ACTH = adrenocorticotropic hormone; CT = computed tomography; GI = gastrointestinal; GU = genitourinary; CLL = chronic lymphocytic leukemia; MDA-5 = melanoma differentiation—associated protein 5; SCC = squamous cell carcinoma.

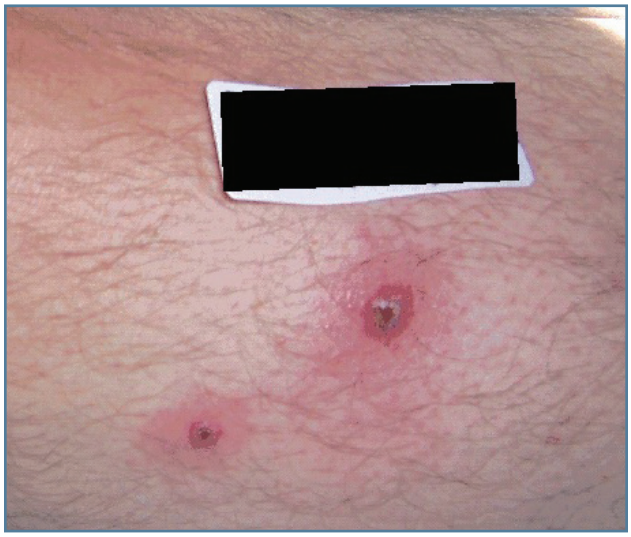


Figure 2.4.5 Sweet's syndrome.

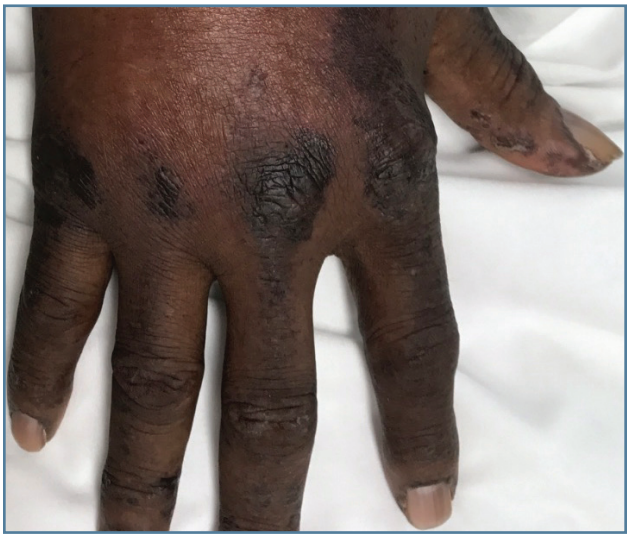


Figure 2.4.6 Dermatomyositis.

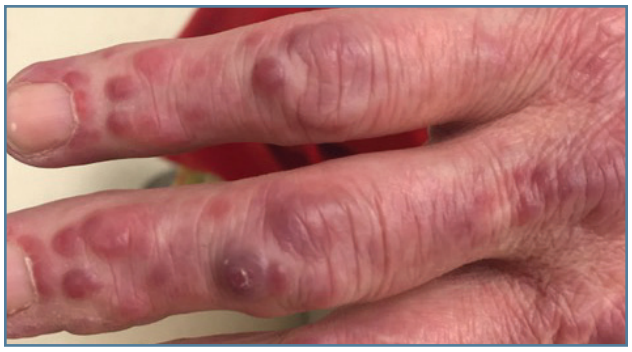


Figure 2.4.7 Multicentric reticulohistiocytosis.

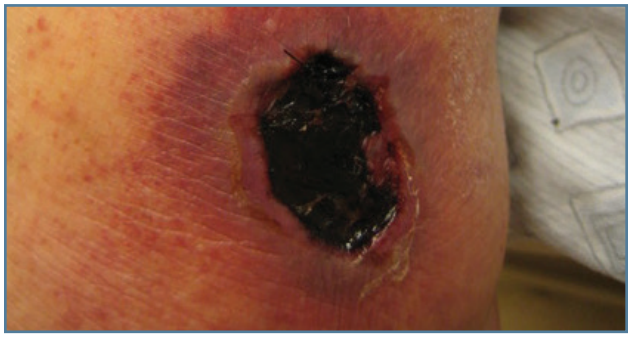


Figure 2.4.8 Cryoglobulinemia.

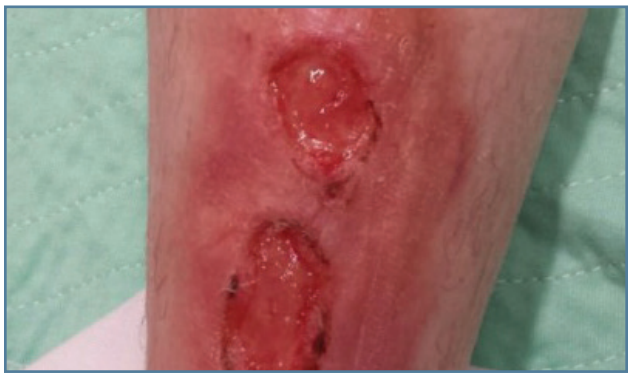


Figure 2.4.9 Necrobiosis lipoidica.

CUTANEOUS MANIFESTATIONS OF HEPATITIS C VIRUS

Cutaneous Findings

- Cryoglobulinemia (types 2 and 3)
- Cutaneous small vessel vasculitis
- Cutaneous polyarteritis nodosa (PAN)
- Porphyria cutanea tarda (PCT)
- Lichen planus (LP)
  - Erosive mucosal variant of LP has the strongest association with hepatitis C virus (HCV)
- Necrolytic acral erythema
- Urticaria
- Sarcoidosis
- Pruritus

Systemic Associations

- Autoimmune thyroiditis
- Membranoproliferative glomerulonephritis
- Arthritis
- Neuropathy
- Lymphocytic sialadenitis (sicca symptoms)

CUTANEOUS MANIFESTATIONS OF ENDOCRINE DISORDERS

Thyroglossal Duct Cyst

- Remnant of the embryonic duct
- Most common cystic abnormality of the neck; present on the midline of the anterior neck
- Histology demonstrates a cyst wall with cuboidal, columnar, or stratified squamous epithelium; additionally, there are thyroid follicles in cyst wall

Thyroid Malignancies

- Papillary thyroid cancer can metastasize to the skin, though this is uncommon
- Medullary carcinoma may be seen in association with multiple endocrine neoplasia type 2A (MEN2A) and MEN2B, which are autosomal dominant syndromes caused by mutations in the *RET* gene, which encodes a tyrosine kinase receptor
- Follicular thyroid cancer may be seen in individuals with Cowden syndrome, which is an autosomal dominant condition caused by a mutation in *PTEN* (phosphatase and tensin homolog), which encodes a tumor suppressor protein. Additional cutaneous manifestations include trichilemmomas, acral keratoses, oral papillomas, acanthosis nigricans, and lipomas

MNEMONIC

Key Cutaneous Features of the MEN Syndromes, Think TAN MEN

Tuberous sclerosis-like (type 1)
Amyloid (lichen and macular, type 2A)
Neuromas (type 2B)

TIP

Key systemic features of MEN2A

- Parathyroid hyperplasia/adenomas
- Thyroid cancer (papillary)
- Pheochromocytoma

Key systemic features of MEN2B

- Thyroid cancer (papillary)
- Pheochromocytoma
- GI ganglioneuromatosis

Cutaneous Manifestations of Hyperthyroidism

- Graves' disease
- Goiter, pretibial myxedema, and ophthalmopathy, including proptosis and diplopia in addition to lid lag and stare
- Nonspecific manifestations
  - Skin: Smooth skin that is warm and moist, hyperhidrosis, pretibial myxedema, thyroid acropachy (clubbing associated with soft tissue swelling and periosteal bone formation), and pruritus
  - Hair: Fine and thin hair, mild diffuse alopecia
  - Nails: Onycholysis, koilonychia
  - Pigmentation: Hyperpigmentation (localized or diffuse) and increased risk of vitiligo
  - Other: Lid lag and stare, tachycardia, increased stool frequency, menstrual abnormalities, anxiety, tremor, and weight loss

Cutaneous Manifestations of Hypothyroidism

- Skin: Dry skin that is pale and cool, hypohidrosis, yellowish hue due to carotenemia, generalized myxedema, eruptive or tuberous xanthomas, easy bruising
- Hair: Coarse and brittle hair, decreased hair growth, alopecia of the lateral third of the eyebrow
- Nails: Brittle nails, onycholysis
- Congenital hypothyroidism: Dry and cool skin, thick lips, delayed dentition, macroglossia, wide-set eyes, broad nose, dwarfism, cutis marmorata, cardiac dysfunction, gastrointestinal dysfunction, and skeletal defects

CUTANEOUS MANIFESTATIONS OF DIABETES MELLITUS

TABLE 2.4.3 CUTANEOUS MANIFESTATIONS OF DIABETES

Dermatosis	Clinical Findings	Additional Information
Acanthosis nigricans	Velvety, hyperpigmented plaques in flexural regions (particularly the posterior neck and axillae)	Common in individuals of African and Hispanic descent. Seen in HAIR-AN syndrome (hyperandrogenism, insulin resistance, acanthosis nigricans)
Diabetic cheiroarthropathy	Thickened skin, which leads to tightness and decreased joint mobility. Inability to approximate palmar surfaces (prayer sign)	Associated with duration of diabetes, retinopathy, and nephropathy. Treat with PT and glucose control
Scleredema	Painless symmetric woody induration of the upper back and neck	Predominantly occurs in obese men with longstanding type 2 diabetes
Necrobiosis lipoidica (NL)	Red-brown papules that progress to yellow-brown atrophic plaques, often with a red-brown inflammatory border. May ulcerate centrally, which occurs in ~35% of cases. Often present on the legs	Only a subset of patients with NL have diabetes or impaired glucose tolerance. Treatment is with high-potency topical steroids under occlusion, intralesional steroids, tacrolimus, PUVA, and/or antimalarials
Diabetic dermopathy	Brown atrophic macules and patches on the shins	Common manifestation. No effective treatment

TABLE 2.4.3 CUTANEOUS MANIFESTATIONS OF DIABETES CONTINUED

Dermatosis	Clinical Findings	Additional Information
Diabetic bullae (bullosis diabeticorum)	Tense bullae on the lower extremities	Unknown cause. Histology with subepidermal split. DIF negative. Resolves over the course of a few weeks
Eruptive xanthomas	Abrupt onset of red-yellow papules that are most commonly on the extensor surfaces and buttocks. Koebnerization may occur	Associated with diabetes, elevated triglyceride levels to >1,500 to 2,000 mg/dL, obesity, alcohol use, and certain medications. In the case of diabetes, tight glycemic control results in regression of lesions
Carotenemia	Diffuse yellow-orange skin discoloration	Caused by an increased serum carotene level due to excessive intake of foods high in β-carotene, such as carrots and yellow squash, and impaired metabolism

DIF = direct immunofluorescence; PT = physiotherapy; PUVA = psoralen plus ultraviolet A (PUVA) photochemotherapy.

2.5 Disorders of Hair and Nails

HAIR DISORDERS

Alopecia: Nonscarring

TABLE 2.5.1 HAIR CYCLING

Phase	Duration	Percent in Each Phase
Anagen = growth phase	2-6 years	85-90%
Catagen = transition phase	2-3 weeks	1-2%
Telogen = shedding phase	2-3 months	5-10%

- Telogen effluvium
  - 3-5 weeks after inciting stressful event there is shift from anagen to telogen
  - 2-3 months later there is release of telogen hair (= club hair) ("clumps of hair" falling out at once). Causes:
    - Endocrine (postpartum, thyroid disease)
    - Nutritional (kwashiorkor)
    - Drug (warfarin, heparin, angiotensin-converting enzyme [ACE] inhibitors, β-blocker, lithium, oral retinoids, selective serotonin reuptake inhibitor [SSRI], amiodarone)
    - Stress (illness, anemia, surgery)
- Anagen effluvium = Sudden loss of anagen hairs
  - Inhibition or arrest of cell division in the hair matrix leads to a thin, weakened hair that fractures. Causes:
    - Radiation
    - Chemotherapy (antimitotic)
    - Mercury (contaminated seafood, antiseptic, fungicide)
    - Boric acid (insecticides)
    - Thallium (2-3 weeks postexposure, insomnia, irritability, CNS and peripheral nervous system [PNS] signs)
    - Severe protein malnutrition
- Loose anagen
  - Loss of clumps of hair ± unruly hair, hair pull shows anagen hair with "ruffled cuticle" which resembles a "crumpled sock"
  - Abnormal adhesion of the inner root sheath to the hair shaft
  - Usually presents in young females
  - Improves with age

- Short anagen syndrome
  - Anagen phase only lasting 1-2 years
  - Hair doesn't grow long
  - No decreased density or hair fragility
  - No identified mutation or associations
  - **Does NOT improve with age**
- Alopecia areata
  - Localized, totalis (entire scalp), universalis (whole body)
  - Ophiasis: Band-like loss over periphery of scalp
  - Normal scalp, exclamation point hair (tapering of hair at proximal end), nail pits
  - Autoimmune disease (thyroid, vitiligo, diabetes, systemic lupus erythematosus [SLE], myasthenia gravis)
  - Biopsy: Peribulbar, perivascular lymphohistiocytic infiltrate, **"swarm of bees"**
  - Treatment: Intralesional triamcinolone (ILTAC), topical steroid, systemic steroid, psoralen and ultraviolet A (PUVA), topical immunotherapy (e.g., anthralin, diphenylcyclopropenone, squaric acid dibutyl ester), minoxidil, cyclosporine, photodynamic therapy, excimer laser, JAK inhibitors
  - Phenomenon of hair "turning white overnight" from diffuse alopecia areata where mostly pigmented hairs are lost

Figure 2.5.1 Alopecia areata.

- Triangular alopecia
  - Congenital or childhood
  - Complete absence of hair or vellus hairs in triangular pattern in the temporal area, frequently bilateral
- Lipedematous scalp (alopecia)
  - Thick boggy scalp with alopecia
  - Affects women with darker skin types
- Postoperative (pressure-induced) alopecia
  - After lengthy surgical procedures (occiput)
  - Up to 28 days after procedure
- Androgenetic alopecia
  - Autosomal dominant (AD), polygenic with variable penetrance, progressive miniaturization of hair, increased telogen hairs
  - Males: Bitemporal, vertex (Hamilton-Norwood classification)
  - Females: Preserved anterior hair line, **"Christmas-tree"** pattern with widened hair part at vertex (Ludwig classification)
  - Type II 5α-reductase activity in dermal papilla and outer root sheath
  - Treatment: Minoxidil, finasteride, oral contraceptive pills, spironolactone, flutamide, cyproterone acetate, transplant
- Trichotillomania
  - Compulsive hair pulling, irregular broken hairs within a geometric localized area
  - Biopsy: Increased catagen hairs, trichomalacia, melanin in follicular canal **(pigment hair cast)**
  - Treatment: Clomipramine, SSRI, *N*-acetylcysteine

Figure 2.5.2 Trichotillomania.

- Traction alopecia
  - Hair loss secondary to tight braids, hair style with traction
  - Ultimately scarring if no intervention
  - Frontal and parietal
- Syphilitic alopecia
  - Secondary syphilis, 3-7% occurrence rate
  - "Moth-eaten": Nonscarring with indistinct margins or diffuse alopecia
  - Also has diffuse presentation resembling telogen effluvium

TABLE 2.5.2 GENODERMATOSES CAUSING SHORT HAIR OR ALOPECIA

Genodermatosis	Defect	Inheritance
Rothmund-Thomson (poikiloderma congenitale)	DNA helicase *(RECQL4)*	AR
Anhidrotic ectodermal dysplasia (Christ-Siemens-Touraine)	Ectodysplasin A *(EDA)*	XLR
Hidrotic ectodermal dysplasia (Clouston syndrome)	Connexin 30	AD
Keratitis-ichthyosis-deafness	Connexin 26	AD
Incontinentia pigmenti (Bloch-Sulzberger)	NF-κB essential modifier *(NEMO)*	XLD
Focal dermal hypoplasia (Goltz)	*PORCN*	XLD
Trichorhinophalangeal syndrome type 1	*TRPS1*	AD
Hay-Wells (ankyloblepharon-ectodermal defects-cleft lip/palate [AEC] syndrome)	*TP63*	AD
Ectrodactyly-ectodermal dysplasia-clefting	*TP63*	AD
Tricho-dento-osseous syndrome	*DLX3*	AD
Cartilage-hair hypoplasia (McKusick's metaphyseal dysplasia)	*RMRP*	AR
Dermatopathia pigmentosa reticularis	Keratin 14	AD
Faciocutaneoskeletal syndrome (Costello)	*HRAS*	AD
Cardiofaciocutaneous syndrome	RAS/ERK pathway (*BRAF* most common)	AD
Hypotrichosis simplex of the scalp	*CDSN* (encodes corneodesmosin)	AD
Papular atrichia	Hairless gene	AR
Hypotrichosis, localized type 1 Hypotrichosis, localized type 2 Hypotrichosis, localized type 3	Desmoglein 4 *(DSG4)* Lipase H (LIPH) Purinergic receptor P2Y *(P2RY5)*	AR AR AR
Ichthyosis follicularis, atrichia, and photophobia (IFAP) syndrome	*MBTPS2*	XLR

AD = autosomal dominant; AR = autosomal recessive; XLD = X-linked dominant; XLR = X-linked recessive.

Alopecia: Scarring

- Lymphocytic
  - Chronic cutaneous lupus erythematosus
    - Red or hyperpigmented plaques with adherent scale
    - Follicular keratosis when scale removed, resembling "carpet-tacking"
    - Residual hypopigmented patches
    - **4-fold increased risk of nonmelanoma skin cancer**

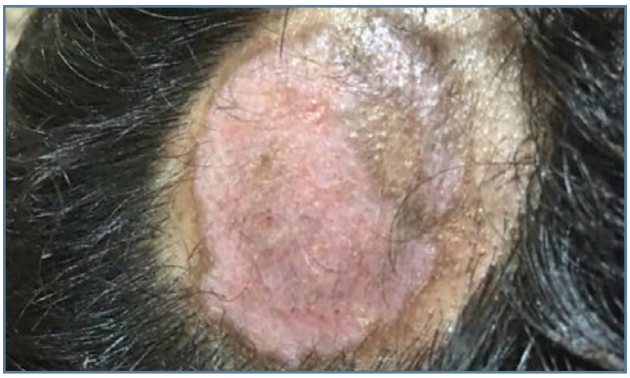


Figure 2.5.3 Chronic cutaneous lupus erythematosus.

- Lichen planopilaris (LPP)
  - Alopecia with perifollicular erythema
  - Frontal fibrosing alopecia (FFA): Elderly women, affecting anterior hair line and eyebrows
    - It is still controversial as to whether LPP and FFA are the same or distinct diseases
  - Graham-Little-Piccardi-Lassueur syndrome
    Scarring alopecia of scalp, nonscarring alopecia of axillary and pubic regions, grouped spinous follicular papules on trunk and extremities (which are histologically lichen planus)
- Central centrifugal cicatricial alopecia
  - Predominantly on the vertex
  - Greatest activity at the periphery
  - Burns out after years or decades
  - Predominantly African American women
  - **Increased risk for uterine fibroids**
  - Associated with mutations in *PADI3* (peptidylarginine deiminase, type III) which is involved in proper hair shaft formation
- Follicular mucinosis
  - Alopecia/broken hairs on scalp, beard
  - Hypoesthetic
  - Mucin in outer root sheath (cystic spaces) and sebaceous gland
  - Primary or secondary to cutaneous T-cell lymphoma (CTCL)
- Keratosis follicularis spinulosa decalvans
  - Scarring alopecia of scalp, eyebrows, and eyelashes and generalized keratosis pilaris
  - Associated with photophobia and corneal dystrophy
- Brocq's alopecia
  - Not distinct entity; end stage of various scarring alopecias
  - **"Footprints in the snow"**
  - Previously known as pseudopelade

- Neutrophilic
  - Dissecting cellulitis (perifolliculitis capitis abscedens et suffodiens of Hoffman)
    - African American males
    - Deep inflammatory boggy nodules ± sinus tracts on the occipital region
    - Biopsy: Follicular plugging, mixed cell inflammatory infiltrate, giant cells
    - **Follicular occlusion tetrad: Acne conglobata, hidradenitis suppurativa, dissecting cellulitis of the scalp, and pilonidal sinus**
  - Folliculitis decalvans
    - Perifollicular erythema and follicular papules/pustules spreading peripherally, resulting in central scarring alopecia
    - Tufted hair: Multiple hairs emerging from dilated follicular opening
    - Biopsy: Suppurative folliculitis with polymorphonuclear leukocytes (PMNs) and eosinophils
- Mixed
  - Acne keloidalis
    - African American males
    - Follicular papules and pustules → persistent firm papule or plaque at neck/occipital scalp
    - Misnomer: There are no keloids on histopathology

Excess Hair Growth

- Hirsutism
  - Terminal hairs in a male pattern in women
  - Secondary to increased androgens OR end-organ response to androgens
  - Eight categories:
    1. Pituitary: Adrenocorticotropic hormone (ACTH) (Cushing's) or prolactin; both stimulate adrenal production of androgens
    2. Adrenal: Congenital adrenal hyperplasia
    3. Ovarian: Polycystic ovary syndrome (PCOS), ovarian tumors, hyperthecosis
    4. Constitutional: Increased end-organ response to normal androgen levels
    5. Hepatic: Decreases sex hormone—binding globulin → increased free testosterone
    6. Ectopic hormone production: Small-cell lung cancer, choriocarcinomas, carcinoids
    7. Iatrogenic: Anabolic steroids
    8. Failure in converting androgens to estrogens (theoretical)
  - Treatment
    - Eflornithine (Vaniqa)
      - Inhibits ornithine decarboxylase located in the root of the hair follicle
    - Oral contraceptives
    - Glucophage: Other oral hypoglycemics used primarily in the treatment of diabetes
    - Spironolactone
    - Finasteride / dutasteride
    - Mechanical hair removal
- Hypertrichosis: Excess growth of hair anywhere on the body
  - Lanuga hairs: Fine nonpigmented hair covering the fetus and shed by first few weeks of life

- Congenital hypertrichosis lanuginosa
  - Silvery, blond and gray hair over entire body at birth or early infancy that is not replaced by vellus hairs
  - Up to 10 cm long and spares only palms, soles, distal dorsal phalanges, and prepuce
  - AD with variable penetrance
  - Dental and ear anomalies
- Acquired hypertrichosis lanuginosa
  - Paraneoplastic secondary to cancer (lung, colon, etc.): Lanugo hair on face or entire body

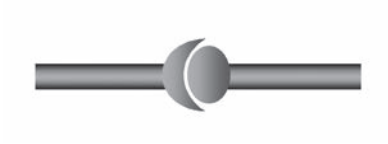
- Terminal hairs
  - Acquired generalized
    - Most often drug related (cyclosporine, minoxidil, phenytoin, psoralens)
    - Also POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes), juvenile dermatomyositis, juvenile hypothyroidism, acrodynia, anorexia, HIV, traumatic brain injury
  - Acquired localized
    - Subepidermal blistering diseases
      - Porphyrias (mainly porphyria cutanea tarda [PCT] and erythropoietic protoporphyria [EPP]), sun-exposed areas
      - Bullous pemphigoid
    - Repeated trauma, friction, irritation, or inflammation
    - PUVA, topical steroids, topical tacrolimus, anthralin, topical creams containing mercury or iodine
    - Trichomegaly: HIV, porphyrias, hypothyroidism, dermatomyositis, SLE, anorexia, kala-azar, medications (cyclosporine, topiramate, latanoprost, bimatoprost, interferon alfa, cetuximab, gefitinib)
  - Congenital generalized
    - Maternal ingestion of minoxidil or diazoxide
    - Cornelia de Lange, Rubinstein-Taybi, congenital erythropoietic porphyria, mucopolysaccharidoses, fetal alcohol syndrome
  - Congenital localized
    - Synophrys ("unibrow"): Isolated trait, Cornelia de Lange, Waardenburg, Zimmermann-Laband, mucopolysaccharidoses
    - Trichomegaly: Isolated trait, Oliver-McFarlane, Hermansky-Pudlak, fetal alcohol syndrome, Cornelia de Lange, Rubinstein-Taybi
    - Distichiasis (double row of eyelashes): Lymphedema-distichiasis syndrome, Setleis syndrome (double row on top, absent on the bottom lid)

Hair Shaft Abnormality

TABLE 2.5.3 HAIR SHAFT ABNORMALITIES

Hair Shaft abnormality	Condition	Defect	Inheritance
Pili torti: Flattened at irregular intervals and twisted along its axis 	Acquired		Acquired
	Menke's kinky hair	*ATP7A(MKN)*	XLR
	Björnstad	*BCS1L*	AR
	Crandall	Unknown	Unknown believed to be AR
	Bazex follicular atrophoderma	*UBE2A* (proposed)	XLD

TABLE 2.5.3 HAIR SHAFT ABNORMALITIES CONTINUED

Hair Shaft abnormality	Condition	Defect	Inheritance
Trichorrhexis nodosa: Thickened or weak points (nodes) along the hair shaft cause hair to break off easily 			Acquired
	Argininosuccinic aciduria	*ASL* (absent argininosuccinase)	AR
	Citrullinemia	*ASS1* (absent argininosuccinic acid synthetase)	AR
	Menke's kinky hair	*ATP7A*	XLR
	Trichothiodystropy (PIBIDS, Tay)	*ERCC2/XPD* *ERCC3/XPB*	AR
	Netherton	*SPINK5*	AR
Trichoschisis: Sharp transverse fracture 			Acquired
	Trichothiodystrophy	*ERCC2, ERCC3, or GTF2H5*	AR
	Marinesco-Sjögren	*SIL1*	AR
Trichorrhexis Invaginata (bamboo hair) 	Netherton	*SPINK5*	AR
Monilethrix (beaded hair) 	Monilethrix	*KRT81, KRT83, KRT86* Desmoglein 4	AD AR
Pili annulati (ringed hair): Alternating dark and light bands 		Unknown	AD or sporadic
Trichoptilosis (split ends)			Acquired
Pili trianguli et canaliculi (spun glass): Unruly blond hair	Uncombable Hair ("cheveux incoiffalbes")	*PADI3, TGM3, TCHH*	AR >AD
Woolly Hair	Naxos	Plakoglobin	AR
	Carvajal	Desmoplakin	AR

AD = autosomal dominant; AR = autosomal recessive; PIBIDS = photosensitivity, ichthyosis, brittle hair, intellectual impairment, decreased fertility, and short stature; XLD = X-linked dominant; XLR = X-linked recessive.

NAIL DISORDERS

Nail Matrix Abnormalities

- Beau's lines
  - Temporary arrest of the proximal nail matrix
  - Transverse depression in nail plate
  - Any condition that affects the proximal nail fold (PNF): Mechanical, eczema, contact dermatitis
  - If all nails affected think recent systemic illness or medication

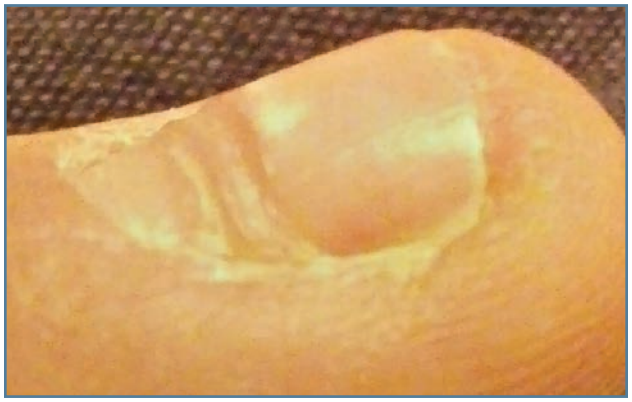


Figure 2.5.4 Beau's lines.

- Onychomadesis
  - "Nail shedding"
  - Complete arrest of nail matrix: Severe form of Beau's lines with the same causes
  - **Common feature following hand-foot-and-mouth disease**
- Koilonychia
  - "Spoon nails"
  - Iron deficiency anemia
  - Physiologic in children

Figure 2.5.5 Leukonychia.

- True leukonychia
  - Parakeratotic cells on the ventral surface of the nail plate
  - Most often secondary to trauma
  - Diffuse: Nail plate completely white
    - Sporadic, inherited or associated with systemic disease
  - Striate: Transverse white lines
    - Due to manicures or ill-fitting shoes
    - Mees' lines from arsenic or thallium
      - Paired lines

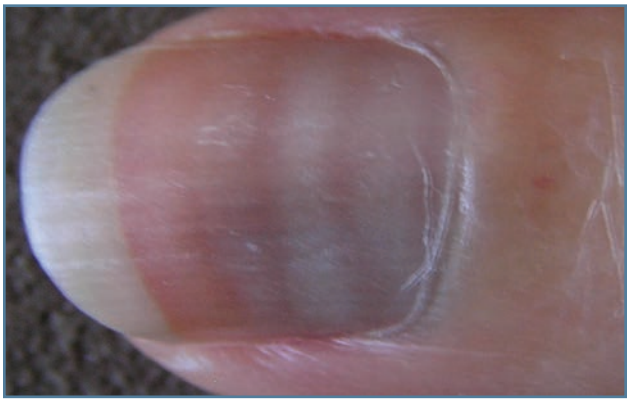


Figure 2.5.6 Mees' lines.

- Pitting
  - Parakeratotic cells in the dorsal nail plate detach leaving pits from abnormal keratinization of the proximal matrix
  - Psoriasis: Irregular pitting
  - Alopecia areata: Geometric pitting
  - Eczema: Irregular and coarse pitting
  - Rosenau's depression: Small pitted craters found on the middle and ring finger and are reported to occur in diabetes mellitus
  - Elkonyxis: Large punched-out pits at the lunula described in syphilis, reactive arthritis and oral retinoids
- Trachyonychia
  - Nail roughness, "sandpaper" nails
  - Lichen planus, psoriasis, eczema, and alopecia areata
  - Twenty-nail dystrophy in children self-limiting and regresses spontaneously
- Onychorrhexis
  - Longitudinal ridging and fissuring
  - Aging of the matrix
  - If severe and associated with thinning, indicative of lichen planus

- Habit tic deformity
  - Parallel transverse depression in the nail
  - Repetitive trauma to the matrix
- Onychoheterotopia
  - Abnormally placed nail due to displaced matrix material

Nail Bed Abnormalities

- Onychauxis
  - Subungual hyperkeratosis that gives the illusion of nail plate thickening
  - Psoriasis, onychomycosis, and eczema
- Oncholysis
  - Distal nail plate detachment
  - Psoriasis, blistering diseases
  - Environmental: Water, irritants, allergens, trauma, ultraviolet light
  - Drugs: Tetracyclines (photo), fluoroquinolones, psoralens, taxanes, nonsteroidal antiinflammatory drugs (NSAIDs), retinoids, 5-fluorouracil (5-FU)
  - Tumors: Squamous cell carcinoma (SCC), subungual exostosis, fibromas
  - Infections: Human papillomavirus (HPV), *Candida*

Figure 2.5.7 Oncholysis.

- Apparent leukonychia
  - White discoloration that fades with pressure and does not move distally with nail plate growth
  - Transparent nail plate
  - Muehrcke's lines: Double white transverse lines associated with hypoalbuminemia
  - Half-and-half nails (Lindsay's nails): Chronic renal insufficiency
  - Terry's nails: Entire nail bed except narrow distal end; liver failure, congestive heart failure (CHF), diabetes, age

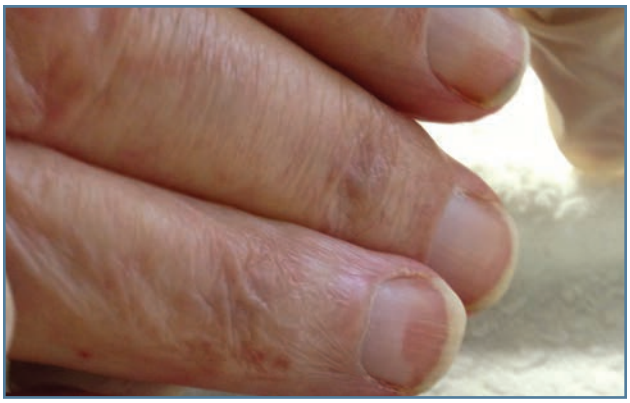


Figure 2.5.8 Terry's nails.

- Splinter hemorrhages
  - Damage to nail bed capillaries that are longitudinally oriented; most often distal
  - Do not blanch
  - Traumatic, psoriasis, onychomycosis
  - Proximal hemorrhages: Endocarditis, vasculitis, dialysis, antiphospholipid syndrome, and trichinosis (may be transverse)

Nail Plate Abnormalities

- Onychoschizia
  - Distal nail peeling of the surface
  - Harsh solvents and nail polish removers
- Pincer nail
  - Overcurvature of the nail in the transverse plane
  - Trauma, pressure from shoes, onychomycosis, renal failure, inherited, and β-blockers
- Brachyonychia
  - Short nails, "racquet nail"
  - Usually the thumb
  - Often inherited as autosomal dominant
- Dolichonychia
  - Elongated slender nails
  - Marfan's and Ehlers-Danlos syndromes
- Hapalonychia
  - Soft nails
  - Associated with onychoschizia and trachyonychia
  - Seen in malnutrition, anorexia, bulimia, retinoid therapy
- Onychogryphosis
  - Hypertrophy of the nail plate, often horn-like due to trauma

- Most often due to self-neglect in association with age and peripheral vascular disease

- Retronychia
  - Proximal nail plate growth into proximal nail fold
    - **Layers of multiple intact nails**
  - Caused by trauma
- Platonychia
  - Increase curvature in the long axis
  - Autosomal dominant
  - Has also been associated with iron deficiency
- Sclerodynia
  - Hard nails
  - Associated with systemic sclerosis
- Pachyonychia
  - Nail plate thickening
  - Seen when the rate of linear nail growth slows (aging or yellow nail syndrome)
  - Pachyonychia congenita nails are thickened along with nail bed hyperkeratosis
    - Type I—AD defects in *KRT6a* and *KRT16*
    - Type II—AD defects in *KRT6b* and *KRT17*

Nail Pigment

- Longitudinal melanonychia
  - Melanocyte activation
    1. Racial, pregnancy, trauma, HIV, postinflammatory, Addison's
    2. Drugs: Psoralens, 5-FU, zidovudine (AZT), doxorubicin, hydroxyurea
  - Nail matrix nevi
  - Nail matrix melanoma
    - 0.7-3.5% of all melanomas
    - 25% are amelanotic
    - 15% 5-year survival rate
    - African Americans, Asians, and native Americans are one-third of all nail melanoma cases
  - Melanocyte hyperplasia
  - Nonmelanocytic tumors
- Green nail syndrome
  - **Pyocyanin from *Pseudomonas aeruginosa***
  - Prolonged exposure to water
  - Treat with acetic acid or topical aminoglycosides
- Yellow nail syndrome
  - Associated with lymphedema and respiratory tract diseases (sinusitis, bronchitis, bronchiectasis, or pleural effusions)
  - Linear growth arrested or significantly slowed

Figure 2.5.9 Yellow nail syndrome.

Diseases with Specific Nail Findings

- Psoriasis
  - Up to 50% of patients with psoriasis
  - Often associated with psoriatic arthritis
  - Nail bed psoriasis
    - Onycholysis
    - Splinter hemorrhages
    - Subungual hyperkeratosis
    - Salmon patch or oil drop
  - Nail matrix psoriasis
    - Pitting
    - Leukonychia
    - Red spots in lunula
    - Crumbling
  - Psoriatic onycho-pachydermo-periostitis (POPP): Psoriatic nail changes, tender soft tissue thickening and osteoperiostitis
  - Acrodermatitis continua of Hallopeau
    - Relapsing episodes of painful pustule around and under the nail plate leading to onycholysis and onychomadesis
    - Not usually associated with skin findings yet has preceded generalized pustular psoriasis
    - Acitretin and biologics
- Lichen planus
  - Most commonly occurs in the absence of skin or mucosal findings
  - Thinning, longitudinal ridging and fissuring of the nail plate
  - Dorsal pterygium: Distal extension of the proximal nail fold onto the nail bed
  - Idiopathic atrophy of the nails
    - Variant of lichen planus
    - Almost exclusively seen in Asian children

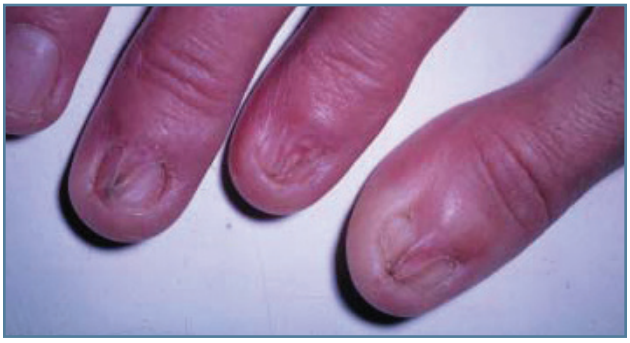


Figure 2.5.10 Lichen planus.

- Lichen striatus
  - Consider if lateral or medial lichen planus–like dystrophy of one nail in child or young person
  - Resolves spontaneously in 4-12 months
- Connective tissue disease
  - Dermatomyositis
    - Ragged cuticles (Samitz sign) with reduced capillary density and dropout; avascular areas alternating with dilated capillary loops
  - Systemic lupus
    - Normal capillary density with dilated tortuous capillaries
  - Scleroderma
    - Tightening of the digits and pterygium inversum unguis (ventral ptergium)

2.6 Plants, Allergens, Irritants, and Creatures of Dermatologic Significance

PLANT DERMATOSES

Can be divided into 4 reaction patterns

- Urticaria (immunologic and toxin mediated)
- Phototoxic (phytophotodermatitis)
- Irritant contact dermatitis (mechanical and chemical)
- Allergic contact dermatitis

Immunologic Contact Urticaria

- Requires prior sensitization
- IgE-mediated release of vasoactive mediators (histamine, prostaglandins, leukotrienes) from mast cells. More common in atopics
- **Celery *(Apium graveolans)* is the most common cause of generalized urticaria or anaphylaxis**

Toxin-Mediated (Nonimmunologic) Urticaria

- Does not need prior sensitization
- *Urtica dioica* (stinging nettle) from family Urticaceae is the most common cause of nonimmunologic urticaria
- Trichomes (sharp hair) have hollow cores that contain histamine, acetylcholine, serotonin
- Treatment: Benign, self-limited; can remove spines with glue/sticking plaster and gauze

Figure 2.6.1 Stinging nettle leaf.

Figure 2.6.2 Stinging nettle trichomes.

Phytophotodermatitis

- Direct toxic immunogenic reaction. Most common causes are family Apiaceae (celery, parsnip, parsley, hogweed) and family Rutaceae (lime, lemon, rue)
- Pathogenesis: UVA + photosensitizers (i.e., furocoumarins) + oxygen → reactive O_2 species → damage to epidermis and dermis → hyperpigmentation in linear streaks
- Psoralens and angelicins are the most common furocoumarins
- Clinically presents as painful, bizarre configuration of erythema, edema, and bullae

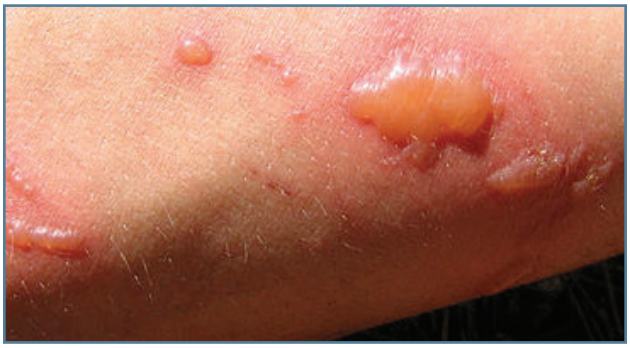


Figure 2.6.3 Phytophotodermatitis.

TIP

Unlike photoallergic reactions, which involve the immune system (type IV reaction), phytophotodermatitis is nonimmunogenic

IRRITANT CONTACT DERMATITIS

Mechanical Irritant Contact Dermatitis

- Direct toxic effect of the irritant on skin without involvement of an immune response
- Physical penetration from spines, thorns, or glochids (tufts of hundreds of short barbed hairs or bristles)
- *Opuntia* cactus spp. (prickly pears) are the most common cause
  - Presents as pruritic papular eruption where the skin comes in contact with glochids
- Treatment: Hot wax, glue, sticking plaster to remove spines/thorns
- There is potential for transmission of bacteria from spines (bacterial inoculation)

Figure 2.6.4 Prickly pear.

TABLE 2.6.1 IMPORTANT INFECTIONS TRANSMITTED BY PLANT CONTACT

Vector	Organism Transmitted
Spines	*Clostridium tetani*
Blackthorns	*Staphylococcus aureus*
Grass, sphagnum moss, rose thorns	*Sporothrix schenckii*
Blackberries	*Mycobacterium kansasii*
Cactus spines	*Mycobacterium marinum*
Spiky tropical vegetation	*Mycobacterium ulcerans*

Chemical Irritant Contact Dermatitis

- Pathogenesis: Exposure to chemical irritant
- Most common plants causing chemical irritant dermatitis

TABLE 2.6.2 PLANT IRRITANT CONTACT DERMATITIS

Chemical	Plant Family (Example)
Calcium oxalate: • Causes "daffodil itch" in florists • Severe reaction to oral exposure can cause salivation, burning, mucosal edema, vesicles, hoarseness • Seen with oral exposure to dumb cane	Asparagaceae (century plant) Amaryllidaceae (daffodil) Araceae (dumb cane and philodendron) Bromeliaceae (pineapple) Asparagaceae (hyacinth) Polygonaceae (rhubarb)
Thiocyanates	Alliaceae (garlic) Brassicaceae (black mustard)
Ranunculin	Ranunculaceae (buttercups)

TABLE 2.6.2 PLANT IRRITANT CONTACT DERMATITIS CONTINUED

Chemical	Plant Family (Example)
Phorbol esters	Euphorbiaceae (florist's croton, poinsettia, leafy spurge)
Capsaicin	Solanaceae (capsicum)
Cashew nut shell oil	Anacardiaceae (cashew tree)

Figure 2.6.5 Century plant.

Figure 2.6.6 Century plant.

Figure 2.6.7 Daffodil.

Figure 2.6.8 Dumb cane.

Figure 2.6.9 Hyacinth.

Figure 2.6.10 Rhubarb.

Figure 2.6.11 Buttercups.

Figure 2.6.12 Poinsettia.

Figure 2.6.13 Cashew.

ALLERGIC CONTACT DERMATITIS

TABLE 2.6.3 PLANT ALLERGIC CONTACT DERMATITIS

Allergen	Family/Plant	Notes
Urushiol	Anacardiaceae/*Toxicodendron* (poison ivy, poison oak, poison sumac)	Erythematous pruritic eruption, usually 4-96 hr after exposure; peaks in 1-14 days Black-dot dermatitis Treatment: Wash with soap and water; topical steroids may help if applied early; oral steroids with long taper for 4-6 wk, as there can be rebound with short courses
Sesquiterpene lactones	Asteraceae (chrysanthemum, daisy, artichoke, feverfew, chamomile, ragweed, sunflower, marigold, dandelion)	Cross-react with pyrethrins; avoid permethrin in patients with chrysanthemum allergy
Diallyl disulfide	Alliaceae (onion, garlic, leeks, chives)	
Tulipalin A	Alstroemeriaceae (Peruvian lily)	Most common cause of finger dermatitis in florists/gardeners handling tulip bulbs
Primin Colophony (rosin) and turpentine	Primulaceae (primrose) Pinaceae (pine tree, spruce tree)	Cross-reacts with Balsam of Peru

Figure 2.6.14 Poison ivy rash.

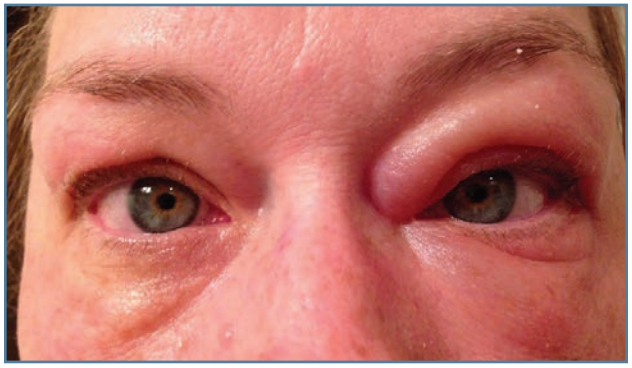


Figure 2.6.15 Poison ivy rash around the eyes.

Figure 2.6.16 Poison ivy plant.

Figure 2.6.17 Poison oak.

Figure 2.6.18 Poison oak late summer or autumn.

Figure 2.6.19 Poison sumac.

Figure 2.6.20 Chrysanthemum.

Figure 2.6.21 Daisy.

Figure 2.6.22 Ragweed.

Figure 2.6.23 Peruvian lily.

Figure 2.6.24 Primrose..

TIP

Cross-reactants to Anacardiaceae

- Cashew nut tree
- Japanese lacquer tree
- Mango tree
- Rengas tree
- Indian marking nut tree
- Gingko tree
- Brazilian pepper tree

Caterpillars *(Lepidoptera)*

- Lepidopterism: Dermatitis caused by caterpillars, cocoons, butterflies, or moths
- Erucism: Envenomation by caterpillars
- Ophthalmia nodosa: Ocular lesions from caterpillar hairs

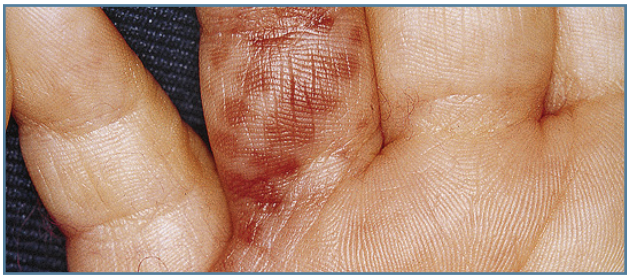


Figure 2.6.25 Puss caterpillar exposure.

TABLE 2.6.4 MOTHS/CATERPILLARS OF DERMATOLOGICAL SIGNIFICANCE

Moth/Caterpillar	Photo	Clinical Findings
Gypsy moth caterpillar	 *Figure 2.6.26 Gypsy moth caterpillar.*	Dermatitis
Io moth caterpillar	 *Figure 2.6.27 Io moth caterpillar.*	Dermatitis
Saddleback caterpillar	 *Figure 2.6.28 Saddleback caterpillar.*	Dermatitis
Puss moth caterpillar	 *Figure 2.6.29 Puss caterpillar.*	Dermatitis with characteristic "tram-track" hemorrhage Spines contain high concentration of oak tannins

TABLE 2.6.4 MOTHS/CATERPILLARS OF DERMATOLOGICAL SIGNIFICANCE CONTINUED

Moth/Caterpillar	Photo	Clinical Findings
Giant silkworm moth caterpillar	 *Figure 2.6.30 Giant silkworm moth.*	Local and severe systemic reaction, e.g., renal failure, bleeding diathesis
Pine processionary moth caterpillar	 *Figure 2.6.31 Pine processionary caterpillar.*	Urticaria (immunologic), angioedema, anaphylaxis Lytic bone lesions of the digits

SPIDERS

Most spider bites result only in local cutaneous reaction, but some spider bites can be more serious and even fatal.

TABLE 2.6.5 CLINICALLY IMPORTANT SPIDERS

Name	Description	Toxin	Clinical Findings
Black widow spider *(Latrodectus)*  *Figure 2.6.32 Black widow spider.*	Large, black, shiny spider with an hourglass-shaped red marking on the abdomen	α-Latrotoxin → depolarizes neurons	Acute pain and edema at bite site (no necrosis) Latrodectism: Chills, **vomiting, cramps, spasms, priapism** Treatment: Antivenin, benzodiazepines, IV calcium gluconate
Brown recluse spider *(Loxosceles)*  *Figure 2.6.33 Brown recluse spider.*	Small body with long delicate legs, dark brown fiddle pattern on cephalothorax	Sphingomyelinase D	Erythema and edema → vesicle → necrosis and eschar Hemolytic anemia, DIC Treatment: Rest, ice, elevation; avoid surgery
Hobo spider/funnel web spider *(Tegenaria)*  *Figure 2.6.34 Hobo spider.*	Relatively large with a herringbone-striped pattern on the abdomen	Atracotoxins	Painless bite → induration, erythema, and numbness → necrotic eschar Headache, visual disturbances, MI Treatment: Supportive

TABLE 2.6.5 CLINICALLY IMPORTANT SPIDERS CONTINUED

Name	Description	Toxin	Clinical Findings
Wolf spider *(Lycosidae)*  *Figure 2.6.35 Wolf spider.*	Brown to gray spider with peach-colored stripe on cephalothorax; eyes arranged in 3 rows	Histamine	Very painful bites → lymphangitis or eschar Treatment: Supportive
Jumping spider *(Phidippus)*  *Figure 2.6.36 Jumping spider.*	Dark body hairs and various white patterns depending on the species: unique eye arrangement, with largest 2 eyes in the middle front row	Hyaluronidase	Painful bite Treatment: Supportive
Sac spider *(Cheiracanthium)*  *Figure 2.6.37 Sac spider.*	Beige or pale yellow	Lipase	Painful bites Treatment: Supportive
Tarantula *(Theraphosidae)*  *Figure 2.6.38 Tarantula.*	Large, brown to black, hairy spiders have urticating hairs that are thrown toward perceived attackers		Hairs can penetrate skin, with wheal and flare **Ophthalmia nodosa can lead to blindness** Treatment: Supportive

DIC = disseminated intravascular coagulation; IV = intravenous; MI = myocardial infarction.

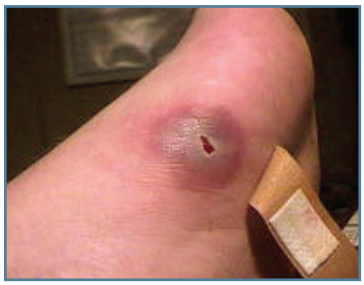


Figure 2.6.39 Brown recluse spider bite.

TICKS

- Divided into hard ticks and soft ticks
- Hard ticks have hard dorsal plate (scutum) and are important disease vectors
- Soft ticks lack scutum and transmit borrelial relapsing fever
- Female ticks are bigger than male ticks
- Tick bites are more common in spring and summer
- Remove ticks with tweezers if still attached to the skin

TABLE 2.6.6 MEDICALLY IMPORTANT TICK SPECIES

Name	Description and Site Predilection	Diseases Transmitted/Caused
Amblyomma (lone star tick)  *Figure 2.6.40 Female lone star tick.*	Characteristic single white dorsal spot (lone star) Prefers lower legs	Human monocytic ehrlichiosis Southern tick-associated rash illness (STARI) RMSF Tularemia
Dermacentor (wood tick, American dog tick)  *Figure 2.6.41 Wood tick.* *Figure 2.6.42 Dermacentor /wood tick.*	Large tick with ornate scutum with deep punctations Prefers head and neck	*D. variabilis* (dog tick): Major vector for RMSF *D. andersoni* (wood tick): Major vector for Colorado tick fever and RMSF Both can cause tick paralysis from release of neurotoxin if attached >4 days
Ixodes (blacklegged tick/deer tick)  *Figure 2.6.43 Deer tick.*	Teardrop shaped with dark legs and cream-colored engorged abdomen Prefers trunk	Lyme disease Babesiosis Human granulocytotropic anaplasmosis
Rhipicephalus (brown dog tick)  *Figure 2.6.44 Brown dog tick.*	Teardrop shaped with brown legs with inornate scutum	RMSF Boutonneuse fever
Ornithodoros spp. (soft tick)  *Figure 2.6.45 Soft tick.*	Lack scutum	Borrelial relapsing fever

RMSF = Rocky Mountain spotted fever.

MITES

Scabies

- Caused by *Sarcoptes scabiei* var. *hominis*
- Transmission by direct personal contact or by fomites
- Adult mite burrows into stratum corneum and causes intensely pruritic erythematous papules and burrows (pathognomonic feature)
- Sites of predilection: Finger and toe web spaces, nipples, axillae, male genitals, and umbilicus
- Males can develop, on external genitalia, pruritic nodules that can last for months
- Crusted scabies is seen in immunocompromised hosts where patients have 1,000s of mites vs 10-15 in immunocompetent hosts
- Even after successful treatment, patients can have postscabetic itch that can last for weeks to months
- Histopathology: Pink "pigtail" structures attached to stratum corneum (fragments of adult mite exoskeleton)
- Diagnosis: Skin scraping (mineral oil), dermoscopy, biopsy, polymerase chain reaction (PCR)
- Treatment: Permethrin 5% cream with 2 topical treatments spread 1 week apart. Ivermectin 200-400 μg/kg twice, 1-2 weeks apart. Others: Malathion, crotamiton, precipitated sulfur
  - Failure to treat head and neck is the most common cause of recurrence in children
  - Treat close contacts at the same time to prevent "ping-pong" infestation

TABLE 2.6.7 OTHER MITES OF SIGNIFICANCE

Acarus (grain mite)	Baker's itch
Liponyssoides sanguineus (house mouse mite)	Transmits rickettsialpox
Cheyletiella	Walking dandruff in pets. May cause papules and vesicles in humans
Demodex folliculorum	Rosacea, blepharitis, HIV folliculitis Treatment: Permethrin
Dermatophagoides (house dust mite)	Allergic reactions
Glycyphagus (cheese mite)	Grocer's itch
Leptotrombidium (Trombicula)	Dermatitis; can transmit scrub typhus
Trombicula alfreddugesi (chigger mite/red bug)	Chigger bites Summer penile syndrome in children

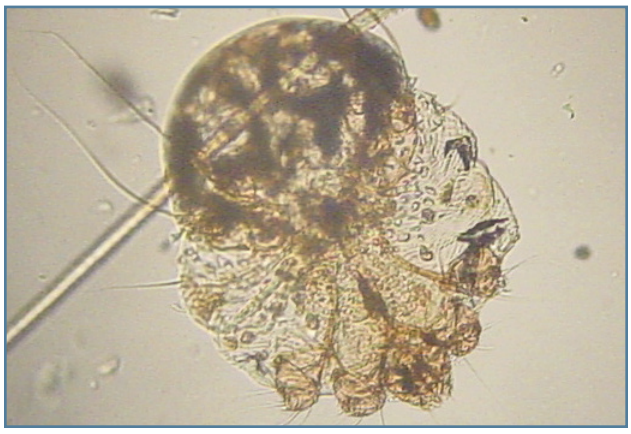


Figure 2.6.46 Sarcoptes scabei.

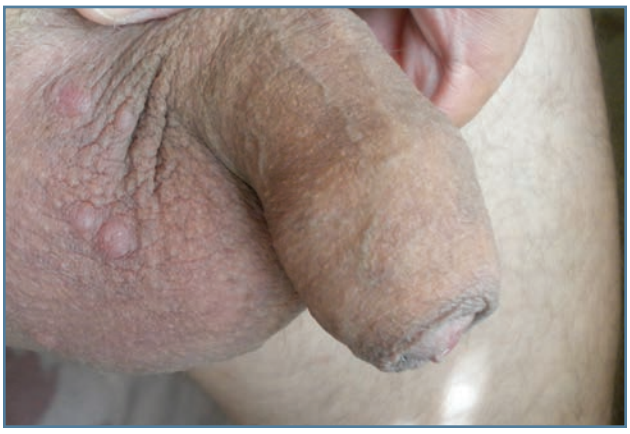


Figure 2.6.48 Scabies on scrotum.

Figure 2.6.47 Scabies burrow.

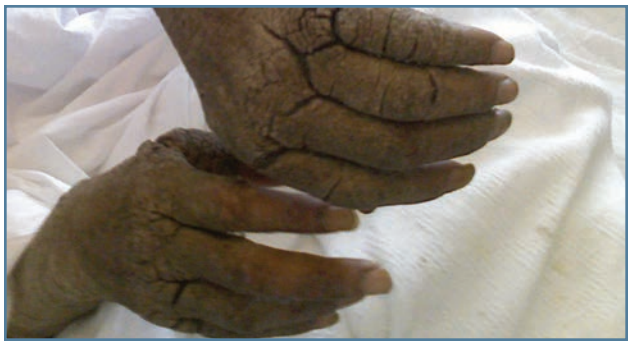


Figure 2.6.49 Crusted scabies.

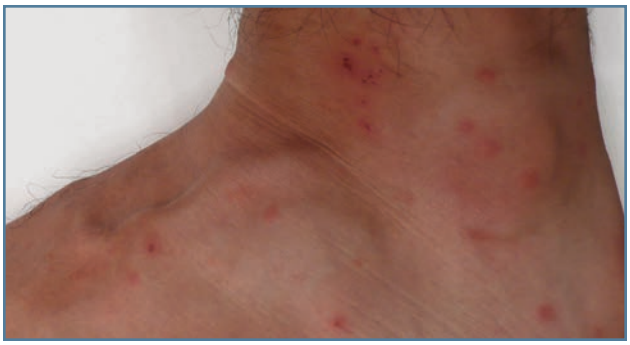
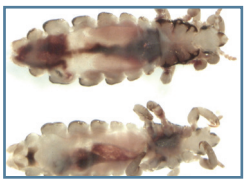


Figure 2.6.50 Chigger bites.

LICE

TABLE 2.6.8 LICE

Head lice *(Pediculosis capitis)* 2-3 mm in size with 6 legs and long narrow body  *Figure 2.6.51 Pediculus humanus.*	Involves scalp hair Spread via direct contact and fomites Intense pruritus Secondary pyoderma Nits and/or adult lice on hair are visible to naked eye	Permethrin Malathion Ivermectin
Crab lice/pubic lice *(Phthirus pubis)* Shorter and squatter than head or body lice  *Figure 2.6.52 Phthirus pubis.*	Mostly involves pubic area but can also involve beard, eyelashes, axillae, or perianal area Transmitted via sexual or close contact Pruritic, perifollicular erythema and excoriations Maculae ceruleae: Asymptomatic, slate-gray irregular macules on lower abdomen and inner thighs; Associated with chronic infestation	Permethrin Ivermectin Check for other STDs
Body lice *(Pediculus humanus var. corporis)*  *Figure 2.6.53 Pediculus humanus.*  *Figure 2.6.54 Body lice nits.*	Commonly found in homeless, refugees, victims of wars and natural disaster Nits and louse rarely found on patient's skin and reside within clothing seams Pinpoint red macules, papules, excoriations mostly over neck, back, shoulders, and waist Vector for epidemic typhus, trench fever, and relapsing fever	Discard bedding and clothing in tightly sealed plastic bags and then incinerate Hot ironing of clothing or bedding seams Mass delousing with DDT, malathion, permethrin

DDT = dichlorodiphenyltrichloroethane; STD = sexually transmitted disease.

OTHER INFESTATIONS

Tungiasis

- *Tunga penetrans* (burrowing flea)
- Endemic in Central and South America, Africa, India, and Pakistan
- Female flea burrows into the skin, especially on the feet, and then enlarges up to 1 cm in size
- Presents as 1- to 2-cm painful and pruritic nodule or multiple papules with a central punctum
- Complications: Gangrene, tetanus, amputation
- Differential diagnosis: Myiasis, pyoderma, plantar wart, verruga peruana, persistent insect bite
- Treatment: Remove flea with needle, electrodesiccation and curettage, excision
- Prevention: Wear shoes and avoid sitting on sandy beaches in endemic areas

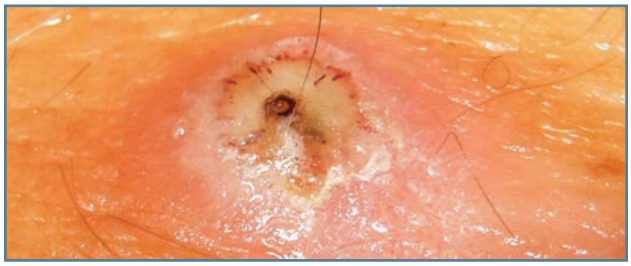


Figure 2.6.55 Tunga penetrans infestation.

Figure 2.6.56 Tunga penetrans.

Myiasis

- Infestation of skin by fly larvae
- More common in tropical and subtropical regions
- 3 types of myiasis:
  - Furuncular myiasis: Caused by human botfly *(Dermatobia hominis)* and tumba fly (Cordylobia anthropophaga). Eggs are deposited on host via mosquito or clothing
  - Wound myiasis: Caused by screw worm *(Cochliomyia hominivorax)*. Eggs are deposited directly on the wound, especially on the scalp, and may burrow into brain tissue
  - Migratory/creeping myiasis: Caused by *Gasterophilus intestinalis*. It resembles cutaneous larva migrans but is larger, slower, and persists longer as a furuncle- like lesion called a *warble*
- Treatment: Surgical excision, ivermectin, **tetanus vaccination**

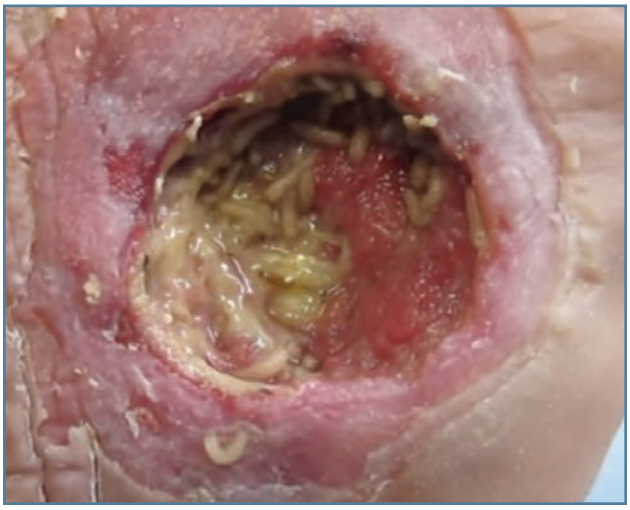


Figure 2.6.57 Wound myiasis.

OTHER BITES

TABLE 2.6.9 OTHER BITES

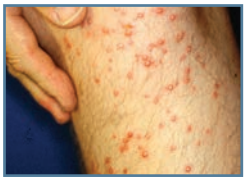
Organism	Notes	Clinical Features	Treatment
Fire ants  *Figure 2.6.58 Fire ant bites.*	Inject venom (solenopsin D), which causes release of histamine	Sterile pustules, usually in clusters	Symptomatic: Antihistamines, cold compresses, TCS Epinephrine for anaphylaxis

TABLE 2.6.9 OTHER BITES CONTINUED

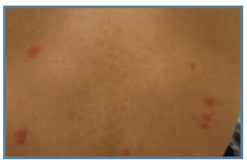
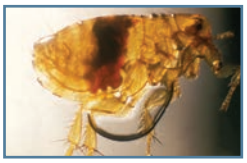
Organism	Notes	Clinical Features	Treatment
Blister beetle  *Figure 2.6.59 Blister beetle.*	Produces cantharidin, a contact irritant that causes blistering	Blisters "Nairobi eye"; pustule with halo of erythema	Avoidance Wash with soap and water
Bedbugs  *Figure 2.6.60 Bedbug bites.* *Figure 2.6.61 Bed bugs.*	Hide in cracks and crevices and feed at night More common in shelters, refugee camps	Linear group of papules: "breakfast, lunch, and dinner" sign Possible vector for hepatitis B and Chagas disease	Insecticides: Dichlorvos, permethrin
Triatomine reduviid, aka "kissing" or "assassin" bug  *Figure 2.6.62 Triatomine bug.*	Found in stone walls, piles of tiles or bricks Tan and dark tiger stripes across the abdomen	Vector for American trypanosomiasis, Chagas disease **Romaña's sign:** Unilateral eyelid swelling	Benznidazole, nifurtimox
Fleas  *Figure 2.6.63 Xenopsylla cheopis.*		Intensely pruritic papules, vesicles, and grouped bullae on lower legs Vector for cat scratch disease, endemic (murine) typhus, tungiasis, melioidosis, plague	Lufenuron for infested animals Fipronil, boric acid, pyriproxyfen, insecticides for infested environment
Mosquitos	3 important genera: *Anopheles, Culex,* and *Aedes*	Pruritic edematous papules More severe bite reaction in children and CLL patients *Anopheles* transmits malaria *Culex* transmits filariasis *Aedes* transmits yellow fever, dengue	Prevention: DEET
Flies  *Figure 2.6.64 Sandyfly.* *Figure2.6.65 Black fly.*		Sandfly transmits leishmaniasis Blackfly transmits onchocerciasis and tularemia Deer fly, mango fly, horse fly transmit loiasis and tularemia Tsetse fly transmits African trypanosomiasis	See Section 2.2 Infectious Diseases of the Skin

TABLE 2.6.9 OTHER BITES CONTINUED

Organism	Notes	Clinical Features	Treatment
Centipedes (class Chilopoda)  *Figure 2.6.66 Centipede.*	Nocturnal carnivores	Painful bite wounds Venom contains metalloproteases	Symptomatic therapy only
Millipedes (class Diplopoda)  *Figure 2.6.67 Millipede.*	Harmless vegetarians	Do not bite but cause chemical contact dermatitis due to cyanide and quinones	Symptomatic therapy only
Snake bites  *Figure 2.6.68 Rattlesnake.* *Figure 2.6.69 Coral snake.*	2 main families: *Viperidae* (includes rattlesnakes and copperheads) and *Elapidae* (includes coral snakes and king cobra)	Immediate pain and edema at bite site → necrosis and hemorrhage Systemic symptoms: Hypotension, respiratory distress, neuromuscular blockade depending on species	Antivenin
Dog and cat bites		Local infection and cellulitis are common after bites *Staphylococcus* and *Streptococcus:* Bacteria most commonly transmitted *Pasteurella multocida:* From cat bites and can cause breast implant infection and lung abscess *Capnocytophaga canimorsus:* Causes sepsis and purpura fulminans in immunocompromised host, with high mortality Also anaerobes	Amoxicillin/clavulanate
Human bites	Following fist fights with blows to the mouth, or actual biting	*Staphylococcus:* Most common infection *Eikenella corrodens*	Amoxicillin/clavulanate
Leeches  *Figure 2.6.70 Leeches.*	Found in fresh water Used in medical therapy to enhance survival of skin flaps subjected to venous occlusion	Interfere with platelet aggregation → purpura and bleeding Medical leeches associated with ***Aeromonas hydrophila*** wound infection	Saturated salt solution to facilitate removal

CLL = chronic lymphocytic leukemia; DEET = N,N-diethyl-m-toluamide; TCS = topical corticosteroids.

MEDICINAL PLANTS AND CREATURES

- Chrysanthemum (Compositae family) → pyrethrin
- Mayapple *(Podophyllum peltatum)* → podophyllotoxin
- *Solanaceae* spp. → capsaicin
- Blister beetle *(Lytta vesicatoria)* → cantharidin
- Castor (*Ricinus* spp.) → undecylenic acid
- *Euphorbia peplus* (milkweed)
  - Dual MOA
    1. Rapid induction of necrosis that specifically targets dysplastic cells
    2. Neutrophil-mediated immunostimulatory effects

Figure 2.6.71 Podophyllum peltatum.

MARINE INJURIES

First aid for most marine venoms is immersion in hot water to denature venomous proteins.

TABLE 2.6.10 IMPORTANT MARINE CREATURES

Phylum (Creatures)	Features/Clinical Findings	Treatment
Cnidaria (coral jellyfish, sea anemones)  *Figure 2.6.72 Sea anemone.* *Figure 2.6.73 Jellyfish.*	Have cnidocytes that contain nematocysts = stinging capsule Seabather's eruption: Dermatitis under bathing suit caused by larvae of any cnidarian spp.	**Inactivated by vinegar** (except man-of-war, which discharges in vinegar) Avoid fresh water and ammonia (in urine) Shave with knife edge or credit card edge to remove nematocysts
Echinodermata (sea urchins, starfish, sea cucumbers)  *Figure 2.6.74 Sea urchin.*	Have spicules that cause irritant contact dermatitis and foreign body reaction from calcite crystals	Immersion in hot water
Mollusca (blue-ringed octopus, cone snails)  *Figure 2.6.75 Blue ringed octopus.*	Tetrodotoxin: Deadly neurotoxin in some cone snails, blue-ringed octopus, and pufferfish	Respiratory support

TABLE 2.6.10 IMPORTANT MARINE CREATURES CONTINUED

Phylum (Creatures)	Features/Clinical Findings	Treatment
Chordata (fish)	Scorpion fish have venom in dorsal spines Scombroid poisoning: Toxic reaction to decomposing scombroid fish, with bacteria converting histidine → histamine, which causes sudden onset of red itchy rash (no wheals) within 30 min of consumption. Occasionally, systemic symptoms including diarrhea and nausea	
Cyanobacteria (tuft-forming blue-green algae)	Contains lyngbyatoxin A and debromoaplysiatoxin: Causes seaweed dermatitis	

TIP

- Seabather's eruption = dermatitis under bathing suit caused by stinging larvae of any cnidarian spp.
- Swimmer's itch = occurs in exposed areas and is caused by the cercariae of schistosomes

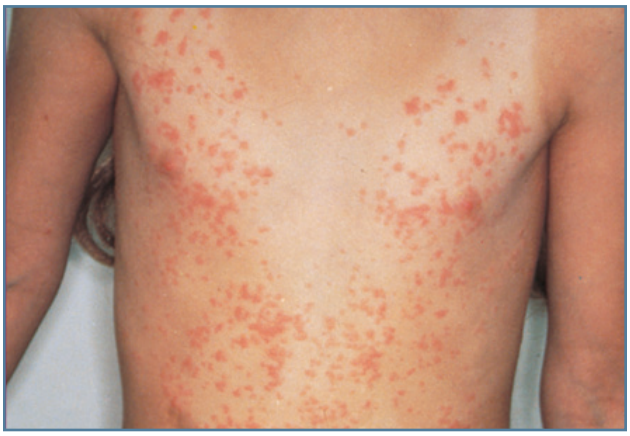


Figure 2.6.76 Sea bather's eruption.

SECTION 1, GENERAL DERMATOLOGY IMAGE ATTRIBUTIONS

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Figure 2.1.2 Rosacea by The Inclusive Derm Atlas Online Gallery
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Figure 2.1.3 Rhinophyma by M. Sand, D. Sand, C. Thrandorf, V. Paech, P. Altmeyer, F. G. Bechara
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Figure 2.6.72 Sea anemone 4321's [CC BY-SA 2.0 (https://creativecommons.org/licenses/by-sa/2.0)], via Wikimedia Commons

Figure 2.6.74 sea urchin)
User: (WT-shared) Pbsouthwood at wts wikivoyage [CC BY-SA 3.0 (https://creativecommons.org/licenses/by-sa/3.0)]

Figure 2.6.75 Blue ringed octopus by Sylke Rohrlach from Sydney [CC BY-SA 2.0 (https://creativecommons.org/licenses/by-sa/2.0)], via Wikimedia Commons

Figure 2.6.76 Sea bather's eruption
Google- From Fitzpathrick's book
https://www.google.com/search?q=sea+bather%27s+eruption&client=firefox-b-1-ab&tbm=isch&tbs=rimg:CaGchhR0vcFjIjiQ1PTUm7ak-CL_1d3AB7B39Kr3o8at0bk21N5RXQ3Gevo3sImSLxI84AA9kBb1Ef8rHU-Vtd7VtrPgCoSCZDU9NSbtqQIEYv6xkmsXbaDKhIJv93cAHsHf0oRAO-JcZQY7pEYqEgmvejxq3RuTbRFtOYk9MbCvNyoSCU3IFdDcZ6-jEQbt2NvX-PJ0jKhIJewiZIvEjzgARdmcFIF_1d6CkqEgkD2QFvUR_1ysRHpK8PvjD5QU-CoSCdRW13tW2s-AEXou3lc1A4Q3&tbo=u&sa=X&ved=2ahUKEwi20sO-JpcHfAhWthOAKHaDvCzAQ9C96BAgBEBs&biw=1280&bih=632&dpr=1#imgrc=1FbXe1baz4CbdM:

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ACNE

ROSACEA

HIDRADENITIS SUPPURATIVA

PSORIASIS

LICHEN PLANUS

ATOPIC DERMATITIS

SEBORRHEIC DERMATITIS

VITILIGO

DISCOID LUPUS

MORPHEA

LICHEN SCLEROSUS

LIVEDO RETICULARIS

MACULAR AMYLOID

LICHEN AMYLOID

PYODERMA GANGRENOSUM

CUTANEOUS T-CELL LYMPHOMA

URTICARIA

DERMATOGRAPHISM

FOLLICULITIS

PARONYCHIA

MOLLUSCUM CONTAGIOSUM

SECONDARY SYPHILIS

PITYRIASIS VERSICOLOR

TINEA CORPORIS

TINEA PEDIS

ONYCHOMYCOSIS

PEMPHIGUS VULGARIS

BENIGN FAMILIAL PEMPHIGUS *(HAILEY-HAILEY)*

ACANTHOSIS NIGRICANS

DERMATOMYOSITIS

NECROBIOSIS LIPOIDICA

ALOPECIA AREATA

SEARCH CONDITIONS A-Z

Chapter 3

PEDIATRIC DERMATOLOGY

Authors: Habeshian, K., Sorrell, J., Marathe, K., Kirkorian, Y.

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3.1 Cutaneous Disorders of the Newborn

NEONATAL SKIN

- Infants: About 50% thinner than adult, less hairy, weaker epidermal:dermal connection
- Premature neonates (<34 weeks): Immature stratum corneum, increased transepidermal water loss (TEWL; dehydration, electrolyte imbalance, thermal instability). Matures in 2-3 weeks

TABLE 3.1.1 NEONATAL PERCUTANEOUS TOXICITY

Compound(s)	Toxicity
Benzocaine, prilocaine, methylene blue	Methemoglobinemia
Isopropyl alcohol	Cutaneous hemorrhagic necrosis
Salicylic acid	Metabolic acidosis, salicylism
Silver sulfadiazine	Kernicterus, argyria, agranulocytosis
Neomycin	Neural deafness
Povidone-iodine	Hypothyroidism

CUTIS MARMORATA

- Reticular, blanchable benign vascular patterning on extremities > trunk, face. Normal finding; physiologic response to cold, usually disappears with rewarming (unlike cutis marmorata telangiectatica congenita [CMTC]; see Disorders Associated with Vascular Dilatation in Section 3.8
- Persistent in trisomy 21, trisomy 18, and Cornelia de Lange syndromes

HARLEQUIN COLOR CHANGE

- Vascular red color change with contralateral blanching, well demarcated at midline
- Usually premature infants

BRONZE BABY SYNDROME

- Gray-brown discoloration of skin, urine, serum due to phototherapy for hyperbilirubinemia

CEPHALOHEMATOMA

- Subperiosteal hematoma in first hours life
- Does not cross midline
- Seen in prolonged, assisted, and difficult labor
- Can calcify, cause hyperbilirubinemia, rarely becomes infected

CAPUT SUCCEDANEUM

- Localized edema of scalp due to labor; often crosses midline
- More frequent in prolonged labor, primigravidas
- "Halo scalp ring" is annular alopecia (transient > permanent) due to pressure necrosis during labor

NEONATAL LUPUS ERYTHEMATOSUS

- Infants of mothers with a tendency for SLE, RA, Sjogren syndrome, or undifferentiated connective tissue disease
- Cutaneous findings in 50-75% of cases: pink plaques on photosensitive areas
- Periorbital "raccoon eyes" and annular erythema or discoid lesions
- Neonatal Lupus Erythematosus (NLE) is the most common cause of congenital heart block

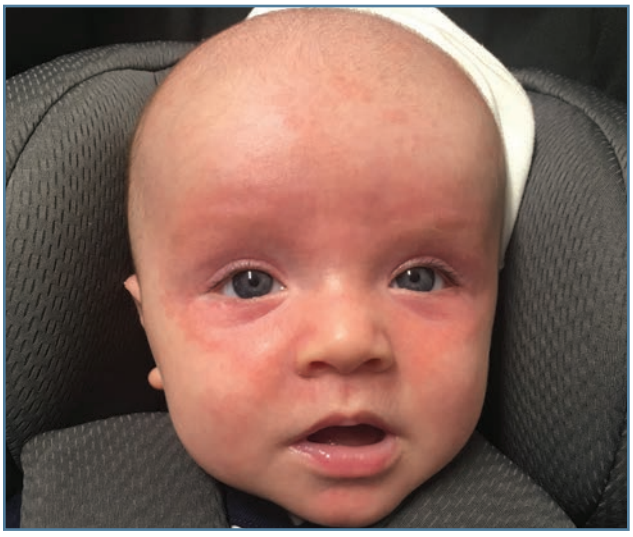

Figure 3.1.1 Neonatal lupus.

SCLEREMA NEONATORUM

- Very rare form of panniculitis
- Premature infants with serious underlying disease
- Often fatal entity
- Rapidly progressive, wax-like hardening of the skin within the first few days/weeks of life, symmetric but spares palms/soles/genitalia
- Histopathology: Needle-shaped clefts within necrotic adipocytes with little surrounding inflammation

TIP

Post-steroid panniculitis also has needle-shaped clefts with little inflammation

SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN (SFNN)

- Uncommon localized subcutaneous nodules in newborns on buttocks, thighs, arms, face, and shoulders
- Healthy full-term infants
- First weeks of life
- May be associated with perinatal trauma, asphyxia, maternal cocaine use, hypothermia, and cardiac surgery
- Increase in incidence recently with use of therapeutic hypothermia to reduce neonatal brain injury
- **Calcification common, and its resolution may be associated with a profound hypercalcemia**
- Histopathology: Lymphocytes, giant cells, and histiocytes are common with needle-shaped clefts and fat necrosis, calcification

TIP

SFNN

- More inflammation
- Milder disease
- More localized
- More calcification
- Less fibrous

TIP

Calcium levels should be followed for several months; hypercalcemia onset can be delayed

TABLE 3.1.2 TRANSIENT BENIGN NEONATAL RASHES

Rash	Onset and Duration	Appearance/Distribution
Miliaria	1-2 wk Resolves in 1-2 d	Erythematous fine, uniform papules (miliaria rubra/prickly heat) to vesicles (miliaria crystallina/sudamina) in intertriginous areas. Due to occluded eccrine ducts
Neonatal acne (neonatal cephalic pustulosis)	First 30 d Lasts a few months	Erythematous papules/pustules on cheeks, chin, and forehead. *Malassezia* species implicated. No treatment. Neutrophils with debris on smear
Erythema toxicum neonatorum	24-72 hr Resolves in 2 wk	Erythematous macules with central vesicle/pustules. Eosinophils on smear. No treatment. Common in full-term infants
Sucking blisters	Birth+	Usually solitary, oval, noninflammatory bullae or erosions at site of neonate's sucking, e.g., hand or wrist. Most common on wrist
Transient neonatal pustular melanosis	At birth	Small pustules with no underlying erythema. Collarette when ruptured. Heals with hyperpigmented macule. More common in darkly pigmented neonates, up to 1%. Neutrophils on smear
Seborrheic dermatitis	2-4 wk Resolves by 1 yr	Irregular salmon-pink patches with waxy scaling in seborrheic distribution (scalp, forehead, chest, eyebrows, ears, intertriginous areas)

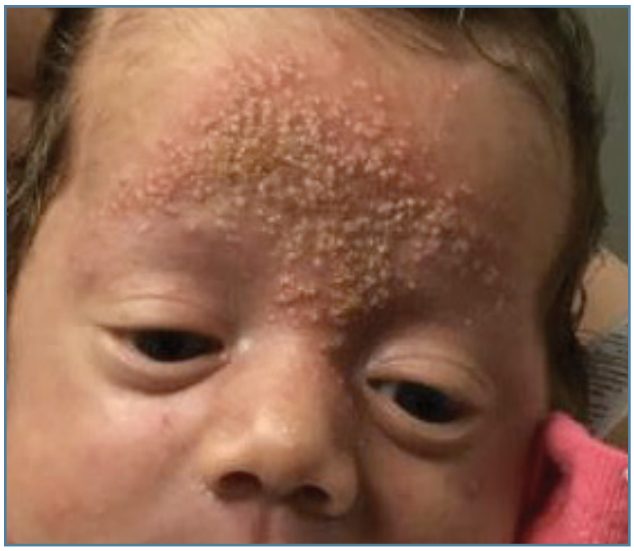

Figure 3.1.2 Neonatal cephalic pustulosis.

Figure 3.1.3 Congenital facial milia in a patient with Bazex syndrome.

TABLE 3.1.3 DISORDERS WITH MILIA

Disorder	Description
Bazex syndrome	Milia, follicular atrophoderma, multiple BCCs, abnormal hair
Rombo syndrome	Milia, vermicular atrophoderma, BCCs, trichoepitheliomas
Epidermolysis bullosa	Dystrophic forms
Down syndrome	Milia-like calcinosis cutis
Oro-facial-digital syndrome	X-linked dominant defect in CXORF5 (*OfD1*)
Epstein pearls	Milia on mucosa
Bohn nodules	Milia on palate

TABLE 3.1.4 DIAPER DERMATITIS

Type	Symptoms
Irritant dermatitis	Diaper-covered surfaces, spares folds. Chronic wetness, increased pH, diarrhea
Candidal dermatitis	Bright red, moist patches with satellite pustules. Intertriginous involvement or thrush
Seborrheic dermatitis	Groin, scalp, intertriginous areas. Salmon-colored, waxy scaling patches and plaques
Psoriasis	Well-demarcated, pink plaques with minimal scale, creases involved. Most common presentation of psoriasis in infants
Bullous impetigo Perianal streptococcal disease	Flaccid bullae with honey-colored crusts. Bright red, well-defined erythema perianally and in creases
Jacquet's erosive dermatitis	Severe erosive papules, nodules May cause pain with urination Multifactorial etiology: Yeast, irritant dermatitis, and moisture; Hirschsprung's

TABLE 3.1.4 DIAPER DERMATITIS CONTINUED

Type	Symptoms
Perianal pseudoverrucous papules and nodules	Erythematous flat-topped verrucous papules and nodules in children with chronic fecal incontinence Brown, orange crusted plaques with vesicles and bullae. Perineal, perioral areas, and distal extremities
Acrodermatitis enteropathica/ zinc deficiency	Secondary to low serum zinc level 1. Premature infants: Poor absorption, inadequate stores, and increased zinc requirement 2. Healthy infants: Low breast milk zinc levels with normal maternal serum zinc level 3. Acquired form: Malabsorption and/or inadequate nutritional intake (i.e., total parenteral nutrition) 4. Autosomal recessive inherited form: Defect in intestinal zinc-specific transporter SLC39A4 that manifests when infant is weaned off breast milk (due to greater availability of zinc in maternal breast milk than nonmaternal source) Alkaline phosphatase (zinc-dependent enzyme) also low
Langerhans cell histiocytoses (LettererSiwe disease)	Yellowish-brown, crusted papules with petechiae in a seborrheic distribution $CD1a^+$, $S100^+$ Langerhans cells with comma-shaped or reniform nuclei. Multisystem involvement may be present
Granuloma gluteale infantum	Red-purple, granulomatous nodules Secondary to local irritation, maceration, and Candida (multifactorial)
Allergic contact dermatitis	Topical preparations (or foods rarely); dyes
Cystic fibrosis	Resembles zinc deficiency Pedal edema common Failure to thrive, hepatosplenomegaly, infections, malabsorption
Biotin deficiency/multiple carboxylase deficiency	Resembles zinc deficiency, but affects all biotin-dependent enzymes Neonatal form: Autosomal recessive; holocarboxylase synthetase; vomiting Juvenile form: Autosomal recessive; biotinidase; optic atrophy and hearing loss All: Seizures (6 mo of age), hypotonia, ataxia, lactic acidosis/ketosis, hyperammonemia, alopecia. Treatment: Biotin lifelong
Atopic dermatitis	Uncommon primary cause of diaper dermatitis, but patients with atopic dermatitis at increased risk of diaper dermatitis
Miliaria	Blocked eccrine ducts secondary to heat and humidity of diaper area. May be superficial, small, clear vesicles (miliaria crystallina) or small, erythematous papules/pustules (miliaria rubra/miliaria pustulosa)
Scabies	Lesions tend to be more nodular under diaper
Kawasaki's disease	Two-thirds of patients present with confluent, tender erythema in the perineum. Later desquamates
Congenital syphilis	Condylomata lata or generalized papulosquamous eruption of secondary syphilis may be present in diaper area
Human immunodeficiency virus	Very severe erosive diaper dermatitis. May be complicated by secondary bacterial and viral infections

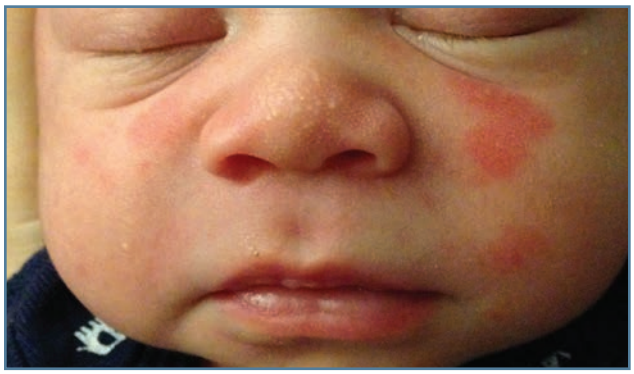

Figure 3.1.4 Erythema toxicum neonatorum.

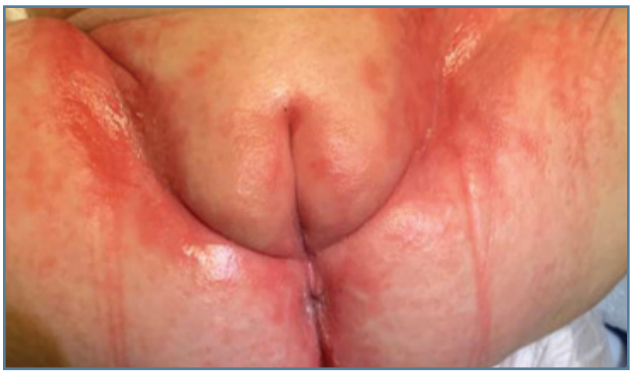

Figure 3.1.5 Seborrheic dermatitis.

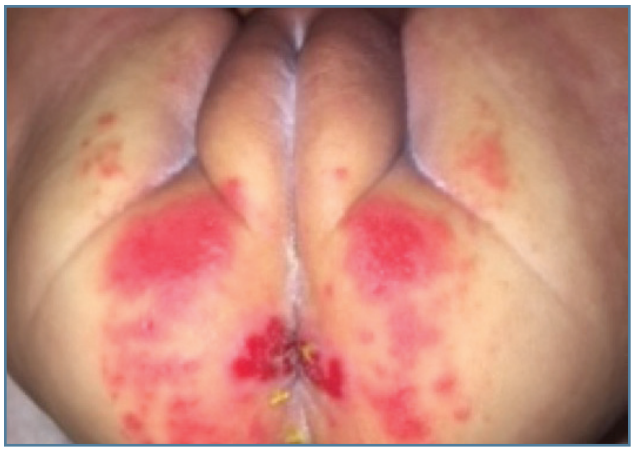

Figure 3.1.6 Jacquet's diaper dermatitis.

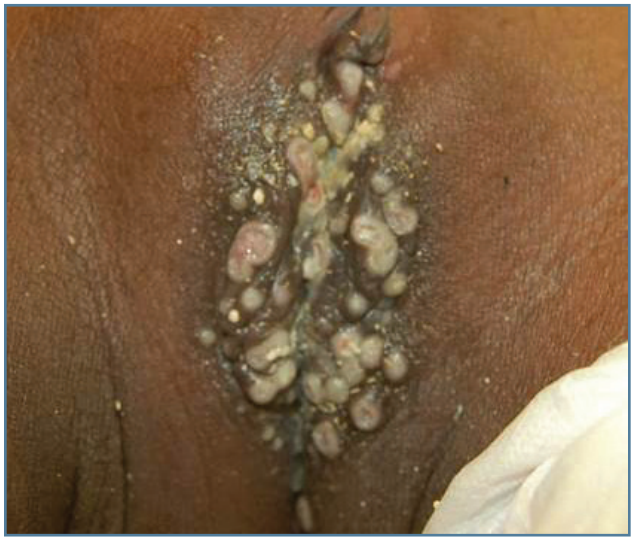

Figure 3.1.7 Perianal pseudoverrucous papules and nodules.

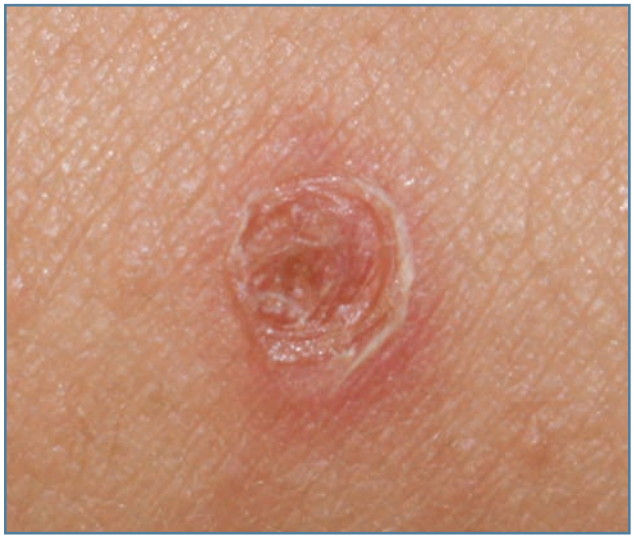

Figure 3.1.8 Bullous impetigo.

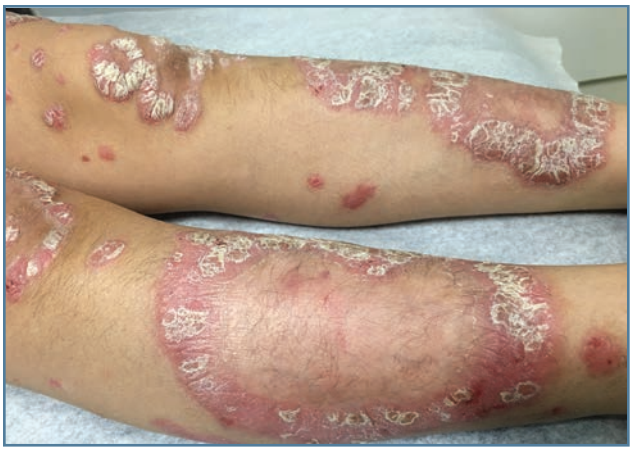

Figure 3.1.9 Plaque psoriasis.

TABLE 3.1.5 CUTANEOUS SIGNS OF SPINAL DYSRAPHISM: IN MIDSACRAL REGION

• Hypertrichosis	• Hemangiomas
• Dimpling	• Dermoid cysts/sinuses
• Skin tags	• Telangiectasia, capillary malformations, and nevi less likely
• Tails/pseudotails	• Gluteal cleft asymmetry/deviation
• Lipomas	• Aplasia cutis

- Any two or more findings at high risk for dysraphism
- MRI is imaging of choice. Ultrasound may be considered in those under 4 months (but not highly sensitive)

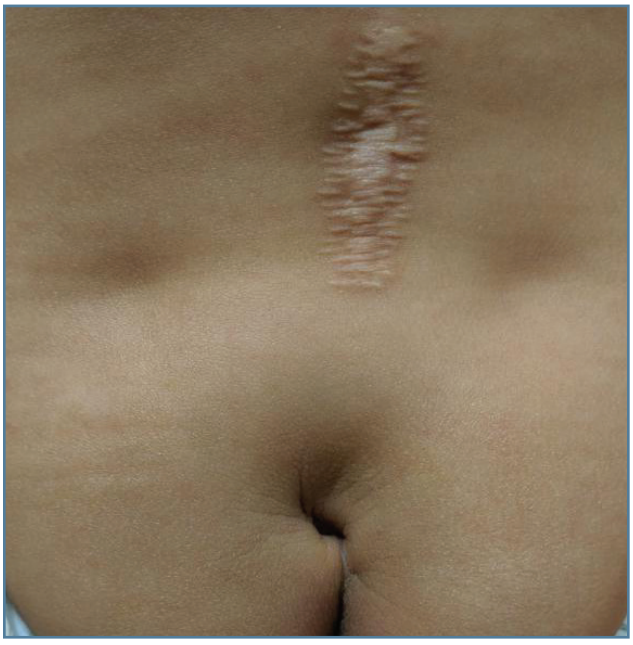

Figure 3.1.10 Spinal dysraphism.

PEDAL PAPULES OF INFANCY

- Soft, nontender papules located on the medial aspect of heel
- Not associated with any systemic disorder. Do not interfere with ambulation

APLASIA CUTIS CONGENITA (ACC)

- Localized developmental defect involving variable skin thickness
- Along developmental suture lines on the scalp (80-90%) > trunk or extremities
- May rarely be associated with underlying bony abnormalities, skeletal abnormalities, brain malformations, cleft lip, syndactyly
- Hair collar sign is a ring of dark, long hair at the periphery of ACC, encephalocele or other type of neural tube defect
- Associated syndromes:
  - Bart's syndrome: Dystrophic epidermolysis bullosa with congenital absence of skin
  - Setleis syndrome: Homozygous defect in *TWIST2* gene. Bitemporal aplasia cutis congenita, leonine facies, absent multiple rows of eyelashes, multiple rows of upper eyelashes
  - Adams-Oliver syndrome: Autosomal dominant (AD) defect in *ARHGAP31*. Aplasia cutis congenita and limb, cardiac, neurological defects and vascular malformations/cutis marmorata

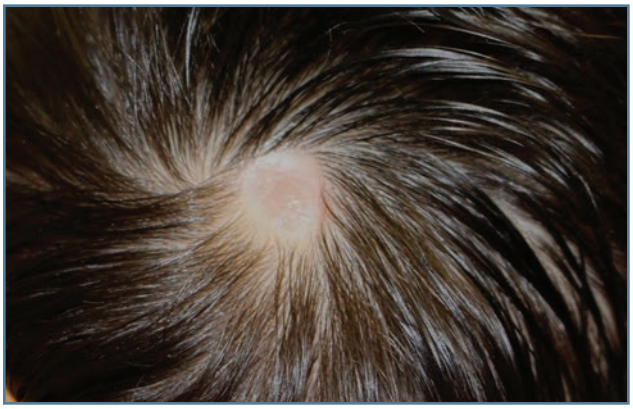

Figure 3.1.11 Aplasia cutis.

TABLE 3.1.6 DEVELOPMENTAL DEFECTS

Defect	Location	Features
Dermoid cyst	Orbital ridge, less commonly midline	Nontender mobile nodule. If midline, may connect with CNS
Dermoid sinus	Nasal bridge, midline neck and back	Small pit with tuft of hair/white discharge associated. May connect with CNS. Portal for infection
Cephalocele	Occiput, nasal bridge, orbits, forehead	Herniation of CNS through skull defect. Compressible mass transilluminates. Increases in size with crying/straining. Associated with hypertelorism, facial clefting, and brain abnormalities
Nasal glioma	Nasal bridge	Ectopic neuroectoderm (extra- or intranasal). Firm, noncompressible flesh-bluish nodule. Associated with hypertelorism. Transilluminates. Does not increase in size with crying/straining
Heterotopic brain tissue	Nasal bridge, head, and neck	No intracranial connection
Congenital lip pits (congenital fistulas of the lower lip)	Usually lower lip	Usually blind pits. May connect with salivary glands > salivary discharge. AD. Associated with cleft lip/palate, bony defects, Van der Woude syndrome, popliteal pterygium syndrome
Skin dimpling defects	Overlying sacrum or bony prominences	Pits or creases. May be normal variant or associated with spinal cord defects, cleft lip/palate, congenital rubella/varicella, Zellweger, Bloom, Freeman-Sheldon syndromes
Amniotic constriction bands	Hands, limbs	Congenital constriction bands associated with amputation of digits/limbs

TABLE 3.1.6 DEVELOPMENTAL DEFECTS CONTINUED

Defect	Location	Features
Raised limb bands (acquired raised limb bands)	Extremities, trunk	Acquired linear pink raised bands, nonconstricting
Preauricular pits or sinus	Preauricular	Defect in fusion of first 2 branchial arches. Can become infected
Accessory tragi	Preauricular, also lateral cheeks, neck	Fleshy papules ± cartilage. Singular or multiple. Associated with branchial arch syndromes (Goldenhar, oculo-auriculo-vertebral). Can be associated with hearing or genitourinary defects
Branchial cleft cysts or sinus	Lower third of the lateral neck (near anterior border of sternocleidomastoid)	1st and 2nd branchial cleft defect. Can open to skin surface or pharynx. Often becomes chronically inflamed over time
Thyroglossal cysts or sinus	Midline neck	Results from embryonic descent of thyroid. May contain thyroid tissue. Moves with swallowing
Bronchogenic cysts	Suprasternal notch	Often drains fluid
Congenital cartilaginous rest (wattle)	Anterior neck or lower half of sternocleidomastoid	Fleshy papules, often cartilaginous
Pterygium colli	Neck	Congenital folds of the neck. Syndrome associations: Down, Turner, Noonan, LEOPARD, multiple pterygium syndrome, trisomy 18
Supernumerary nipples (polythelia)	Along milk lines (face, neck, chest, abdomen, genitals, thighs)	Small, pink-brown papules to nipple-like nodules
Urachal cyst or sinus	Umbilicus	Persistent urachus. May drain urine
Omphalomesenteric duct remnant (vitelline)	Umbilicus	Polyp or umbilicoileal fistula. May drain feces

AD = autosomal dominant; LEOPARD = lentigines, electrocardiographic conduction defects, ocular hypertelorism, pulmonary stenosis, abnormalities of the genitalia, retarded (slowed) growth, deafness.

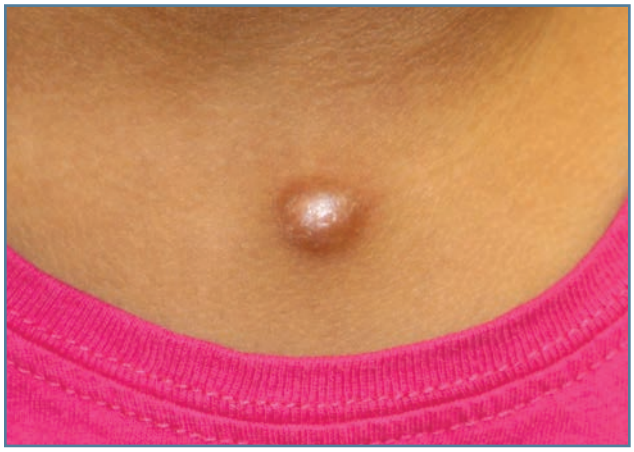

Figure 3.1.12 Branchial cleft cyst.

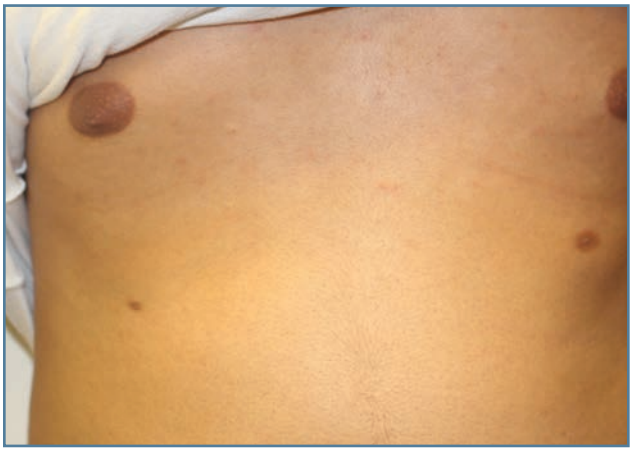

Figure 3.1.13 Supernumerary nipples.

TABLE 3.1.7 CONGENITAL INFECTIONS

Infection	Skin Findings	Extracutaneous Findings	Other
Rubella	Extramedullary hematopoiesis: "Cranberry muffin"/"blueberry muffin" lesions, petechiae/purpura	IUGR, microcephaly, chorioretinitis, HSM	Congenital heart disease, cataracts, pneumonia. Deafness 50%. Most severe in first trimester
Varicella	Cicatricial lesions	Chorioretinitis, limb paresis, and hypoplasia. Neurologic and eye abnormalities	Greatest risk in first 20 wk of pregnancy
Herpes simplex virus (HSV)	Vesicles and pustules on an erythematous base with scarring, often favors scalp	Microcephaly, chorioretinitis, sepsis, multiorgan failure, encephalitis, neurologic sequelae. 50-75% mortality if untreated	Majority HSV-2, 85% acquired during birth
Parvovirus B19	Blueberry muffin lesions	Anemia, hydrops fetalis	Highest risk: Infection before 20 wk, affects fetuses of nonimmune
Syphilis, early congenital (symptoms start 0-2 yr; mother usually has early syphilis)	Snuffles (rhinitis) Saddle nose Skin lesions resemble those of acquired secondary syphilis—morbilliform, papular, pustular Syphilitic pemphigus (vesiculobullous lesions on palms and soles) Condylomata lata around anus and skin folds	Bone lesions, epiphysitis can lead to Parrot pseudoparalysis Enlarged epitrochlear lymph nodes and spleen	May be asymptomatic at birth/look normal at birth. Infection through placenta usually after 4th month Cornea, bones, CNS Hydrocephalus
Syphilis, late congenital (symptoms start > 2 yr)	Rhagades Gummas Hutchinson teeth Mulberry molars Saddle nose Saber shins Higoumenakis sign (unilateral thickening of inner 1/3 of clavicle)	Interstitial keratitis Perisynovitis (Clutton's joints) Gummas in long bones and skull CNS lesions (tabes dorsalis, generalized paresis) 8th nerve palsy	Paroxysmal cold hemoglobinuria
Cytomegalovirus	Blueberry muffin lesions and petechiae	IUGR, microcephaly and chorioretinitis, thrombocytopenia, HSM, pneumonitis	Most reactivation of latent maternal infection. Also in breast milk. Greatest risk with infection in first trimester. *Acyclovir not effective against CMV
Toxoplasmosis	Nonspecific. Petechiae/rash, blueberry muffin lesions	Neurologic sequelae, chorioretinitis, intracranial calcification	Acquired from cats
Candidiasis	Monomorphous papulovesicles; pustules widespread	Pneumonia, sepsis occasionally	Appears about 12 hr after birth. More common in low birth weight infants

TABLE 3.1.7 CONGENITAL INFECTIONS CONTINUED

Infection	Skin Findings	Extracutaneous Findings	Other
Staph scalded skin syndrome (Ritter's disease)	Diffuse tender erythema and superficial blistering. Flexural/perioral accentuation	Excessive fluid loss, fever, conjunctivitis, rhinitis pneumonia, endocarditis. Mortality due to sepsis	Toxin (exfoliative toxin) mediated. Group II phage. Desmoglein 1
Omphalitis	Periumbilical erythema, induration, tenderness. May have discharge	Sepsis, thrombosis of portal venous system	*Staphylococcus aureus, Streptococcus pyogenes,* gram negatives
Breast abscess	Erythema, induration, and tenderness of enlarged breast	Fever, irritability	Full-term infants. 1-6 wk of life. Usually *S. aureus,* occasionally group B strep, gram negatives

HSM = hepatosplenomegaly; IUGR = intrauterine growth retardation.

Figure 3.1.14 Staphylococcal scalded skin syndrome.

TIP

Be able to differentiate early/late congenital syphilis features

TIP

Blueberry muffin lesions occur secondary to extramedullary hematopoiesis or certain neoplasms (e.g., neuroblastoma, leukemia, histiocytosis) and purpuric macules and papules present within 1-2 days of birth, present in 30% of neonates with TORCH syndrome (toxoplasmosis, other agents, rubella, CMV, herpesvirus [and parvovirus, enterovirus])

3.2 Eczematous Eruptions in Childhood

ATOPIC DERMATITIS

- Clinical: In infants presents on the cheeks/extensors (spares diaper area); exacerbation to face due to combined irritant from teething/foods; in childhood and adulthood is more chronic with lichenification and increased involvement of flexural areas
- Associated with a family or personal history of atopy (asthma, hay fever, allergic rhinitis)
- Increased susceptibility to viral (herpes, molluscum, papilloma), bacterial (especially *S. aureus*), and dermatophyte infections
- Concepts in treatment include avoidance of irritants, antiinflammatory medication, and gentle skin care

HYPER-IGE SYNDROME (HIES)

- See Section 3.23

WISKOTT-ALDRICH SYNDROME

- See Section 3.23

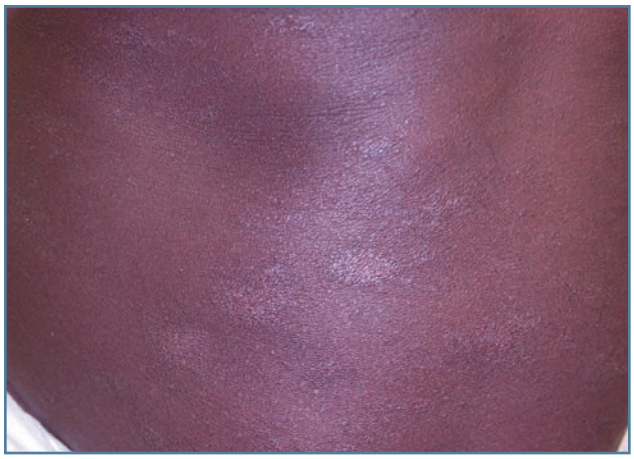

Figure 3.2.1 Atopic dermatitis.

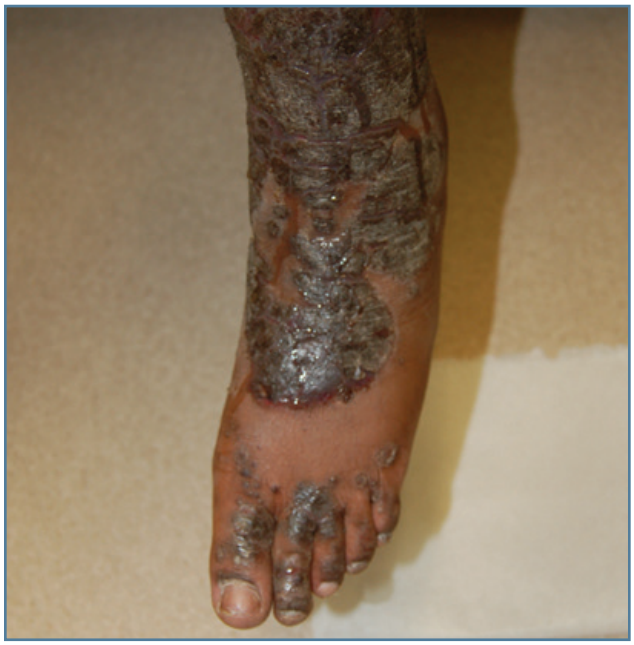

Figure 3.2.2 Atopic dermatitis.

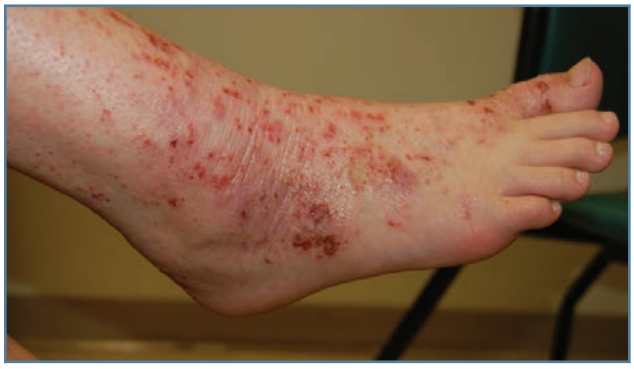

Figure 3.2.3 Atopic dermatitis.

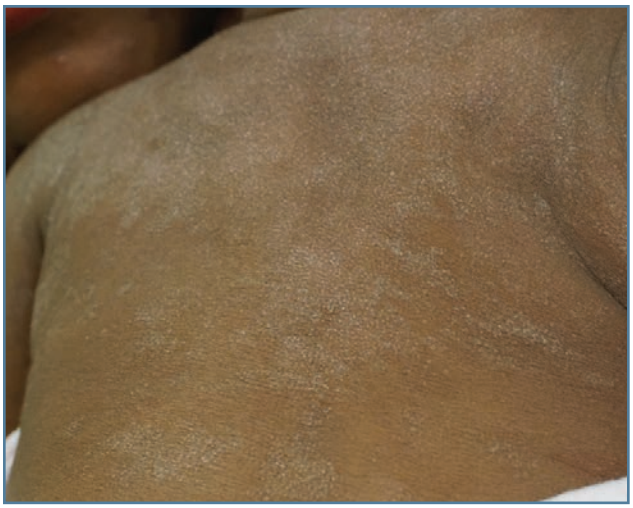

Figure 3.2.4 Atopic dermatitis.

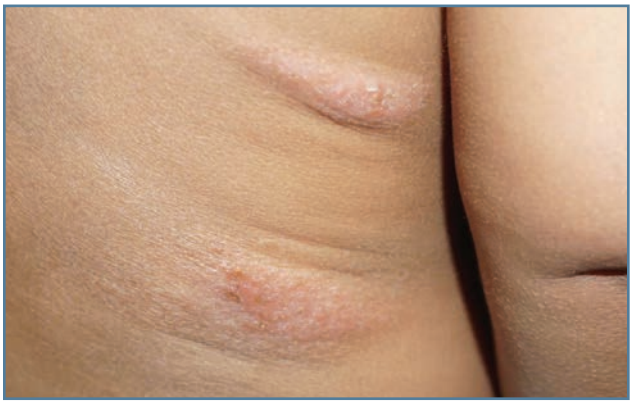

Figure 3.2.5 Atopic dermatitis nummular.

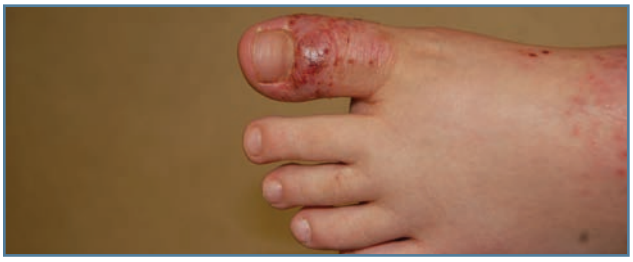

Figure 3.2.6 Atopic dermatitis toe.

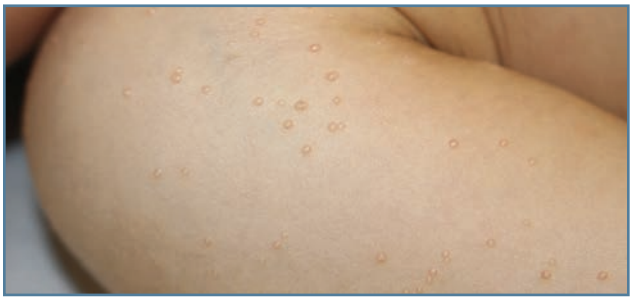

Figure 3.2.7 Molluscum.

3.3 Papulosquamous and Related Disorders

PITYRIASIS RUBRA PILARIS (PRP)

- Chronic inflammatory skin disorder with follicular keratotic papules coalescing into yellow-pink scaly plaques with islands of sparing, hyperkeratosis of palms and soles
- Usually spontaneous but some cases due to activating mutations in *CARD14* (psoriasis 2 [PSORS2]) that lead to increased NF-κB signaling
- Treatments include topical corticosteroids, tazarotene, keratolytics, oral retinoids, UVB phototherapy, methotrexate, cyclosporine, azathioprine, tumor necrosis factor (TNF) inhibitors, ustekinumab

TABLE 3.3.1 PITYRIASIS RUBRA PILARIS TYPES

Type	Designation	Features
I	Classic adult	Follicular papules starting on face and progressing caudally; generalized keratoderma with islands of sparing; typically resolves within 3 yr
II	Atypical adult	More ichthyosiform scaling, longer duration
III	Classic juvenile	Same as type I
IV	Circumscribed juvenile	Thick plaques on elbows, knees, palms, soles; most common type in children
V	Atypical juvenile	Sclerodermatous changes on palms and soles
VI	HIV-related	Nodulocystic and lichen spinulosus—like lesions; erythroderma

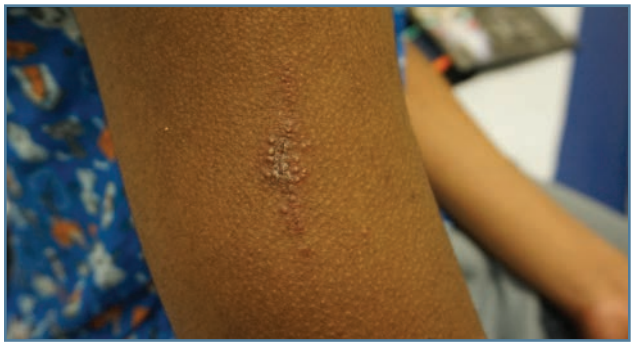

Figure 3.3.1 Lichen spinulosus.

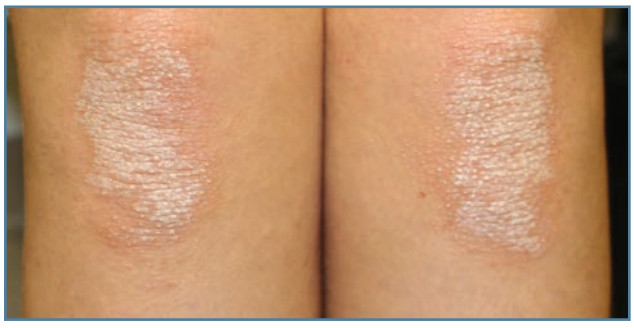

Figure 3.3.2 Pityriasis rubra pilaris.

PITYRIASIS LICHENOIDES

- Refers to a spectrum of disorders with pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica (PLC) representing two polar ends. Skin lesions appear in crops; overall duration varies
- PLEVA: Acute form with reddish brown macules and papules rapidly evolving into vesicular, necrotic, or purpuric lesions; heals with varioliform scars
- PLC: Chronic form with scaly papules; heals with dyspigmentation (hypo), no scarring
- Mucha-Habermann disease: febrile ulceronecrotic form with high fever, arthralgias; gastrointestinal (GI), pulmonary, CNS involvement
- Treatment: Phototherapy most effective. Oral antibiotics 2nd line. Methotrexate for severe cases (alternatives include cyclosporine)

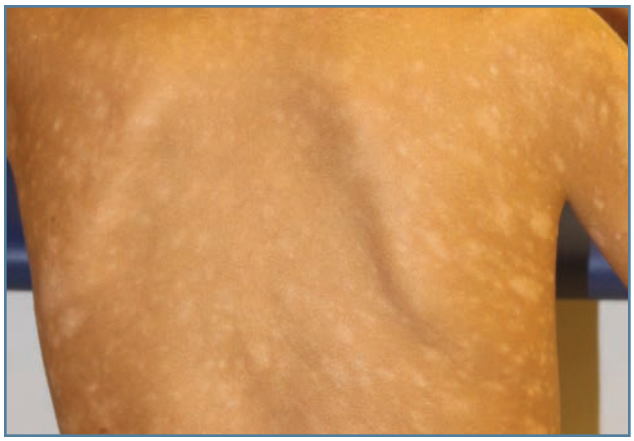

Figure 3.3.3 Pityriasis lichenoides chronica.

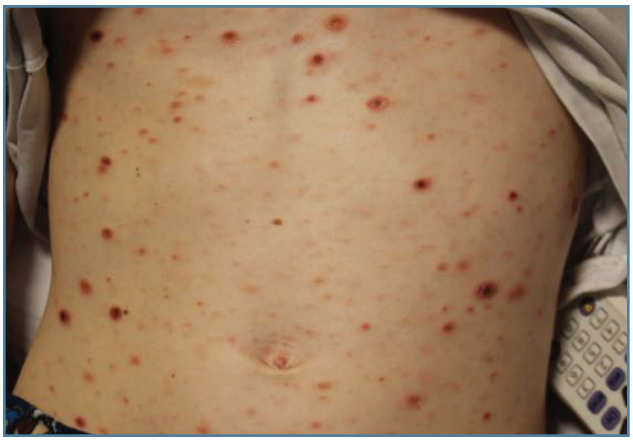

Figure 3.3.4 Pityriasis lichenoides et varioliformis acuta.

3.4 Disorders of the Hair and Nails: Nonsyndromic

- See Section 3.28

3.5 Cutaneous Tumors and Tumor Syndromes

PIGMENTED LESIONS

- Congenital melanocytic nevi
  - Melanocytic nevi present at birth or within the first years
  - Approximately 1% of the population
  - Somatic mutation in *NRAS* >> *BRAF* gene
  - Larger lesions may have cobblestoned, verrucous surface and hypertrichosis
    - Small congenital nevi: Less than 1.5 cm in diameter
    - Medium congenital nevi: 1.5-20 cm in diameter
    - Large or giant congenital melanocytic nevi (GCMN): Greater than 20 cm or 10% body surface area
      - Risk of melanoma in GCMN is approximately 4.5-10%, often by 5 years of age. Axial lesions have greatest risk
      - GCMN overlying the spinal column and skull or multiple satellite lesions can be associated with neurocutaneous melanosis (symptoms of increased cranial pressure, spinal cord compression, or leptomeningeal melanoma)
      - Symptomatic neurocutaneous melanosis = poor prognosis (50% develop leptomeningeal melanoma)
      - MRI to rule out CNS involvement

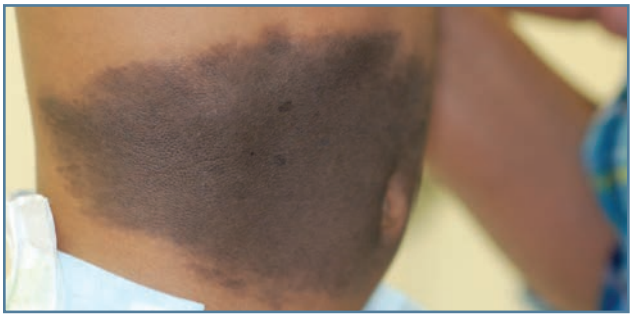

Figure 3.5.1 CMN.

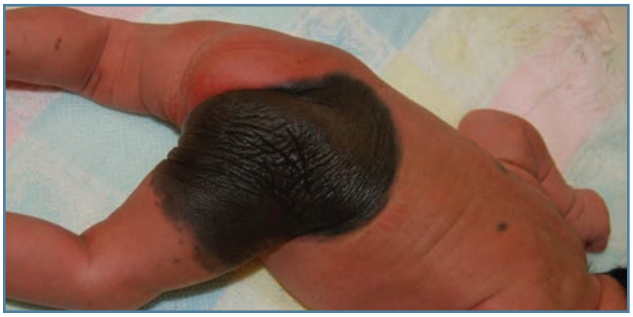

Figure 3.5.2 CMN buttock.

TIP

MRI of brain for GCMN to rule out neurocutaneous melanosis

- Melanoma
  - Incidence: 5-6 cases per million
  - Prepubertal children represent 0.3-0.4% of all melanoma cases
  - Risk factors: >50 nevi, clinically atypical nevi, history of excessive UV exposure, immunosuppression or photosensitivity, family history of melanoma
  - African Americans more likely to have palm/sole, nailbed, mucosal melanoma
  - Increased risk of melanoma in children with:
    - Familial melanoma gene (tumor suppressor gene *p16* or *CDKN2A*, a cyclin-dependent kinase inhibitor, located on chromosome 9p21). Also elevated risk of pancreatic cancer
    - Xeroderma pigmentosum (2,000× greater frequency)
    - FAMM (familial atypical mole/melanoma) syndrome/dysplastic nevus syndrome
    - Giant congenital nevi and neurocutaneous melanosis
  - Sun protection counseling, clinical suspicion and early detection important

TABLE 3.5.1 CLINICAL SIGNS OF MELANOMA

Letter	Stands for:	Signs of Melanoma
A	Asymmetry	Two halves do not look alike
B	Border irregularity	Notched, scalloped, irregular edges
C	Color changes	Any changes: Red, blue/black, white
D	Diameter > 6 mm	Not applicable to congenital nevi
E	Enlargement/evolution	Changes in size

MNEMONIC

ABCDs of Pediatric Melanoma

Amelanotic
Bleeding bumps
Color uniformity
De novo, any diameter

- Spitz nevi (epithelioid cell and/or spindle cell nevomelanocytic nevi)
  - Subtype of melanocytic nevus, first 2 decades (although 1/3 occur in adults)
  - Eruptive smooth dome-topped tan-pink papule on the face or neck
  - Pigmented and atypical variants are described (i.e., pigmented spindle cell nevus of Reed)
  - Starburst dermoscopic pattern for pigmented lesions
- Halo nevus (Sutton's nevus)
  - Melanocytic nevus with a halo of white depigmentation evenly surrounding it. Eventually, nevus disappears followed slowly by repigmentation
  - May occur with blue nevi, Spitz nevi, neurofibromas, melanoma
  - Typically appear in older childhood on the trunk
  - A halo nevus may appear in the setting of vitiligo as well
  - Full skin exam to rule out concurrent melanoma
- Nevus spilus (speckled lentiginous nevus [SLN])
  - Tan-brown regularly bordered macule with melanocytic nevi arising with it
  - Rare melanoma arising in nevus component of SLN
  - Associations include **phakomatosis pigmentovascularis** (nevus spilus and nevus flammeus), **phakomatosis pigmentokeratotica** (nevus spilus and organoid nevus and hemiatrophy, neurologic deficits)
  - Generalized nevus spilus associated with nevus anemicus and primary lymphedema
  - 2% of population
- Becker's melanosis/nevus
  - Typically large, light brown to tan macules with or without an increased amount of darker hair growing within it
  - Most common location on the shoulders, upper chest, or back of teenaged boys
  - Usually, unilateral and may be associated with an underlying arrector pili smooth muscle hamartoma "pseudo-Darier's sign"
  - Increased melanin in epidermis, not increased melanocytes

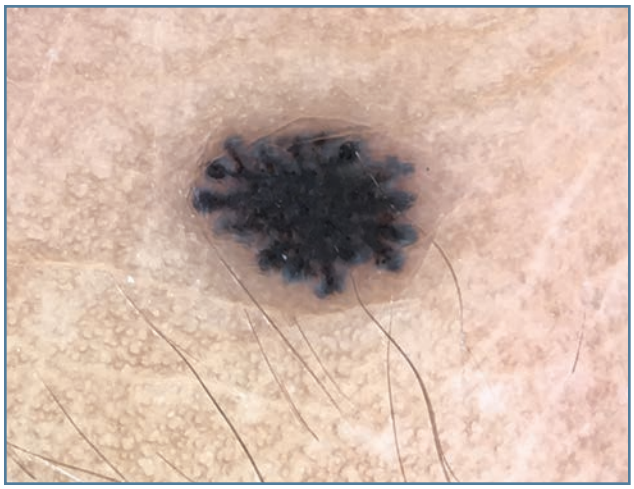

Figure 3.5.3 Spitz nevus.

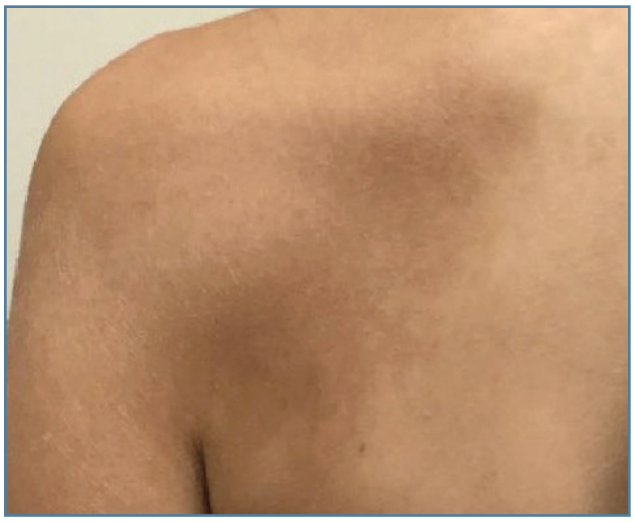

Figure 3.5.4 Becker's nevus.

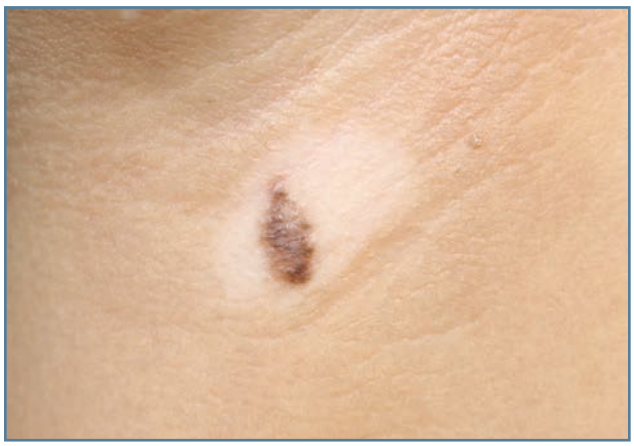

Figure 3.5.5 Halo nevus.

TUMORS OF THE EPIDERMIS

- Epidermal nevi
  - Hamartomas of epidermal structures
  - Typically present at birth, but may arise later, even into adulthood
  - Epidermal nevi with hyperkeratosis at birth may result in generalized epidermolytic ichthyosis in offspring, particularly in extensive lesions due to mosaicism
  - Many of the larger lesions follow the lines of Blaschko
  - Epidermal nevus syndrome consists of epidermal nevus in association with neurologic, ocular, and/or musculoskeletal anomalies
  - Somatic mosaicism of *FGFR3, PIK3CA, RAS, KRAS, HRAS, NRAS* genes
- Inflammatory linear verrucous epidermal nevus
  - Blaschkolinear scaly erythematous plaque, often on extremities
  - Usually appears during childhood
  - Treatment is topical antiinflammatory agents, usually not effective
- Basal cell nevus syndrome (Gorlin syndrome)
  - AD
  - PATCHED gene defect (tumor suppressor)
  - Early onset of numerous basal cell carcinomas, palmar pits, odontogenic keratocysts of jaws
  - Medulloblastoma and meningiomas possible as well as ovarian and cardiac fibromas. Cleft palate, bifid ribs, and other musculoskeletal abnormalities, calcification of falx cerebri, agenesis of corpus callosum
  - Associated with advanced paternal age
  - Vismodegib, a hedgehog pathway inhibitor, is a treatment option

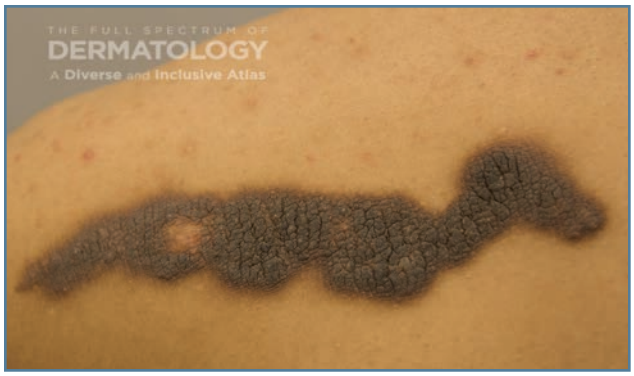

Figure 3.5.6 Epidermal nevus.

TUMORS OF THE EPIDERMAL APPENDAGES

- Nevus sebaceus (NS)
  - Waxy orange-tan plaque with alopecia. Usually present from birth. Head and neck
  - Neoplasms associated: trichoblastoma, syringocystadenoma papilliferum (SCP), (syringocystadenoma papilliferum is the most common benign tumor according to a review of 596 cases [30/596]). Trichoblastomas were identified in 28/596 cases. A subsequent report of 155 cases showed trichoblastoma rather than SCP as the most common tumor arising in NS, BCC < 1%
- Nevus sebaceus syndrome (Schimmelpenning-Feuerstein-Mims syndrome)
  - Somatic mosaicism (AD lethal)
  - Extensive nevus sebaceous along Blaschko's lines, BCC
  - Cranial asymmetry and somatic overgrowth, kyphoscoliosis, mental retardation (MR), seizures, horseshoe kidney, constricting the aorta
  - Eye abnormalities including coloboma, lid lipodermoid
  - Vitamin D—resistant rickets
- Nevus comedonicus
- Pilomatricoma
  - AD
  - β-Catenin gene defect
  - Superficial circumscribed nodule, often bluish in color. Calcification common. "Rocker bottom sign" present
  - Multiple tumors associated with:
    - Myotonic dystrophy (Steinert syndrome)
    - Rubinstein-Taybi syndrome (mental retardation, broad thumbs and toes, and facial abnormalities—CREB-binding protein defect)
    - Also associated with Turner's syndrome, Gardner syndrome, trisomy 9
    - Path: Hair follicle differentiation. "shadow cells" or "ghost cells" present
- Cylindromatosis, familial
  - AD
  - *CYLD* gene mutation
  - Multiple reddish-pink nodules occurring on scalp (turban tumors) and face
  - May be associated with multiple trichoepitheliomas (Brooke-Spiegler syndrome) and milia (milia and trichoepitheliomas + cylindromas
- Angiofibromas
  - Uniform flesh-colored to red papules over nose and cheeks
  - Multiple lesions associated with tuberous sclerosis (adenoma sebaceum), multiple endocrine neoplasia (MEN) type 1, Cowden, Birt-Hogg-Dubé
- Connective tissue nevi
  - Present at birth or in early childhood
  - Collagenomas may be autosomal dominant inherited
  - "Shagreen patch" of tuberous sclerosis is a type of connective tissue nevus (collagenoma)
  - Eruptive lesions symmetrically distributed over the back, beginning in adolescence
  - Elastomas in Buschke-Ollendorff syndrome (*LEMD3* gene) (dermatofibrosis lenticularis disseminata) are symmetric and associated with osteopoikilosis
  - Seen in Proteus syndrome

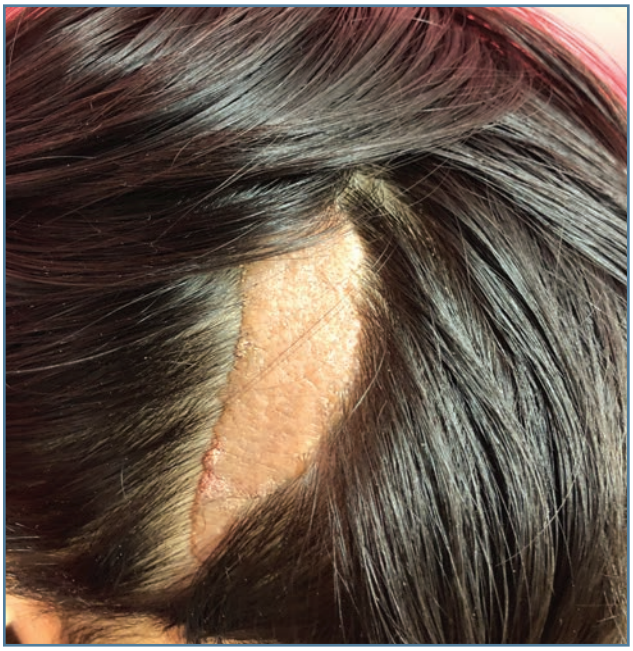

Figure 3.5.7 Nevus sebaceus.

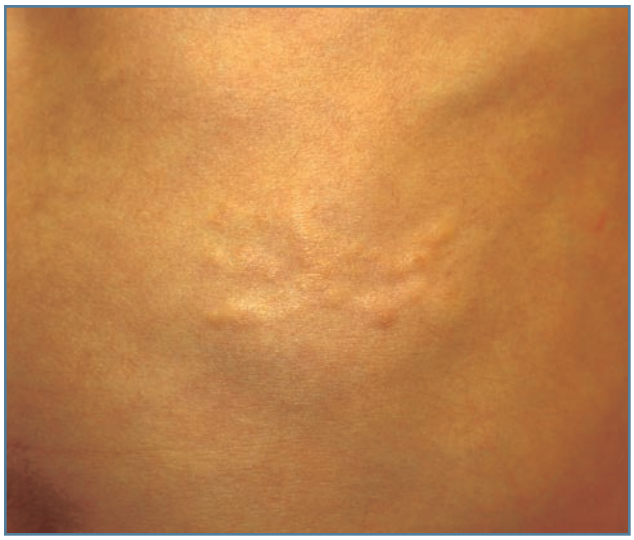

Figure 3.5.8 Elastoma Buschke-Ollendorf.

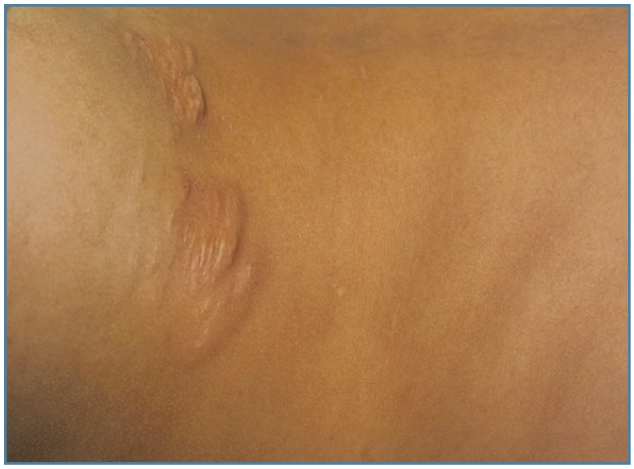

Figure 3.5.9 Collagenoma.

FIBROMATOSES

- Recurring digital fibroma of childhood
  - Typically arise during the first year of life
  - Painless nodules that spare the thumb and great toe
  - High recurrence rate with surgery, spontaneous regression
  - Pathognomonic small, round, red perinuclear intracytoplasmic periodic acid—Schiff (PAS)$^{+}$ inclusion bodies in the proliferating fibroblasts on histopathology, thought to be aggregates of actin
- Infantile myofibromatosis (congenital generalized fibromatosis)
  - Often present at birth
  - Both localized and generalized forms exist
  - Generalized form has visceral involvement
  - **80% of the mortality is secondary to lung, GI, and CNS involvement, failure to thrive, and infection**
  - Tends to regress spontaneously on skin
- Fibrous hamartoma of infancy
  - Generally present in first 2 years of life; upper trunk and in the genital region
  - 15% recurrence after excision

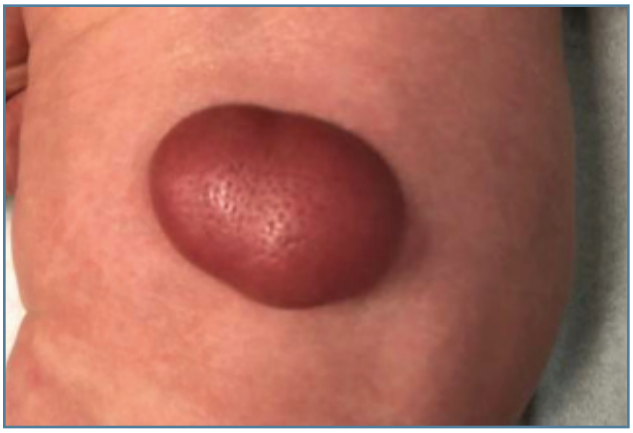

Figure 3.5.10 Fibrous hamartoma of infancy.

TUMORS OF FAT, MUSCLE, AND BONE

- Lipomas
  - Bannayan-Zonana syndrome, Bannayan-Riley-Ruvalcaba syndrome: see Section 3.22
  - Muir-Torre syndrome: see Section 3.24
    - Numerous benign and malignant tumors of the GI tract, and diverticulosis
    - Laryngeal and breast cancer. Benign and malignant tumors of the genitourinary (GU) system. Malignancies often less aggressive than in patients without Muir-Torre
  - PTEN Hamartoma Tumor Syndrome (Cowden syndrome)
    - AD
    - *PTEN* gene defect (Cowden-like syndrome: *BMPR1A* gene defect)

TIP

Sclerotic fibromas are characteristic in Cowden Syndrome

- Multiple tricholemmomas beginning in adolescence in midfacial distribution. Acral keratoses, lipomas, skin tags, and oral papillomas may also be present. Macrocephaly, mild MR, and scrotal tongue are early signs. Hamartomas of breast, GU system, and thyroid occur

- Lhermitte-Duclos disease (cerebelloparenchymal disorder VI)
  - May represent Cowden's with greater CNS involvement
  - Allelic with Bannayan-Zonana syndrome and juvenile polyposis syndrome
- Encephalocraniocutaneous lipomatosis
  - Encephalocraniocutaneous lipomatosis is a rare condition characterized by developmental delay and unilateral skin and ocular lesions and cerebral malformations. It tends to have lipomas on the scalp +/- alopecia
- Michelin tire baby
  - Michelin tire baby syndrome is a very rare condition where newborns have numerous cutaneous folds thought to be from excess fat

- Miscellaneous
  - Steatocystoma multiplex
    - AD
    - Defect in the keratin 17 gene
    - Numerous cysts may be associated with nail dystrophy, natal teeth (pachyonychia congenita)
  - Mastocytosis
    - Accumulation of mast cells in the skin and other organs
    - Clinically, several forms exist
    - Rarely, mast cell or other leukemias may develop in systemic mastocytosis
    - Treatment with antihistamines, both H1 and H2 blockers, psoralen and UVA (PUVA), and corticosteroids, oral cromolyn for GI symptoms

1. Solitary mastocytoma
   - Flesh-colored to yellow or tan papule or plaque with peau d'orange appearance
   - Can be multiple but usually no more than a few in number
   - Urticate on stroking (positive Darier sign) in nearly all cases; can blister
2. Maculopapular cutaneous mastocytosis (urticaria pigmentosa)
   - Typically presents in early childhood. 50% of cases occurring before 6 months of age
   - Few to numerous macules, papules, nodules, and vesicles with tan to red-brown pigmentation
   - Pruritus, diarrhea, shortness of breath, joint pains, and fatigue in minority
   - Darier's sign is usually positive
   - Mast cell degranulators must be avoided in extensive cases to prevent possible anaphylaxis:
     - **Aspirin, alcohol, opiates, polymyxin B, quinine, scopolamine, amphotericin B, and tubocurarine**
3. Diffuse cutaneous mastocytosis
   - Diffuse involvement of the entire skin surface
   - Orange color often present with vesicles and bullae at sites or urtication. Peau d'orange skin changes
   - Germline kit mutation may be associated with more severe and longstanding disease.
4. Telangiectasia macularis eruptiva perstans
   - Rare in childhood

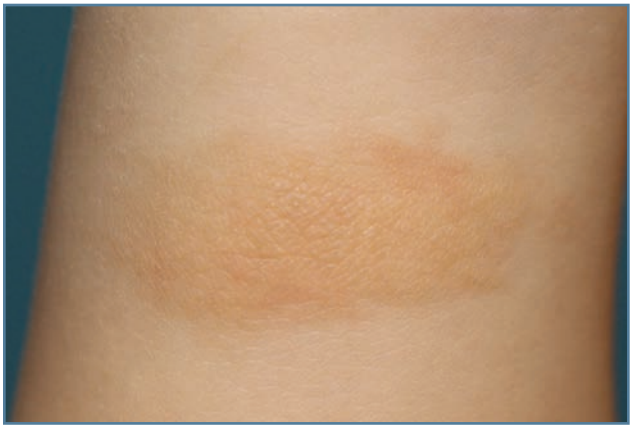

Figure 3.5.11 Mastocytoma.

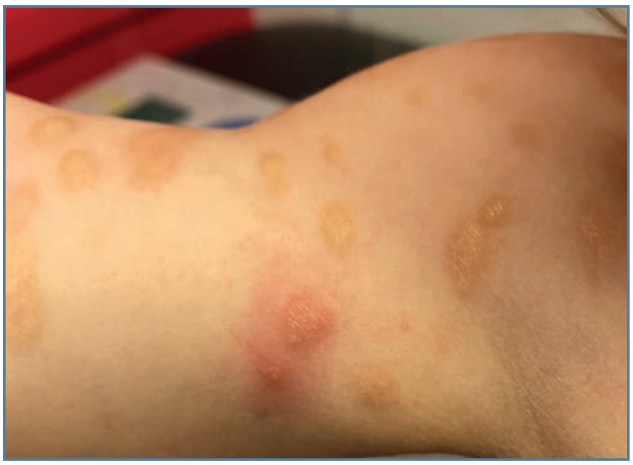

Figure 3.5.12 Maculopapular cutaneous mastocytosis (urticaria pigmentosa).

3.6 Histiocytosis and Malignant Skin Disorders

LANGERHANS CELL HISTIOCYTOSES

- Prior nomenclature includes: Letterer-Siwe disease, eosinophilic granuloma, Hand-Schüller-Christian disease, congenital self-healing reticulohistiocytosis
- Spectrum of diseases characterized by Langerhans cell proliferation
- Extent and number of organ systems involved determine prognosis
- BRAFV600E mutations associated with multisystem disease and poorer response to therapy
- Skin findings include yellow to brown, crusted papules often purpuric or hemorrhagic in a seborrheic distribution
- $CD1a^+$, $S100^+$ Langerhans cells with comma-shaped nuclei
- A Tzanck smear of vesicles may aid in diagnosis
- Oral mucosal and gingival lesions can occur, affecting dentition; **alveolar bone loss with "floating" teeth on X-ray**
- Bone most commonly involved, tends to occur in older children and adults, as does pulmonary disease
- Diabetes insipidus may result when the skull involved
- Lymph node, bone marrow, and liver disease may also occur

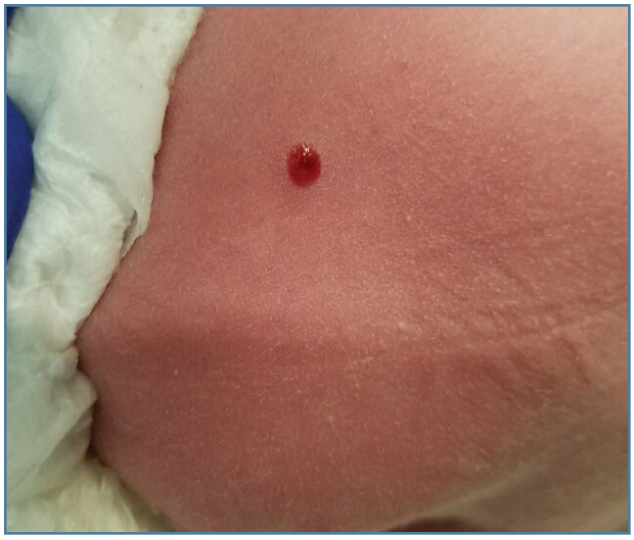

Figure 3.6.1 Langerhans cell histiocytosis.

JUVENILE XANTHOGRANULOMAS (JXG)

- Yellowish to orange papules typically erupt within the first year of life
- Solitary lesions are most common; but multiple, nodular, plaque, and giant forms are described
- Extracutaneous ocular lesions most common (0.4%) with multiple lesions
  - **Eye lesions usually occur within the first 2 years of life**
  - Glaucoma, uveitis, hyphema, or heterochromia iridis
- Multiple JXGs are associated with neurofibromatosis 1 (NF-1) and juvenile myelomonocytic leukemia (JMML)

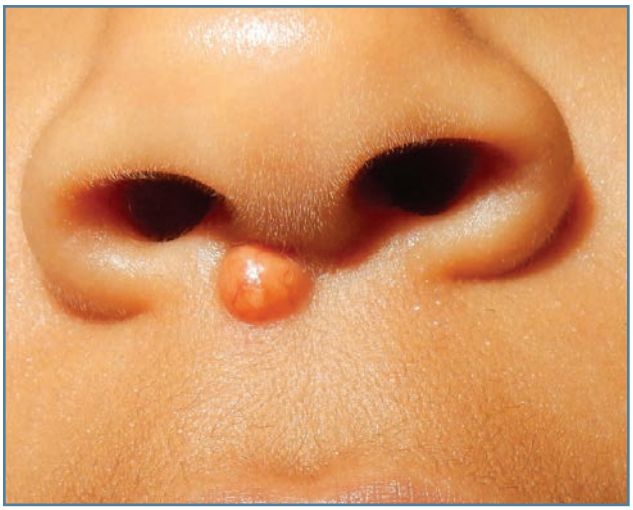

Figure 3.6.2 Juvenile xanthogranulomas JXG. (Courtesy of Michael Cardis, MD).

BENIGN CEPHALIC HISTIOCYTOSIS

- Benign self-healing non-Langerhans histiocytoses
  - Asymptomatic and no visceral involvement
  - Reddish yellow papules on the head, neck, and upper trunk
  - Appear around 18 months of age
  - Boys are affected twice as often as girls
  - Spontaneous resolution occurs over several years
  - Histologically, the histiocytic infiltrate is S100/CD1a negative

3.7 Disorders of Pigmentation Except Hypopigmentation

DISORDERS OF ABNORMAL PIGMENTATION

- Albinism: See Section 3.18

WAARDENBURG AND PIEBALDISM

- See Section 3.18

DISORDERS OF HYPERPIGMENTATION

- Congenital dermal melanocytosis (Mongolian spot)
  - Deep blue-gray macular pigmentation
  - Most commonly on buttocks/lower back in African American/Asian neonates
  - Extensive Mongolian spots seen in GM1 gangliosidosis, Hunter/Hurler syndrome
- Nevus of Ota (oculodermal melanocytosis/nevus fuscoceruleus ophthalmomaxillaris)
  - Deep blue macular pigmentation involving trigeminal nerve (V1, V2) distribution
  - Most common in the Japanese population and in women (5:1)
  - Underlying mucosa, conjunctiva, and tympanic membranes may be pigmented
  - Color may darken with menses and age
  - Responds to laser therapy
  - Rarely, melanoma can arise within nevus of Ota (choroid is most common site)
- Nevus of Ito (nevus fuscoceruleus acromiodeltoideus)
  - Same as nevus of Ota but in a lateral supraclavicular or lateral brachial nerve distribution
- Other conditions with dermal melanocytosis:
  - Incontinentia pigmenti
  - Naegeli-Franceschetti-Jadassohn
    - Keratin 14 mutation, palmar/plantar hypohidrosis, hyperkeratoses, reticular pigmentation, poor dentition, no dermatoglyphics
  - Dermatopathia pigmentosa reticularis
    - *KRT14* mutation, triad of generalized reticulate hyperpigmentation, noncicatricial alopecia, onychodystrophy; adermatoglyphia, PPK, hypo/hyperhidrosis
- Blue nevus
  - Melanocytic nevus characterized by dark blue papule
  - Acquired or congenital melanocytic lesion
  - 3 types: Common blue nevus, cellular blue nevus, and combined blue nevus
  - **Multiple epithelioid blue nevi associated with LAMB syndrome (Carney complex)**

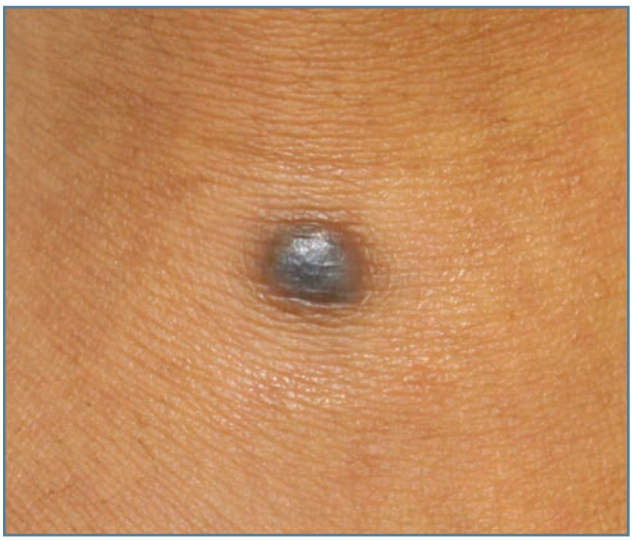

Figure 3.7.1 Blue nevus.

3.8 Vascular Disorders of Infancy and Childhood

INFANTILE HEMANGIOMAS

- Often not seen at birth but become apparent within the first weeks of life
- Undergo a rapid proliferative phase over the first 3-9 months (up to 18 months), then shrink or involute over several years
- Most resolve by 10 years of age
- Treatment: Propranolol, timolol, Intralesional or systemic corticosteroids, surgical intervention, pulsed dye laser, vincristine, or α-interferon (which can cause spastic diplegia, permanent side effect)
  - Clinical practice guidelines for treatment Krowchuk et al, Pediatrics, 2019
    - Life-threatening complication
    - Functional impairment or risk thereof
    - Ulceration or risk thereof
    - Evaluation to identify important associated structural anomalies
    - Risk of leaving permanent scarring or distortion of anatomic landmarks
- Lesions prone to cause functional impairment typically located in the periorbital region, and near the nose or mouth
- Life-threatening complications can occur with visceral lesions
- Laryngeal involvement in beard distribution
- Ulceration in the anogenital region
- GLUT1 positive
- PHACE syndrome
  - **P**osterior fossa malformations (Dandy-Walker most common), facial **h**emangiomas, **a**rterial abnormalities, **c**oarctation of the aorta, **e**ye abnormalities, and **s**ternal nonunion or supraumbilical raphe
  - Potential stroke risk when starting propranolol requires close monitoring
- LUMBAR syndrome (previously called SACRAL and/or PELVIS syndrome)
  - Perineal or lumbosacral hemangioma in association with spinal dysraphism (especially tethered cord), congenital cutaneous, renal, and urogenital anomalies, anorectal malformations
- Diffuse congenital hemangiomatosis
  - Sporadic, multiple 0.2- to 2.0-cm hemangiomas in generalized distribution, involving any organ,
  - Liver hemangioma may be complicated by obstructive jaundice, portal hypertension, hemorrhage, high-output congestive heart failure (CHF) (potentially fatal)
  - **Treat with oral propranolol**
  - **Screening liver ultrasound for ≥5 cutaneous infantile hemangiomas**

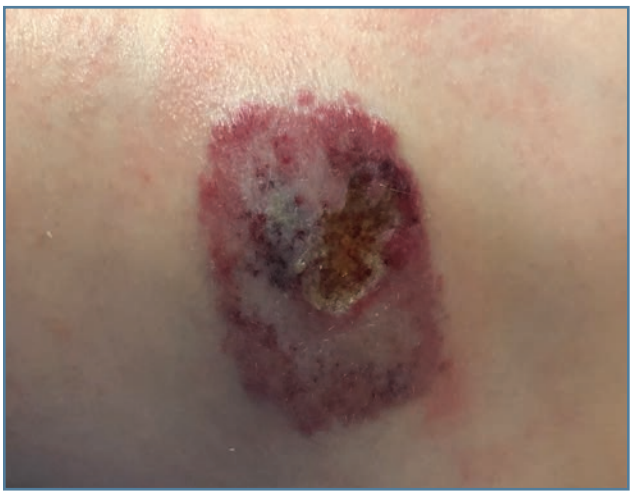

Figure 3.8.1 Infantile hemangioma, ulcerated.

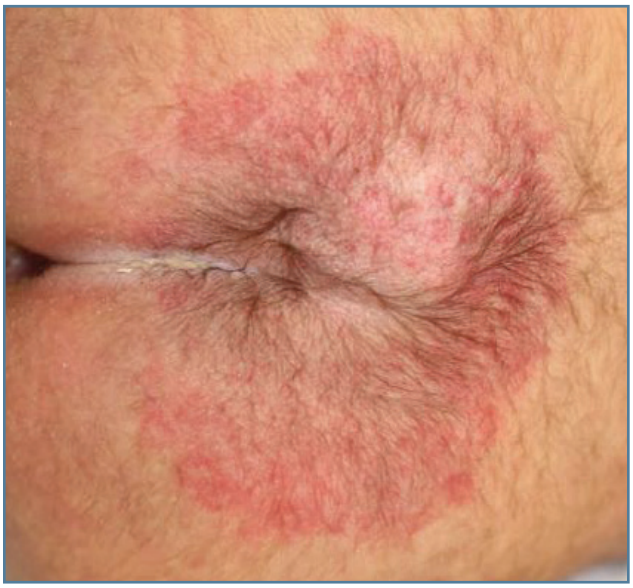

Figure 3.8.2 LUMBAR.

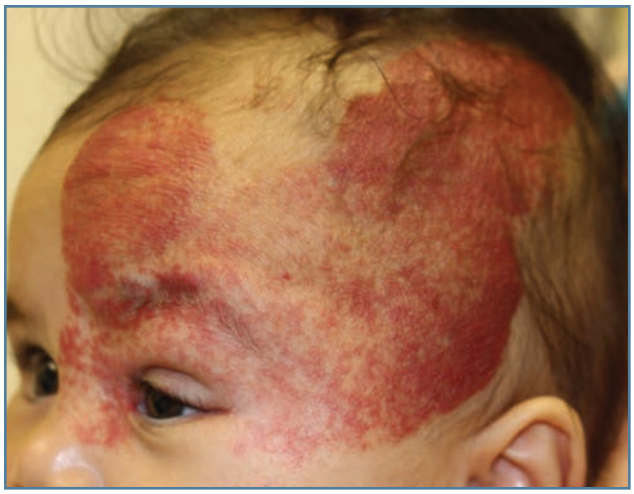

Figure 3.8.3 PHACE.

NONINVOLUTING CONGENITAL HEMANGIOMA (NICH)

- Plaque-like with a pink or purple color and prominent overlying coarse telangiectasias and peripheral pallor
- Mix of high and low flow
- Grows proportionally or expands slowly
- Biopsy: Thin-walled channels that are lined by plump endothelial cells and one or more layers of pericytes. GLUT1 negative
- Treatment: Surgical excision

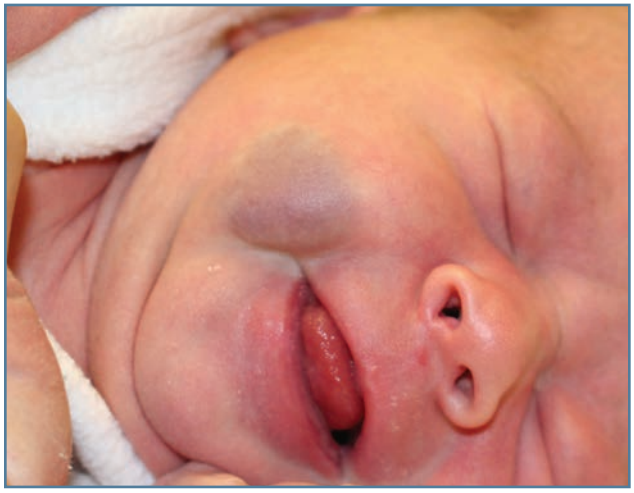

Figure 3.8.4 Congenital hemangioma.

RAPIDLY INVOLUTING CONGENITAL HEMANGIOMA (RICH)

- Pink-red to bluish-red, often large vascular tumor with characteristic pale halo
- Multifocal variants described. Prenatal diagnosis by ultrasound
- Can be associated with transient coagulopathy due to localized intravascular coagulation, high-output cardiac failure
- Biopsy: Small capillary lobules separated by abundant collagen. Prominent draining channels. **GLUT1 negative**
- Involute spontaneously, rapidly within 1 year. May have residual atrophic skin

KASABACH-MERRITT PHENOMENON

- Due to kaposiform hemangioendothelioma or tufted angioma
- Rapid, painful growth of vascular lesion is a clue
- **Confused with child abuse**
- **Consumptive coagulopathy** with potential for disseminated intravascular coagulation (DIC) and high-output cardiac failure

VASCULAR MALFORMATIONS

- Nevus simplex (stork bites, salmon patches, nevus flammeus neonatorum)
  - V-shaped distribution on central forehead, nuchal region common. Less commonly on eyelids, upper lip, scalp, overlying spine
  - Facial lesions typically resolve spontaneously
- Capillary vascular malformations (port wine stain)
  - ***GNAQ* mutation**
  - Lesions in V1 distribution may have associated ipsilateral ophthalmic and/or meningeal anomalies (Sturge-Weber syndrome)
  - Increased risk with bilateral lesions and when V2/V3 involved in addition to V1
  - V2/V3 involvement may result in jaw or dental anomalies

- Sturge-Weber syndrome (SWS)
  - Sporadic, somatic *GNAQ* mutations (also in isolated facial port-wine stains [birthmarks; PWS]),
  - M = F
  - PWS facial capillary malformation at birth (embryonic neurovascular segment, unilateral > bilateral)
  - Neurologic: **Seizures** by 1-2 years, mental retardation, cerebral atrophy, ipsilateral leptomeningeal angiomatosis (vascular malformations), **tram-track cortical calcifications**
  - Ophthalmic: Choroid malformations, ipsilateral **glaucoma**, blindness
  - Work-up: Neuro referral, MRI, ophthalmological exam. Glaucoma risk factor = upper eyelid involvement
  - SWS risk factor = highest with forehead (including upper eyelid) + hemifacial distribution of PWS, also associated with median segment (nasal bridge/glabella/mid-forehead) PWS
  - Newer mutations identified include GNA11 and GNB2
- Phakomatosis pigmentovascularis
  - Type 1: Nevus flammeus + epidermal nevus
  - Type 2: Nevus flammeus + dermal melanocytosis ± nevus anemicus
  - Type 3: Nevus flammeus + nevus spilus ± nevus anemicus
  - Type 4: Nevus flammeus + dermal melanocytosis + nevus spilus ± nevus anemicus
  - Type 5: Cutis marmorata telangiectatica congenita + dermal melanocytosis (associated findings can include ocular abnormalities, choroidal melanoma and hemihypertrophy of the limbs, visual vascular anomalies)
- Klippel-Trenaunay-Weber syndrome
  - Sporadic, somatic *PIK3CA* mutations in some.
  - May also be associated with coagulopathy, digital defects, MR, glaucoma
  - Port-wine stains (lower > upper extremity), hemihypertrophy of limb, lymphatic and deep venous insufficiency of affected limb.
  - Parkes-Weber syndrome has the above, plus arteriovenous fistulas, caused by somatic mutations in RASA1
- Megalencephaly-capillary malformation syndrome
  - Formally MCMTC (macrocephaly-cutis marmorata telangiectatica congenita)
  - Reticulated port wine stains
  - Asymmetric somatic growth
  - CNS and neurological abnormalities
  - *PIK3CA* gene (same as CLOVES [congenital lipomatous (fatty) overgrowth, vascular malformations, epidermal nevi and scoliosis/skeletal/spinal anomalies] syndrome)
- Diffuse capillary malformation with overgrowth (DCMO)
  - Extensive capillary malformation; often reticular in pattern
  - Associated with mild overgrowth
  - No macrocephaly, good prognosis

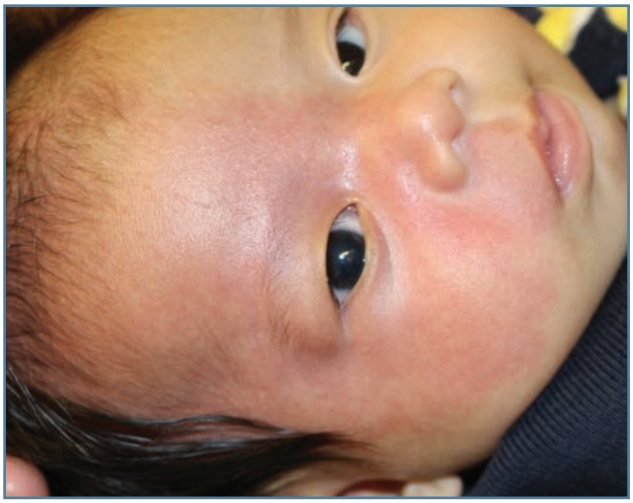

Figure 3.8.5 Port wine stain.

VENOUS MALFORMATIONS

- Maffucci syndrome
  - Sporadic, parathyroid hormone/parathyroid hormone—related protein (PTH/PTHrP) type I receptor
  - Progressive growth of vascular hamartomas and enchondromas
  - Approximately 1/3 of patients develop malignancies including chondrosarcomas, fibrosarcomas, angiosarcomas, gliomas and teratomas
- Blue rubber bleb nevus syndrome (Bean syndrome)
  - Sporadic, some AD (*TIE2*, tyrosine kinase activating mutation)
  - Compressible, rubbery blue-red masses (venous malformations)
  - Painful, ±increased sweat over lesion
  - Often associated with similar gastrointestinal lesions. GI bleeding, resulting in anemia, **intussusception**
- Multiple cutaneous and mucosal venous syndrome (VMCM)
  - AD
  - Due to activating mutations in gene encoding tyrosine kinase receptor *(TEK [TIE2])*
  - Venous malformations involving skin, mucosa, GI tract. Maxillary, mandibular deformity can occur

ARTERIOVENOUS MALFORMATIONS

- Capillary malformation-arteriovenous malformation syndrome
  - Due to germline mutation in *RASA1* gene encoding p120-RasGAP
  - Capillary malformations: Small, multifocal often with blanched halo, randomly distributed (single capillary-venous malformation [CVM] less common) associated with visceral arteriovenous malformation (AVM) or arteriovenous fistula (AVF)
  - Parkes Weber syndrome: Variant with SOMATIC mutation in RASA1 with port wine stain and AVM/AVF of the affected limb
  - Cobb syndrome
    - Dermatomal capillary malformation on the trunk
    - Associated with underlying spinal AV malformation at the same spinal segment

LYMPHATIC MALFORMATIONS

- Lymphatic malformations (cystic hygroma, lymphangioma circumscriptum, and lymphangioma simplex)
  - Do not undergo a rapid proliferative phase
  - Grow as the child grows; may become focally thickened
  - May be macrocystic or microcystic
  - Associated with Proteus syndrome, Klippel-Trenaunay-Weber syndrome
- Microcystic lymphatic malformation (lymphangioma circumscriptum)
  - Localized lymphatic malformation characterized by superficial clear or hemorrhagic vesicles and flesh-colored papules ("frog spawn" appearance)
  - Histologically characterized by deep-seated, thick-walled vesicles
  - Commonly, they are located on the shoulders, neck, axilla, tongue, and mucous membranes
  - **Recurrences are common postexcision**
- Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT)
  - Hundreds of cutaneous reddish-brown to bluish-purple vascular papules to nodules. Present at birth
  - Skin lesions can mimic multifocal infantile hemangiomas
  - Severe GI bleeding (hematemesis and melena), thrombocytopenia
  - Biopsy: Dilated vessels in dermis and subcutis lined by hobnailed endothelial cells that have formed intraluminal papillary projections. GLUT1 negative, CD31 positive, LYVE-1 positive
  - Treatment: Systemic corticosteroids, interferon, vincristine
- Hereditary lymphedema (Milroy disease): See Section 3.20

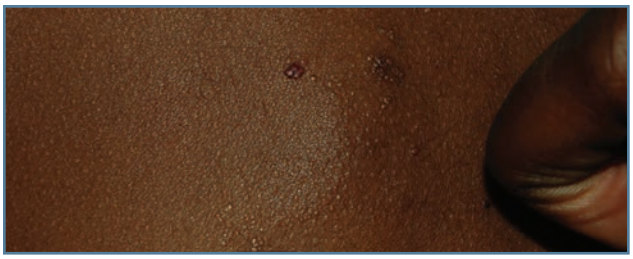

Figure 3.8.6 Microcystic.

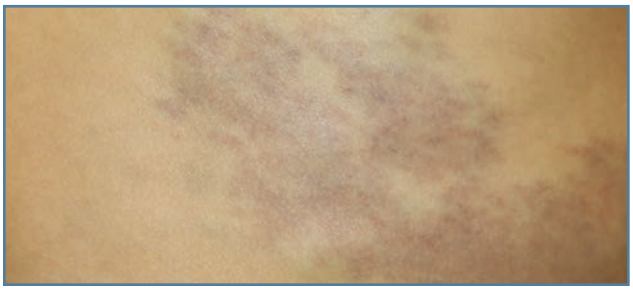

Figure 3.8.7 Venous malformation.

TIP

Sirolimus (rapamycin)

- mTOR inhibitor → downregulation of PI3K/AKT signaling pathway
- Efficacious for complex vascular malformations including lymphatic malformations, Kasabach-Merritt phenomenon

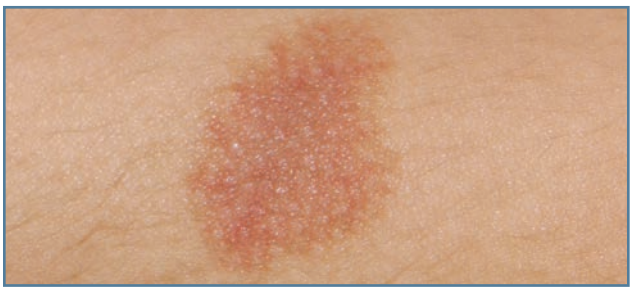

Figure 3.8.8 CM-AVM.

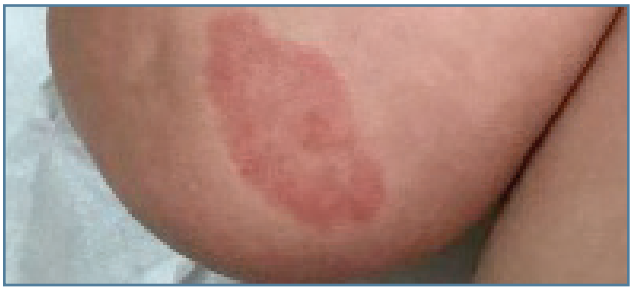

Figure 3.8.9 CM-AVM.

ANGIOKERATOMAS

- A dilatation of the superficial vessels with overlying hyperkeratosis of the epidermis. They do not blanch. Six types exist:
  - Solitary or multiple angiokeratomas: Typically on lower extremity following trauma
  - Angiokeratoma circumscriptum: Usually begin in infancy/early childhood. Females affected 3 times more often than males. No tendency to spontaneously involute
  - Angiokeratoma of Mibelli: Occurs on the extremities more often in girls during late childhood. Lesions on hands and feet may be associated with acrocyanosis, chilblains, or frostbite with abnormal immunoglobulin levels
  - Angiokeratoma of Fordyce: Characterized by angiokeratomas occurring on the scrotum or labia. Generally, onset begins in adulthood but may occur in adolescence. Can be associated with varicocele, hernia, prostatitis, bladder or epididymal tumors, lymphogranuloma venereum (LGV), or thrombophlebitis
  - Angiokeratoma corporis diffusum: Most commonly seen with Fabry syndrome. See Section 3.25
  - **Fucosidosis: Has disseminated angiokeratomas similar to those in Fabry syndrome secondary to deficiency of α-L-fucosidase**
  - **May be associated with other lysosomal storage disorders including mannosidosis**

DISORDERS ASSOCIATED WITH VASCULAR DILATATION

- Livedo reticularis
  - Fixed vascular reticulated patterning
  - Associated with autoimmune diseases, rheumatic fever, neurologic disorders, drug/medication, neoplasms, vasculitis, infection, metabolic disorders, hematologic diseases, pancreatitis, and cryoglobulinemia
    - Drug induced: **Amantidine**
  - Syndromal associations include: Sneddon syndrome (livedo reticularis, cerebrovascular accidents, anti-phospholipid antibodies), anti-phospholipid antibody syndrome, Churg-Strauss syndrome, and homocystinuria
- Auriculotemporal syndrome (Frey's syndrome)
  - Hyperhidrosis with cutaneous flushing in the distribution of the auriculotemporal nerve on gustatory or olfactory stimulation
- Erythromelalgia
  - Painful burning and redness of distal extremities
  - Precipitated by heat and improved by cooling
  - May be idiopathic, familial, or associated with an underlying condition such as thrombocythemia
  - May be associated with *SCN9A* mutation (Na^+ channels)
- Cutis marmorata telangiectatica congenita
  - A vascular anomaly that is usually present at birth and improves with age
  - A segmental reticular, blue-red mottling of the skin
  - Some cases appear to be due to dilated capillaries and veins
  - Can be distinguished from "physiologic" cutis marmorata of the newborn by simply warming the infant. The reticulated pattern will disappear in "physiologic" cutis marmorata
  - Can have associated limb discrepancies, patent ductus arteriosus (PDA), arterial stenosis and glaucoma

TELANGIECTASES

- Spider angiomas (nevus araneus)
  - Central arteriole with peripheral branches
  - Very common
  - May regress spontaneously
- Angioma serpiginosum
  - Red, vascular macules in a linear distribution
  - Typically begins in childhood on the lower extremity and buttocks in females (90%)
  - Histologic examination reveals dilated capillaries in the upper dermis
- Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease): 3.20
- Ataxia-telangiectasia (Louis-Bar syndrome): See Section 3.20

3.9 Bullous Disorders of Childhood

- See Table 3.15.1 Epidermolysis Bullosa

3.10 Exanthematous Diseases of Childhood

TABLE 3.10.1 EXANTHEMS, ENANTHEMS, AND OTHER ERUPTIONS

Disease	Classic Designation	Exanthem	Enanthem	Etiology/ Infectivity	Extracutaneous	Complications/Other
Varicella	Chickenpox Late fall, winter, spring 1-14 yr old	"Tear drop" vesicles on red base; centrally necrotic or crusted lesions; all stages simultaneously		VZV (dsDNA herpesvirus)	1. Fever, malaise 2. Pneumonia (especially in immunocompromised) Do not give aspirin = Reye's syndrome	Pneumonitis more severe and common in adults Congenital varicella = hypoplastic limbs, scars, ocular, CNS disease
Measles (rubeola)	First disease	Morbilliform rash begins behind ears, spreads downward; not pruritic; lasts 4-7 d	Koplik spots: Blue-gray specks on erythematous buccal mucosa (appear before rash). Fades within 2-3 d after onset of rash	ssRNA paramyxovirus Airborne	3 C's: Cough, coryza, conjunctivitis; high fever	Pneumonia, otitis media, diarrhea, postinfection encephalomyelitis; vitamin A can decrease mortality, especially in malnourished
Scarlet fever	Second disease School-aged children Fall, winter, spring	Sandpaper rash; Pastia's lines (accentuation in skin folds); circumoral pallor; desquamation as rash fades after 4-5 d	Strawberry tongue (white, then red); petechiae on palate	Group A β-hemolytic streptococcus (pyrogenic exotoxin) Airborne or fomites	Fever, sore throat abrupt-onset fever, headache, vomiting, malaise, sore throat	Rx: PCN
Rubella (German measles)	Third disease Mild prodrome: Malaise, cough, fever	Confluent rose papules, which begin centrally on face and spread acrally with rapid fading	Erythema; petechiae on soft palate = Forscheimer's spots	ssRNA togavirus Respiratory, adolescent, spring	Fever, adenopathy, arthralgias, sub-occipital/posterior auricular	Teratogenic congenital rubella = cataracts, deafness, cardiac (PDA)
Erythema infectiosum	Fifth disease 5- to 15-yr-olds, winter/spring	"Slapped cheeks" 1-4 d then generalized lacy rash lasts 4-9 d Rash waxes/wanes several weeks with physical stimuli (temperature, sunlight)	None	Parvovirus B19 (only ssDNA virus) Respiratory, blood, vertically from mother to fetus	**Arthritis or arthralgias more common in adults**	Aplastic crisis in sickle cell, other hemolytic anemia (G6PD deficiency), spherocytosis thalas-semia Possible fetal, death all 3 trimesters, > in 2nd Hydrops fetalis—fetal ascites, pleural and peri-cardial effusions
Papular-purpuric "gloves and socks" syndrome		Purpuric macules and papules acrally. Sharp demarcation along ankle and wrists, resolves in 2 wk	Erythema; palatal erosions; intraoral aphthae	Parvovirus (ssDNA virus)	Flu-like symptoms	Peaks spring/summer in young adults

TABLE 3.10.1 EXANTHEMS, ENANTHEMS, AND OTHER ERUPTIONS CONTINUED

Disease	Classic Designation	Exanthem	Enanthem	Etiology/ Infectivity	Extracutaneous	Complications/Other
Roseola infantum (exanthem subitum)	Sixth disease	After fever declines, erythematous rose-pink macules with halo, papules on trunk minimal, acrally rash resolves 1-2 d without desquamation	Red macules/ streaks on soft palate (Nagayama spots)	HHV-6 (HHV-7) (dsDNA viruses)	High fever for 3 d Rash begins as fever ends (fever, fever rash, rash)	**Palpebral edema (= Berliner's sign)** Most common complication = seizures
Gianotti-Crosti syndrome (papular acrodermatitis of childhood)	1-6 yr old Any season	Flesh-colored to red lichenoid papules or papulovesicles on face, buttocks, extremities (spares trunk)		Unknown; possibly HepB, EBV associated	Mild LAD/HSM low-grade fever	Resolves in few weeks to months Avoid steroid creams as may make rash worse
Unilateral laterothoracic exanthem		Pink macules, papules confluent unilaterally in axilla, arm, trunk, may spread bilaterally	None	Presumed viral	Fever, conjunctivitis, diarrhea, rhinopharyngitis lymphadenopathy	Spontaneous resolution in 4-6 wk Young children (22 mo)
Hand-foot-and-mouth disease		Macules progress to gray, football-shaped vesicles/pustules on a red base on dorsal hands/feet/groin	Vesicles on oral mucosa, oral lacerations	Coxsackievirus A16, A6 (ssRNA picornavirus)	12-24 hours of fever, anorexia, malaise, abdominal pain, myocarditis, pneumonia, encephalitis	Resolves spontaneously, 1 wk A6 more severe blistering, widespread disease and subsequent onychomadesis
Mononucleosis	Young children/ adolescents	Morbilliform rash on trunk, upper extremities; spreads to entire body; periorbital edema		EBV (dsDNA herpesvirus)	Triad: Fever, LAD, sore throat; malaise, headache, HSM	Ampicillin/amoxicillin = florid rash
Toxic shock syndrome	Adolescents/ young adults	Scarlatiniform rash that later desquamates, erythema, edema, palms, soles		*Staphylococcus aureus* TSS toxin-1; also streptococcal	High fever, vomiting, hypotension, diarrhea, multisystem failure, strawberry tongue, conjunctival hyperemia	Sources include: Tampons, wounds
Kawasaki's disease	Mucocutaneous lymph node syndrome Winter/spring, 6 mo-6 yr	Generalized polymorphous exanthem Groin/palmoplantar erythema Early findings: Erythematous desquamating peripheral eruption	Strawberry tongue: Dry, red mucosa	Unknown	4 of 5 criteria: Fever 5 d > 38.3°C AND 1. Palmoplantar erythema, edema, desquamation of tips of digits 2. Conjunctivitis 3. Strawberry tongue/ red fissured lips 4. Cervical adenopathy 5. Rash	**Cardiac aneurysm in 19% untreated** Treatment: ASA 80-90 mg/kg/d + IVIG Cardiovascular complications are most significant causes of long-term morbidity/ mortality Leading cause of acquired heart disease in children Echo at baseline
Henoch-Schonlein purpura		Palpable purpuric papules and macules on lower extremities surfaces and buttocks	None	Unknown; suspect postinfectious hypersensitivity reaction	Joint pain, abdominal pain, nephritis with hematuria Scrotal	Glomerulonephritis IgA vasculitis

ASA = acetylsalicylic acid; dsDNA = double-stranded DNA; EBV = Epstein-Barr virus; G6PD = glucose 6-phosphate dehydrogenase; HepB = hepatitis B virus; HHV = human herpesvirus; HSM = hepatosplenomegaly; IVIG = intravenous immunoglobulin; LAD = lymphadenopathy; PCN = penicillin; PDA = patent ductus arteriosus; ssDNA = single-stranded DNA; VZV = varicella-zoster virus.

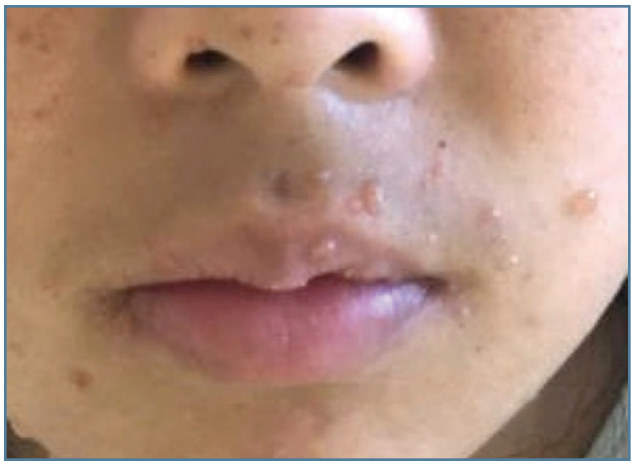

Figure 3.10.1 Varicella.

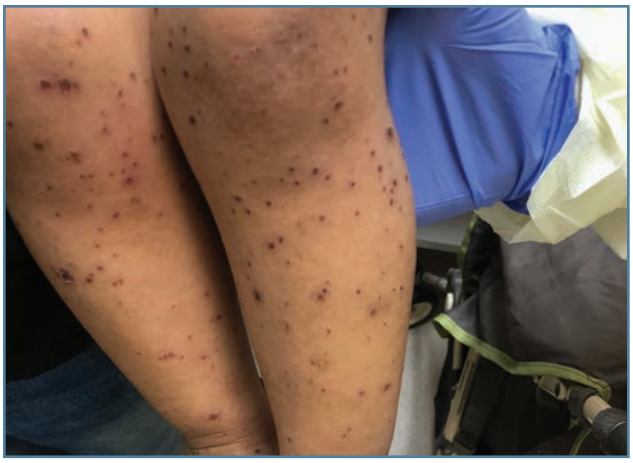

Figure 3.10.3 Hand foot and mouth—legs.

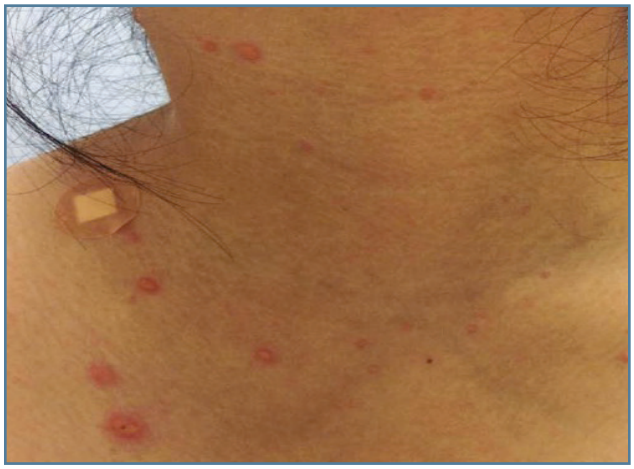

Figure 3.10.2 Varicella.

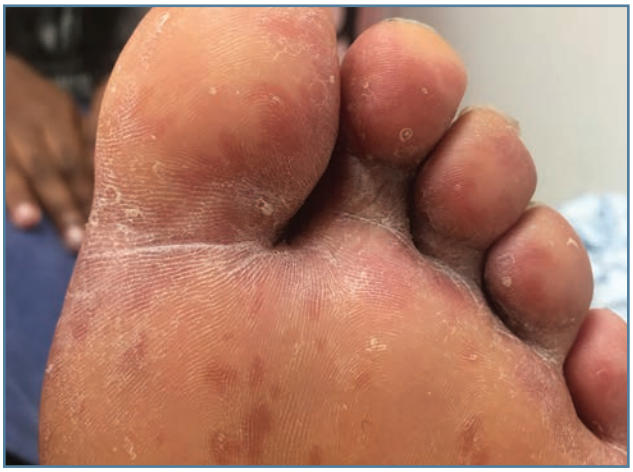

Figure 3.10.4 Hand foot and mouth—foot.

3.11 Photosensitivity and Photoreactions: Nonsyndromic Photosensitivity Disorders

POLYMORPHOUS LIGHT ERUPTION (PMLE)

- When occurs in children, often starts on face as eczematous eruption
- Usually erupts several hours after exposure
- Lesions resolve in 1-2 weeks without continued sun exposure
- Variant: Juvenile spring eruption
- Dull-red edematous papules
- Helices of ears, dorsal hands, trunk
- Boys > girls; age 5-12

ACTINIC PRURIGO

- Spontaneous resolution may occur during late teen years
- Very itchy papules, plaques, and nodules with excoriations and scars
- Affects exposed sites on face and distal extremities, also buttocks
- Scarring possible
- Oral or ocular mucosa affected in 30-50%; cheilitis in many

HYDROA VACCINIFORME

- Chronic, rare, idiopathic scarring photodermatosis. Some cases associated with chronic Epstein-Barr virus (EBV) infection
- Boys > girls; mean age at onset, 8 yr
- Itchy edematous papule, vesicle, or bulla that appears each summer on exposed skin after sun
- Heals with varioliform scarring
- Tends to improve by late teens

PHOTOSENSITIVITY FROM EXOGENOUS AGENTS

- See Phytophotodermatitis in Section 2.6 Plants and Creatures

3.12 Skin Signs of Other Systemic Diseases

CHRONIC GRANULOMATOUS DISEASE

- XR (AR rarer)
- Cytochrome subunit gp91^{phox} defect resulting in impaired neutrophil NADPH oxidase system
- Mild dermatitis. Lymphadenopathy/hepatosplenomegaly (LAD/HSM). Increased infections: Pneumonia, perianal abscesses, rhinitis, stomatitis, diarrhea, osteomyelitis

3.13 X-Linked Recessive Syndromes

- Chondrodysplasia punctata (Conradi-Hünermann syndrome). See Section 3.16
- Hypohidrotic ectodermal dysplasia with immunodeficiency (*NEMO* mutation). See Section 3.28

3.14 X-Linked Dominant Syndromes

MNEMONIC

X-Linked Recessive Syndromes
CHAD'S KINKY WIFE GOT LUCKY

Chronic granulomatous disease
Hunter's disease
Anhidrotic ectodermal dysplasia
Dyskeratosis congenita
SCID
Menkes **K**inky hair disease
Wiskott-Aldrich
Ichthyosis
X-linked **F**abry's disease
Ehlers-Danlos V and IX
G6PD deficiency
Lesch-Nyhan

MNEMONIC

X-Linked Dominant Syndromes
The CHICAGO Bulls Dominated Because They Had the MIDAS Touch

Conradi-**H**ünermann
Incontinentia pigmenti
CHILD
Albright's
Goltz
Oro-facial digital syndrome
Bazex
MIDAS (microphthalmia, dermal aplasia, and sclerocornea)

3.15 Hereditary Blistering Disorders

- Epidermolysis bullosa: Three main types depending on depth of mutated protein/blister
- Clinical pearl: It is difficult/unreliable to discern specific type in infancy based on clinical findings alone (specific features arise later in childhood/adulthood)
- Epidermolysis bullosa simplex (EBS): Autosomal dominant (AD), keratin 5 and 14 mutations resulting in bullae within basal cell keratinocytes. Superficial blistering, least scarring form of epidermolysis bullosa
  - EBS, Dowling-Meara (DM): Widespread bullae **(some herpetiform),** confluent palmoplantar keratoderma (PPK), significant mucous membrane and laryngeal/esophageal involvement, nail dystrophy, and early death
  - EBS, other non-DM/generalized (formerly EBS, Koebner): Generalized bullae starting in infancy with mild mucosal involvement
  - EBS with muscular dystrophy: Plectin mutation
  - EBS with pyloric atresia: Plectin mutation
  - EBS with mottled pigmentation: Keratin 5 mutation
  - Autosomal recessive EBS: Keratin 14 or *BPAG1* mutation
  - EBS Ogna variant: Plectin mutation. Above symptoms with generalized contusiform bruising
- Junctional epidermolysis bullosa (JEB): Autosomal recessive (AR), laminin 5 and BPAG2 (BP180, collagen type XVII) mutations causing blisters in the lamina lucida
  - Herlitz type: Laminin 5 mutations. Severe form with generalized bullae, **nonhealing granulation tissue (esp. perioral, intertriginous)**, nail dystrophy, **tooth dysplasia (enamel defects)**, anemia, growth retardation, tracheobronchial stenosis. Fatal by age 3-4 years
  - Non-Herlitz generalized: Laminin 5, BPAG2/BP180 mutations. Bullae that heal with atrophic scars, nail dystrophy, scarring alopecia. Normal life span
  - Non-Herlitz localized: BP180 mutation. Subtype: Generalized atrophic benign epidermolysis bullosa (GABEB): Extensive skin atrophy of the anterior lower legs
  - JEB w/pyloric atresia: $\alpha_6\beta_4$-Integrin mutations
  - JEB inversa: Laminin 5. Intertriginous involvement
- Dystrophic epidermolysis bullosa: Collagen type VII mutations causing blisters in the sublamina densa
  - Dominant dystrophic EB
    - Hyperplastic Cockayne-Touraine: Bullae localized to extremities resolving with milia and scarring, mild mucosal involvement, dystrophic nails
    - Albopapuloid Pasini variant: Widespread bullae healing with hypopigmented scar-like white papules, nail dystrophy, mild mucosal involvement
    - Localized congenital absence of skin (formerly called Bart's syndrome): Usually of the shins, feet, nail dystrophy. **Now known that can be associated with any EB subtype**
    - Transient bullous dermatosis of newborn: Transient form of the disease
    - Pretibial
    - Pruriginosa
  - Recessive dystrophic EB
    - Severe, generalized (Hallopeau-Siemens): Generalized bullae, healing with chronic scars that **develop numerous fatal squamous cell carcinomas (SCCs)**, digital fusion with **mitten deformity (pseudosyndactyly)**, flexion contractures, significant mucosal scarring including corneal involvement, gastrointestinal (GI) tract strictures, microstomia, dysplastic teeth, renal failure, malnutrition, death
    - Generalized, other (non-Hallopeau-Siemens)
    - Inversa
    - Centripetalis: Blistering starts on acral sites, moves toward trunk over years
- Epidermolytic ichthyosis: AD, keratins 1 and 10 gene. Bullae and erythroderma at birth, generalized verrucous ichthyosis later (no collodion membrane)
- Superficial epidermolytic ichthyosis (ichthyosis bullosa of Siemens): AD, keratin 2e gene. Fragile blisters at birth, hyperkeratotic plaques on the elbows and knees later
- Hailey-Hailey disease: AD, calcium-transporting ATPase 2C1. Flexural erosions in 2nd/3rd decade of life, then develop overlying vegetative plaques; acantholytic "dilapidated brick wall" appearance histologically
- Kindler syndrome: AR, *KIND1* (kindlin-1, expressed in basal keratinocytes, attaches actin cytoskeleton to extracellular matrix). Acral blistering in infancy, **photosensitivity, progressive poikiloderma**, wrinkling (especially dorsal hands/feet), palmoplantar hyperkeratosis, nail dystrophy, dental caries, phimosis, digital webbing, pseudoainhum

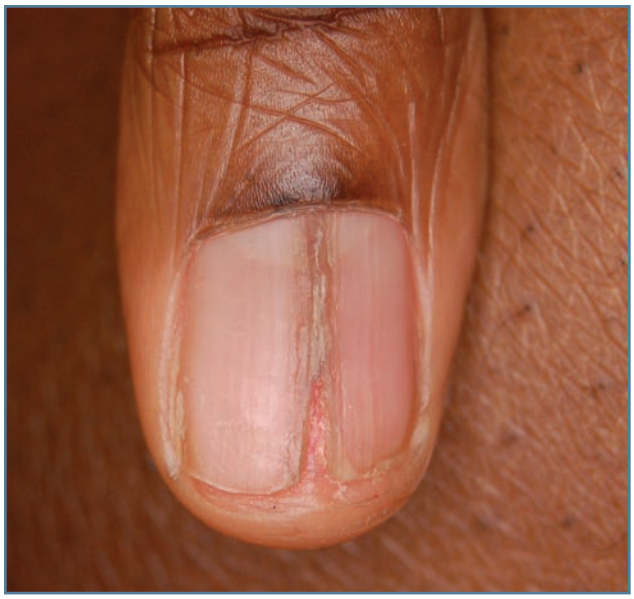

Figure 3.15.1 Median nail dystrophy.

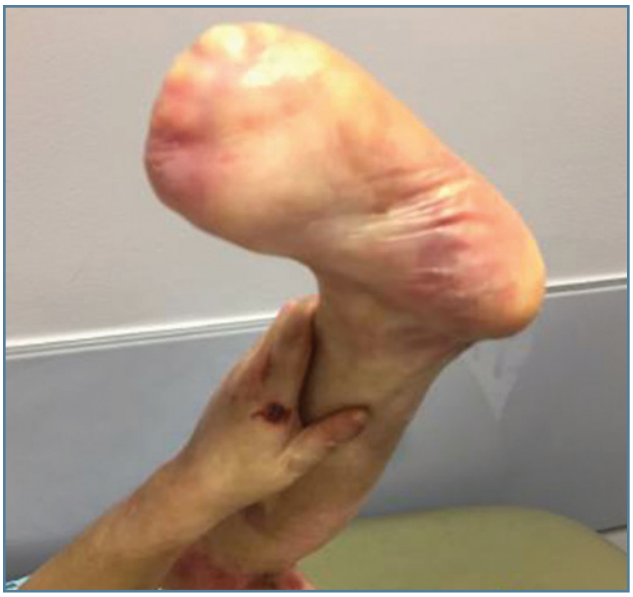

Figure 3.15.2 Recessive dystrophic epidermolysis bullosa mitten deformity.

TABLE 3.15.1 EPIDERMOLYSIS BULLOSA

Location	EB Type/Clinical Features	Inheritance	Defect
Epidermolysis Bullosa Simplex (EBS)			
Epidermal (basal layer)	Dowling-Meara, generalized; at birth; herpetiform blisters; nail dystrophy; PPK; milia EM: Clumped, loss of filaments	AD	Keratin 5/14
Intraepidermal	Weber-Cockayne: Palms, soles; childhood or adult onset	AD	Keratin 5/14
	Koebner: Generalized; at birth	AD	Keratin 5/14
	Muscular dystrophy (EBS lethalis): Generalized; adult-onset MD; scarring; urethral seizures; laryngeal webs; many die early	AR	Plectin
	Lethal acantholytic EB: Birth; denuded skin; absent hair/nails; +natal teeth; car-diomyopathy		Desmoplakin Plakoglobin (but no cardiac problems)
Junctional Epidermolysis Bullosa (JEB)			
Basement membrane	**Pyloric atresia**; severity variable; hemidesmosomal; malformed ears; GU abnormal	AR	$\alpha_6\beta_4$-Integrin
Lamina lucida	Herlitz: Atrophic scarring; generalized prominent beet-red granulation tissue. Severe: Generally lethal at <2 yr old	AR	Laminin 332
	Non-Herlitz: Severity variable; alopecia; dental problems common GABEB: Collagen 17 (BP180) mild subtype; atrophic patches; lower legs; nail dystrophy; alopecia; hypoplastic tooth enamel	AR	Type XVII collagen/(BPAg2) Laminin 332

TABLE 3.15.1 EPIDERMOLYSIS BULLOSA CONTINUED

Location	EB Type/Clinical Features	Inheritance	Defect
Dystrophic Epidermolysis Bullosa (DEB)			
Dominant	DDEB (Cockayne-Touraine): Less severe blistering but may be generalized or severe at birth; improves with age; nail dystrophy	AD	Type VII collagen
Recessive	RDEB (non-Hallopeau-Siemens): Severity variable	AR	Type VII collagen
	RDEB (Hallopeau-Siemens): Severe blistering; at birth; esophageal stricture; mitten deformity; failure to thrive; dental problems; increased risk for SCC (Marjolin's ulcer)	AR	Type VII collagen EM: Anchoring fibrils are absent

AD = autosomal dominant; AR = autosomal recessive; DDEB = dominant dystrophic epidermolysis bullosa; EBS = epidermolysis bullosa simplex; EM = electron microscopy; GABEB = generalized atrophic benign epidermolysis bullosa; GU = genitourinary; MD = muscular dystrophy; PPK = palmoplantar keratoderma; RDEB = Recessive dystrophic epidermolysis bullosa; SCC = squamous cell carcinoma.

3.16 Ichthyoses and Keratinopathies

ICHTHYOSIS VULGARIS (IV)

- AD
- Homozygous and heterozygous mutation in filaggrin gene
- Fine scales on extensor surfaces, hyperlinear palms/soles. Flexures spared
- Not present at birth, onset after 3 months, face usually spared
- Assoc: Atopy and keratosis pilaris
- Histology: Retention hyperkeratosis with decreased/absent granular layer. EM: Abnormal keratohyalin granules

X-LINKED ICHTHYOSIS

- X-linked recessive (XLR)
- Defect in steroid sulfatase gene (arylsulfatase C), fetal dehydroepiandrosterone sulfate (DHEAS)
- Contiguous gene deletion syndrome may result in Kallmann syndrome and XLR chondrodysplasia punctata
- Brown scales, "dried mud," scales
- Not present at birth, appears within few weeks of life
- Nonlyonized
- Neck involvement prominent; face/other flexures/palms/soles spared
- Assoc: Asymptomatic corneal opacities (50%), cryptorchidism (20%) with increased testicular cancer, prolonged labor in mothers of affected sons
- Histology: Compact hyperkeratosis with normal granular layer

TIP

4 Cs of X-Linked Ichthyosis

1. **C**omma-shaped corneal opacities
2. **C**ryptorchidism
3. **C**-section
4. **C**holesterol sulfate increased

COLLODION BABY

- Shiny, taut membrane at birth
- Ectropion, eclabium associated
- Risk temperature instability, sepsis, dehydration, and electrolyte imbalance
- Phenotype → not a specific genetic diagnosis; must work up for underlying diagnosis

TABLE 3.16.1 DISORDERS ASSOCIATED WITH COLLODION MEMBRANE

• Autosomal recessive congenital ichthyosis (65%)	• Trichothiodystrophy
• Self-healing collodion baby	• X-linked ichthyosis
• Conradi syndrome	• Loricrin ichthyosis

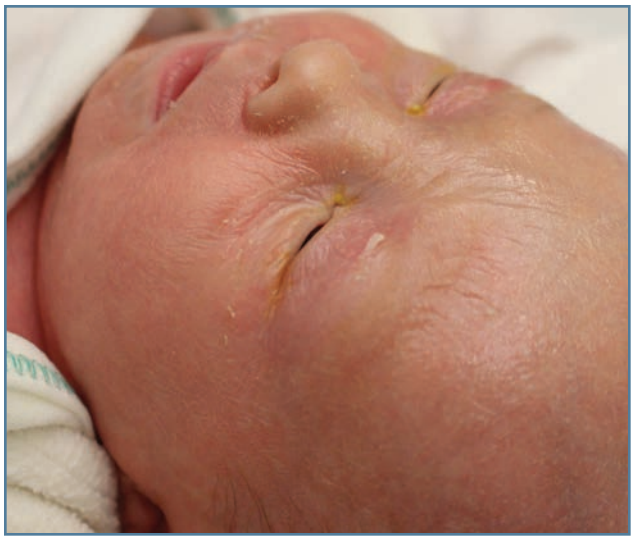

Figure 3.16.1 Collodion neonate.

AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSIS (ARCI)

- Lamellar ichthyosis (LI)
  - AR
  - Transglutaminase 1 defect (type 1), *ABCA12* gene defect (type 2) (copper-binding protein)
  - **Coarse dark thick plates of scale in flexures,** thick palms/soles, prominent flexural involvement
  - Collodion baby, ectropion, eclabium, alopecia

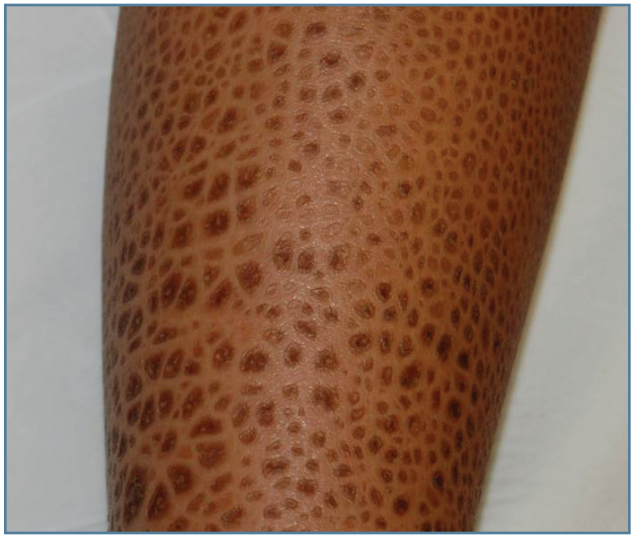

Figure 3.16.2 Lamellar ichthyosis.

CONGENITAL ICHTHYOSIFORM ERYTHRODERMA (NONBULLOUS CONGENITAL ICHTHYOSIFORM ERYTHRODERMA)

- AR
- Defects in transglutaminase-1 gene, 12R-lipoxygenase gene *(ALOX12B),* and the lipoxygenase-3 gene *(ALOXE3)*
- **Fine white powdery scaling** overlying generalized erythema with flexures involved, hyperkeratotic palms and soles, hair and nails may be affected. Loss of eyebrows/eyelashes. Mental and growth retardation. Decreased life expectancy
- Collodion baby (90% present as collodion baby)

HARLEQUIN ICHTHYOSIS

- AR
- *ABCA12* gene defect (copper-binding protein), absent lamellar granules
- **Markedly thick, restrictive diamond-shaped plate-like scales**, severe ectropion with bulging eyes, eclabium
- Death within 1 week usually secondary to respiratory difficulty and sepsis
- Treatment: Isotretinoin may prolong survival

TIP

The most common causes of colloidon baby are lamellar ichthyosis and non-bullous congenital ichthyosiform erythroderma

NONSYNDROMIC ICHTHYOSIS

- Loricrin keratoderma
  - AD, loricrin gene mutation
  - Occasional collodion membrane, generalized non-erythrodermic ichthyosis
  - Honeycomb PPK
  - Pseudoainhum (no starfish keratosis)

- Erythrokeratoderma variabilis (Mendes da Costa syndrome) (EKV)
  - AD
  - *GJB3*, which encodes the gap junction protein, connexins 31 and 30.3
  - *GJB4* gene mutation for EKV with erythema gyratum repens
  - Hyperkeratotic plaques on face and extremities, transient erythematous migratory patches, hypertrichosis
- Progressive symmetric erythrokeratodermia
  - AD
  - Loricrin gene mutation
  - Symmetric progressive erythrokeratodermia in the first year, some overlap with Vohwinkel syndrome, and EKV

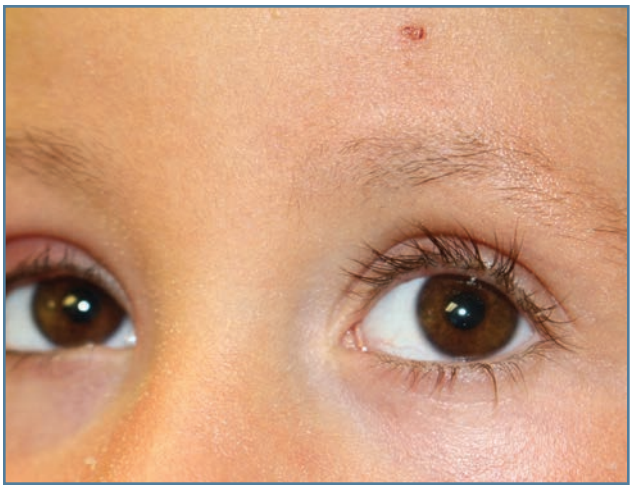

Figure 3.16.3 Netherton syndrome (sparse eyebrows).

SYNDROMIC ICHTHYOSES

- Neutral lipid storage disease with ichthyosis (Chanarin-Dorfman syndrome)
  - AR
  - *CGI58* gene defect
  - Cannot break down triglycerides and these fats accumulate in skin, liver, muscles, intestine, eyes, and ears
  - Fine scaling on erythroderma. May present as collodion baby
  - Ectropion, cataracts, myopathy, and central neuropathy. Fatty liver/hepatosplenomegaly
  - No fasting ketonemia
  - **Histology: Lipid-laden vacuoles in keratinocytes and granulocytes— "Jordan's anomaly"**
  - Neutral lipid storage disease without myopathy due to *PNPLA2* gene defect
- Keratitis, ichthyosis, and deafness syndrome (KID syndrome)
  - AD
  - Heterozygous defects in connexin-26 gene: *GJB2* gene
  - Progressive vascularized keratitis leading to blindness, congenital sensorineural hearing loss, hyperkeratotic skin lesions and increased SCC/skin infections, PPK
- Netherton syndrome
  - AR
  - *SPINK5* gene defect encoding serine protease inhibitor, LEKTI

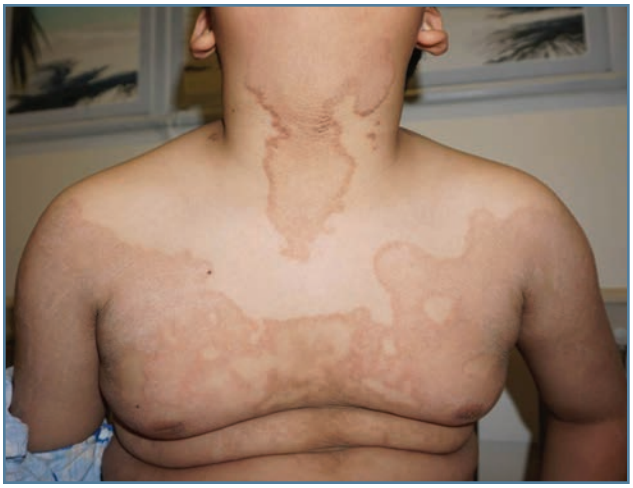

Figure 3.16.4 EKV.

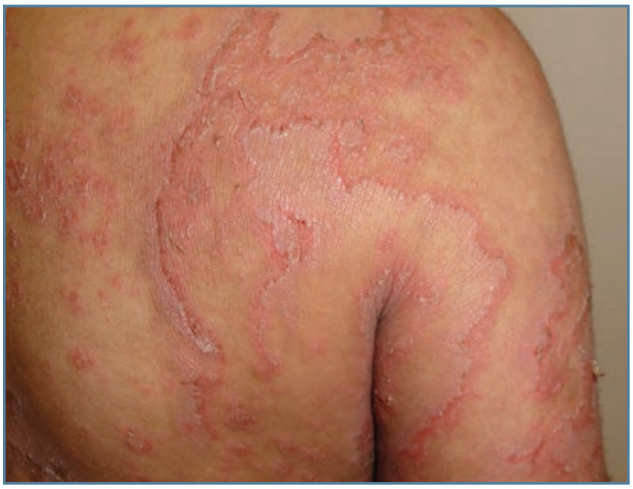

Figure 3.16.5 Nethertons syndrome (ichthyosis linearis circumflexa).

TIP

Four S's of Netherton

1. **S**punky hair
2. **S**alty (hypernatremia dehydration)
3. ***S****PINK5*
4. No **S**irolimus

- Triad
  - Ichthyosis linearis circumflexa (congenital ichthyosiform erythroderma [CIE] or psoriasiform erythroderma may also be seen)
    - Describes classic serpiginous/arcuate double-edged scale
    - Classic scale may not be apparent until later in childhood
  - **Trichorrhexis invaginata (bamboo hair)—eyebrow hair most common site**
    - Describes classic "ball in socket" appearance of hair and leads to fragility and sparse hair
    - Trichorrhexis nodosa is also common but nonspecific (found in multiple inherited/acquired conditions)
  - **Atopy (AD, anaphylactic reaction to foods), pruritus**
- Decreased granular and spinous layers (increased drug absorption, i.e., tacrolimus—avoid use of topical calcineurin inhibitors as systemic absorption has been reported in literature)
- Failure to thrive, **hypernatremic dehydration**, recurrent infections, growth retardation

- Refsum syndrome (phytanic acid storage disease)
  - AR
  - Defect in gene encoding phytanoyl-CoA hydroxylase
  - Infantile form: *PEX1* or *PEX2* gene defect
  - Unable to metabolize phytanic acid
  - Fine scaling, thickened palms and soles, yellow nevi
  - **Retinitis pigmentosa ("salt and pepper" retinitis)**, night blindness, **cerebellar ataxia**, peripheral polyneuritis, deafness, anosmia, cardiomyopathy, epiphyseal dysplasia, bilateral fourth metatarsal shortening
  - Treatment: Diet low in green vegetables, dairy, and ruminant fats
- Sjögren-Larsson syndrome
  - AR
  - Mutation in gene encoding fatty aldehyde dehydrogenase
  - Pruritic velvety ichthyosis as infant, hair/nails normal
  - Mental retardation by age 2-3 years old, seizures, **spastic di/tetraplegia, retinal "glistening white dots,"** photophobia
- Chondrodysplasia punctata (CPXR or Conradi-Hünermann-Happle syndrome)
  - XLR
  - Arylsulfatase E deficiency
  - Ichthyosis, hypogonadism, and anosmia in contiguous gene syndrome (with X-linked ichthyosis and Kallmann syndrome)
  - Facial hypoplasia, hypoplasia of distal phalanges, growth and mental retardation
  - Chondrodysplasia punctata (stippled epiphyses on X-rays)
- X-linked dominant (XLD) chondrodysplasia punctata (Conradi-Hünermann syndrome)
  - XLD
  - *EBP* gene defect (Δ^8-Δ^7 sterol isomerase, emopamil-binding protein)
  - **Whorled/linear, egg shell—like ichthyosis and erythroderma along Blaschko's lines,** follicular atrophoderma, "orange peel" skin, and scarring alopecia
  - Failure to thrive. Flat facies. Tracheal stenosis/calcification. Stippled and punctate calcification of sternum/ribs/scapula. Eye/kidney/CNS abnormalities
  - Acquired cases described as **"stippled epiphyses"** on X-ray with maternal vitamin K deficiency and warfarin teratogenicity
- Rhizomelic chondrodysplasia punctata
  - AR
  - Peroxisomal disorders
    - Type 1: *PEX7* gene defect
    - Type 2: *DHAPAT* gene defect (encodes acyl-CoA:dihydroxyacetonephosphate acyltransferase)
    - Type 3: *AGPS* gene defect (encodes alkyl-DHAP synthase)
  - Diffuse fine scaling, erythema, and alopecia
  - Dwarfism. Punctate chondral calcifications and epiphyseal dysplasia in infancy, cleft vertebrae. Respiratory compromise. Abnormal CNS, death in infancy

- AD chondrodysplasia punctata
  - Diffuse ichthyosis and erythema
  - "Koala bear" facies. Milder skeletal defects, asymmetric epiphyseal stippling
- CHILD syndrome (congenital hemidysplasia with ichthyosiform erythroderma and limb defects)
  - XLD
  - *NSDHL* gene defect encodes 3β-hydroxysteroid dehydrogenase
  - **Unilateral (usually right-sided) yellowish/waxy ichthyosiform erythroderma ("CHILD nevus") that can be diffuse or segmental/blaschkolinear**
    - Often involves skin folds
    - May be complicated by persistent oozing, pain, pruritus
    - Spontaneous remission/recurrence has been described
    - Exophytic verruciform xanthoma—like masses may develop over CHILD nevus
    - Pink papillomatous "strawberry-like" nodules overlying distal dorsal fingers or toes are pathognomonic but may not be present
    - Classic pathology finding: Foamy cells in papillary dermis (verruciform xanthoma—like changes) in addition to psoriasiform changes in epidermis
  - **Associated with** ipsilateral limb defects/visceral hypoplasia (e.g., CNS, lung, heart, kidney defects) and stippled epiphyses on X-rays (resolves later in childhood)

KERATINOPATHIES

- Keratin is expressed in pairs. Keratin type I (keratins 9-20) is acidic, has a lower molecular weight, and is coded on chromosome 17q. Keratin type II (keratins 1-8) is basic, has a higher molecular weight, and is coded on chromosome 12q

TABLE 3.16.2 KERATIN MUTATIONS AND DISEASE ASSOCIATIONS

Type II	Type I	Location of Expression	Associated Disease
1	10	Suprabasal keratinocytes	Epidermolytic ichthyosis, nonepidermolytic Unna-Thost PPK
1	9	Palmoplantar suprabasilar epidermis	Epidermolytic Vorner PPK
2e	10	Granular layer	Ichthyosis bullosa of Siemens
3	12	Cornea	Corneal dystrophy
4	13	Mucosal epithelium	White sponge nevus
5	14	Basal cells	Epidermolysis bullosa simplex
6a	16	Outer root sheath, hyperproliferative keratinocytes	Pachyonychia congenita type I (Jadassohn-Lewandowsky), focal PPK
6b	17	Nail bed	Pachyonychia congenita type II (Jackson-Lawler)
8	18	Simple epithelium	Cryptogenic cirrhosis

PPK = palmoplantar keratoderma.

3.17 Palmoplantar Keratodermas

TABLE 3.17.1 HEREDITARY PALMOPLANTAR KERATODERMAS

Disease	Inheritance	Defect	Clinical Characteristics
Epidermolytic PPK (Vorner)	AD	Keratin 9	Sharply demarcated PPK. May be associated with knuckle pads
Nonepidermolytic PPK (Unna-Thost)	AD	Keratin 1 or 10	PPK with focal oral, genital, follicular keratoses. Mosaic keratin-16 mutation = unilateral palmoplantar verrucous nevus
PPK with deafness	AD	Defect in gene encoding connexin 26 (type 1) Mitochondrial tRNA serine point mutation in *MTTS1* gene (type 2)	PPK, progressive high-frequency sensorineural deafness
Nonepidermolytic palmoplantar keratoderma	AD	Keratin 16 or 1	Nonepidermolytic PPK with focal oral, genital, and follicular lesions
Vohwinkel syndrome—classic (keratoderma hereditaria mutilans)	AD	*GJB2* gene encoding connexin 26	PPK with honeycomb appearance; "little star-shaped" keratoses over dorsal joints of hands and feet and later constricting bands that may cause autoamputation (pseudoainhum); linear keratotic plaques on knees, progressive, bilateral sensorineural deafness
Striated palmoplantar keratoderma	AD	Defect in gene encoding desmoglein 1 (type 1) and desmoplakin 1 (type 2), keratin 1	Linear hyperkeratotic plaques, palm to finger. Onset in teens or later. M > F
Tylosis with esophageal cancer (Howel-Evans syndrome)	AD	*RHBDF2* gene	Nonepidermolytic PPK with esophageal carcinoma, oral leukoplakia
Knuckle pads	AD	Unknown	Assoc. with epidermolytic palmoplantar keratoderma (keratin 9)/Dupuytren contractures
Bart-Pumphrey syndrome	AD	*GJB2* gene	Knuckle pads, leukonychia, sensorineural hearing loss
Acrokeratoelastoidosis	AD	Unknown	Yellow, hyperkeratotic nodules on lateral palms/soles. Histology: Disorganized elastic fibers and hyperkeratosis
Keratosis punctata palmaris et plantaris	AD	*AAGAB* gene	Hyperkeratotic palms/soles with pits along creases
Mal de Meleda	AR	*SLURP1* gene mutation	Erythematous PPK over with transgradient dorsally, elbows and knees, perioral erythema, hyperhidrosis, lichenoid plaques, brachydactyly
Papillon-Lefèvre syndrome	AR	Cathepsin C gene mutation	Erythematous PPK of dorsal soles > palms, periodontitis with early loss of teeth, calcification of dura and choroid plexus, pyogenic infections
Haim-Munk syndrome	AR	Cathepsin C gene mutation	Papillon-Lefèvre with onychogryphosis, pes planus, arachnodactyly

TABLE 3.17.1 HEREDITARY PALMOPLANTAR KERATODERMAS CONTINUED

Disease	Inheritance	Defect	Clinical Characteristics
Naxos disease	AR	Defect in gene encoding plakoglobin	PPK with woolly hair, right ventricular cardiomyopathy, and arrhythmias
Dilated cardiomyopathy with woolly hair and keratoderma (Carvajal syndrome)	AR	Defect in gene encoding desmoplakin	PPK in first year of life, with cardiac/EKG abnormalities, woolly hair, dilated cardiomyopathy (left)
Olmsted syndrome	AD	*TRPV3*	Sharply defined PPK with periorificial keratotic lesions ± pseudoainhum, alopecia, and tooth, nail, and joint abnormalities

AD = autosomal dominant; AR = autosomal recessive; PPK = palmoplantar keratoderma.

TIP

Think of Rip Van Winkle folklore:
Twinkle, twinkle, little star (Vohwinkel)

TIP

HOWL when walk on weight bearing PPK, hurts to swallow (Howel-Evans)

TIP

While partying in Croatia and eating a Slurpee with my spoon hands, I fall on my hands and feet (Mal de Meleda)

TIP

Butterflies don't have teeth, so they lisp cathepsin (Papillon-Lefèvre)

TIP

CarvajaL (L for left)

DIFFUSE PALMOPLANTAR KERATODERMAS (PPKS)

- Unna-Thost palmoplantar keratoderma (PPK) (nonepidermolytic): AD, keratin 1
- Vorner PPK (epidermolytic): AD, keratins 1 and 9
  - Both are diffuse symmetric, nontransgradient PPK, look identical clinically
- Mal de Meleda: AR, *SLURP1*. **Malodorous** transgradient PPK in glove-and-stocking distribution, hyperhidrosis, onset early infancy
- PPK with deafness: AD, type 1: Connexin 26; type 2: *MTTS1*. Mitochondrial serine tRNA mutation
- Vohwinkel syndrome: AD, connexin 26 (*GJB2* gene). Diffuse **honeycombed** PPK, **pseudoainhum, starfish-shaped** keratotic plaques over joints, deafness
- Vohwinkel variant: AD, loricrin. Similar to classic Vohwinkel, plus ichthyosis but no deafness
- Naxos syndrome: AR, plakoglobin. PPK + wooly hair + **arrhythmogenic right-sided** cardiomyopathy
- Bart-Pumphrey syndrome: AD, connexin 26; PPK with **knuckle pads**, leukonychia, deafness, PPK may have honeycomb appearance
- Schöpf-Schulz-Passarge syndrome: AR, *WNT* mutation, PPK + hidrocystoma, basal cell carcinoma (BCC), SCC, hypodontia + eccrine tumors (eccrine syringofibradenoma)
- Olmsted syndrome: AD or XLR; mutilating PPK with periorificial plaques, AD (*TRPV3*), XLR (*MBTPS2*)
- Papillon-Lefèvre syndrome: AR, cathepsin C. Sharply demarcated, transgradient, stocking-glove PPK, periodontitis with tooth loss, asymptomatic dural calcification and choroid attachments
- Haim-Munk syndrome: AR, cathepsin C. PPK + **periodontitis** + acroosteolysis + onychogryphosis
- Erythrokeratodermia variabilis: AD, connexin 31 (type I) and connexin 30.3 mutations (type 2) (gap junction components encoded by the *GJB3, GJB4* genes). Erythematous **migratory** patches, fixed hyperkeratotic plaques, palmoplantar keratoderma

- Symmetric progressive erythrokeratodermia: AR, *KDSR* or *KRT83*. Hyperkeratotic plaques and palmoplantar keratoderma
- Sclerotylosis (Huriez syndrome): AD. Sclerosis of skin, nail hypoplasia, PPK. 15% develop cutaneous SCC and increased risk of bowel cancer

FOCAL PPKS

- Striated PPK (Brunauer-Fohs-Siemens): AD, desmoglein 1 (type I), desmoplakin 1 (type II), *KRT1* (type III)
- Howel-Evans syndrome: AD, tylosis with esophageal cancer (TOC) locus. Focal, pressure-related, nontransgradient PPK; **esophageal cancer**; oral leukoplakia
- Richner-Hanhart syndrome (tyrosinemia type II): AR, deficient hepatic tyrosine aminotransferases. **Painful PPK, pseudoherpetic keratitis**, blindness and mental retardation. Treatment: Low-tyrosine/phenylalanine diet
- Carvajal syndrome: PPK with **dilated left-ventricular** cardiomyopathy and woolly hair: AR, desmoplakin
- Pachyonychia congenita type I (Jadassohn-Lewandowsky)
- Epidermal nevus syndrome: Nevus unius lateris; sporadic inheritance, capillary malformations, café au lait macules, mental retardation and seizures, deafness, hemiparesis, hemihypertrophy of limbs, kyphoscoliosis; rare solid tumors. Biopsy to rule out epidermolytic hyperkeratosis (EHK): if positive for EHK then offspring at risk for generalized EHK

3.18 Disorders with Hypopigmentation

TABLE 3.18.1 ALBINISM

Disorder	Inheritance	Defect	Clinical Findings
Type 1A oculocutaneous albinism (OCA), tyrosinase negative	AR	Tyrosinase, the enzyme that catalyzes the conversion of tyrosine to dopaquinone ~1% of patients with Angelman's syndrome + Prader-Willi syndrome will have OCA2 Both of these syndromes result from deletions in 15q *OCA2* gene	Melanocytes present, no pigment from birth, no pigment over time, decreased visual acuity, nystagmus, photophobia
Type 1B OCA	AR	Tyrosinase, allelic to OCA type 1A	Melanocytes present, no pigment from birth, some improvement over time. Milder eye findings "yellow OCA"
Type 2 OCA, tyrosinase positive	AR	*OCA2* gene mutation Angelman's syndrome + Prader-Willi syndrome will have OCA2 Both of these syndromes result from deletions in 15q *OCA2* gene	Most common form. Minimal pigment at birth, but skin darkens over time. White/yellow/red hair with moderate nystagmus, visual impairment. "Brown OCA" variant in patients of African descent w/brown pigment/fewer sunburns
Type 3 OCA	AR	Tyrosinase-related protein, TRP-1	Minimal to tan pigment from birth. White/red/light brown hair. Nystagmus with light retinal pigment. "Rufous OCA" variant w/red-toned skin and hair
Type 4 OCA	AR	*SLC45A2*	More common in patients of Asian descent, esp. Japanese
Hermansky-Pudlak syndrome	AR (more common in Puerto Ricans)	*HPS1* gene most common; *AP3B1* gene	Lighter than expected skin tone with blue/brown irides Dysfunctional platelets with associated bleeding diathesis, platelets without dense bodies, ceroid lipofuscinosis in phagocytic cells, pulmonary fibrosis, granulomatous colitis, cardiomyopathy, and renal failure; Avoid aspirin and NSAIDs; Platelet transfusions before procedures

AR = autosomal recessive; NSAIDs = nonsteroidal antiinflammatory drugs.

SILVERY HAIR SYNDROMES

- Chédiak-Higashi syndrome
  - AR
  - Defect in *LYST* gene
  - Pigmentary dilution, silvery hair
  - Bleeding diathesis with normal platelet count but prolonged bleeding time, neurologic deterioration, recurrent skin and respiratory tract infections, cardiac/pulmonary/kidney abnormalities
  - "Accelerated phase" with bone marrow suppression
  - **Giant lysosome inclusion granules** in all leukocytes and other cell types
  - Hairs with **regularly spaced** clumps of melanin

TIP

Giant lysosome granules

- Elejalde syndrome (neuroectodermal melanolysosomal disease)
  - Variant of Griscelli syndrome type 1 (GS1); prominent features of GS plus **severe neurologic dysfunction** but not associated with immunodeficiency
- Griscelli syndrome
  - AR
  - Type 1: Defect in gene encoding myosin VA. Type 2: *RAB27A* gene defect
  - Hypopigmentation with silver-gray hair containing **aggregated pigment granules**
    - Type 1: Hypomelanosis with a primary neurologic deficit and no immune abnormalities
    - Type 2: Hypomelanosis with **hemophagocytic syndrome characterized by episodes of massive lymphocyte and leukocyte activation** and organ infiltration, frequent infections occur
    - Type 3: Skin limited

TIP

Large melanosome inclusions but no neutrophilic inclusions

TIP

To help answer board questions regarding errors in pathway of pigmentation, group similar defects together:

1. Disruption of melanoblast migration to target tissues during development: Waardenburg and piebaldism
2. Disruption of melanin synthesis: Oculocutaneous albinism (OCA) and ocular albinism (OA)
3. Disruption of melanosome formation: Chédiak-Higashi and Hermansky-Pudlak
4. Disruption of melanosome transport and transfer to keratinocytes: Griscelli

WAARDENBURG AND PIEBALDISM

TABLE 3.18.2 WAARDENBURG AND PIEBALDISM

Disorder	Gene Defect; Inheritance	Clinical Features
Waardenburg type 1	*Pax3* gene; AD	Depigmented patches. White fore-lock. Dystopia canthorum. Broad nasal root. **Heterochromia iridis. Deafness uncommon**
Waardenburg type 2	*MITF* gene; AD	Depigmented patches. White forelock. **Deafness common.** Dystopia canthorum absent
Klein-Waardenburg type 3	*Pax3* gene; AD	Waardenburg type 1 plus: **Limb defects** including hypoplasia, flexion contractures, and syndactyly
Shah-Waardenburg type 4	Endothelin-3 receptor gene (endothelin-3 ligand or Sox10); AD	Waardenburg type 1 plus: **Hirschsprung disease**
Piebaldism	c-*kit* proto-oncogene; AD	Ventromedial depigmented patches with hyperpigmented borders. **White forelock.** Hetero-chroma iridis

AD = autosomal dominant.

- Tuberous sclerosis (Bourneville's syndrome, epiloia)
  - AD
  - *TSC1* (hamartin) and *TSC2* (tuberin) gene mutations
  - Ash leaf macules (often present at birth), angiofibromas (formally adenoma sebaceum) (>4 years old), connective tissue nevi including shagreen patches (collagenoma) and fibrous forehead plaque, periungual fibromas (Koenen's tumors—puberty), café-au-lait macules and confetti-like white macules can occur. Gingival fibromas and dental enamel pits common
  - Seizures early in life, retinal astrocytoma, congenital cardiac rhabdomyomas (regress in childhood), bilateral renal angiomyolipomas, mental retardation, pulmonary lymphangioleiomyomatosis

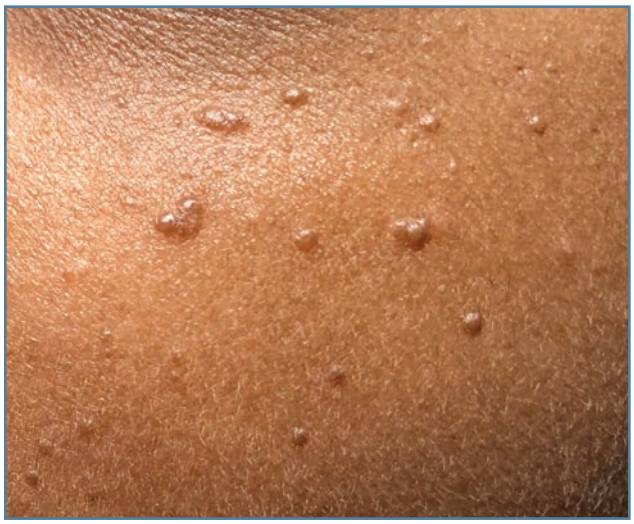

Figure 3.18.1 Tuberous sclerosis.

TIP

Ash leaf macules are the earliest finding in tuberous sclerosis

TIP

NEMO defect: Peg-shaped teeth
Subungual tumors are of late onset

MNEMONIC

FASTT KARRRMA

Forehead plaque
Angiofibromas
Shagreen patches
Tubers, cortical **T**onic-clonic seizures

Koenan tumor
Ash leaf macules
Renal angiomyolipomas
Retinal hamartomas
Rhabdomyomas
Mental retardation (MR)

- Incontinentia pigmenti (Bloch-Sulzberger syndrome)
  - XLD (affected males mosaic or XXY)
  - *NEMO* gene defect (NF-KB)
    - Highly variable clinical presentations. Hyperpigmented grayish-tan macular pigmentation following the lines of Blaschko. Keratitis and retinal vascular anomalies and seizures/MR. Absent or abnormal dentition. Nail dystrophy and subungual keratotic tumors. Alopecia of the scalp vertex and breast hypoplasia
    - 4 classic stages (overlap):
      - Vesicular (birth-2 weeks)
      - Verrucous (2-6 weeks)
      - Hyperpigmented (3-6 months)
      - Hypopigmented (20-30 years)
  - Allelic disorder: Hypohidrotic ectodermal dysplasia with immunodeficiency: X-linked recessive, *NEMO* gene, normal pigmentation
- Hypomelanosis of Ito (incontinentia pigmenti achromians)
  - Somatic mosaicism or chimerism
  - Whorled, linear, and patchy bands of hypopigmentation following the lines of Blaschko
  - May have associated neurologic, eye, and skeletal abnormalities

3.19 Disorders with Pigmented Lesions

FRECKLES (EPHELIDES)

- Light brown, even-bordered macules > in sun-exposed areas
- More prominent in summer/childhood

LENTIGINES

- Well-defined tan-brown macules (bigger than freckles) with increased numbers of epidermal melanocytes

TABLE 3.19.1 SYNDROMES WITH LENTIGINES

Syndrome	Inheritance (Gene Defect)	Clinical Features
Bannayan-Zonana syn-drome/ Bannayan-Riley-Ruvalcaba (and other disorders within spectrum of PTEN hamartoma tumor syndrome, which includes Cowden syndrome)	AD (*PTEN*)	Penile lentigines, macrocephaly, lipomas, and hemangiomas See Section 3.22 for further details on PTEN hamartoma syndrome/Cowden syndrome
Cronkhite-Canada syndrome	Sporadic	Lesions on hands, feet, buccal mucosa, nail dystrophy, hair loss, intestinal polyposis
Centrofacial neurodysraphic lentiginosis (Touraine syndrome)	AD	Mental retardation, mitral valve stenosis, seizures, sacral hypertrichosis, unibrow, high palate, absence of middle incisors, neural tube defect, psychiatric disorder, dwarfism, endocrine abnormalities
Peutz-Jeghers syndrome	AD (*STK11/LKB1* gene defect)	Mucosal lentigines, intestinal polyps. GI adenocarcinoma, breast, pancreatic, endometrial cancer also See Section 3.22
Laugier-Hunziker syndrome	AD (*STK11/LKB1* gene defect)	Mucosal lentigines and longitudinal melanonychia without polyps. Adult onset
Noonan syndrome with multiple lentigines (formerly LEOPARD syndrome)	AD (*PTPN11* gene defect)	Lentigines, EKG abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retarded growth, deafness. Allelic with Noonan syndrome
Carney complex (NAME/LAMB syndrome)	AD (*PRKAR1A* gene)	Lentigines, myxomas, blue nevi, psammomatous melanotic schwannomas, multiple endocrine abnormalities (pigmented nodular adrenocortical disease, testicular tumors)

AD = autosomal dominant; GI = gastrointestinal; PTEN = phosphatase and tensin homolog.

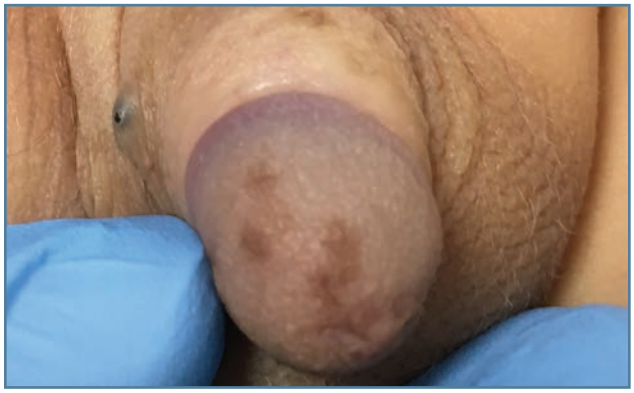

Figure 3.19.1 Penile lentigines in PTEN hamartoma tumor syndrome (Bannayan-Riley-Ruvalcaba).

PEUTZ-JEGHERS SYNDROME

- AD
- *STK11* gene mutation
- Tan-brown melanocytic macules on lips, (Tip: LipSTK) buccal mucosa, and hands/feet (esp. palms/soles). Appear in infancy, usually fade with time
- Numerous polyps throughout GI tract, > jejunum. Genitourinary (GU), bronchial, nasal polyps as well. **Risk of intussusception**
- Increased risk of malignancy: Adenocarcinoma of stomach, colon, pancreas, lung, and urethra. Ductal carcinoma of the breast. Sertoli cell tumors with precocious puberty. Thyroid cancer. Uterine cancer and ovarian sex cord tumors

NOONAN SYNDROME WITH MULTIPLE LENTIGINES (FORMERLY LEOPARD SYNDROME)

- AD
- Some caused by *PTPN11* gene mutation
- LEOPARD: Lentigines, EKG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retarded growth, and deafness
- May be associated with pectus excavatum/carinatum, hypertrophic cardiomyopathy, café noir spots on trunk

MNEMONIC

LEOPARD syndrome

Lentigines
EKG abnormalities
Ocular hypertelorism
Pulmonary stenosis
Abnormal genitals
Retarded growth
Deafness

CARNEY COMPLEX (NAME AND LAMB SYNDROMES)

- AD
- Type 1: *PRKAR1A* gene mutation. Type 2 on chromosome 2
- Many lentigines characteristically centrofacial/mucosal and conjunctival. Red hair and blue nevi. **Psammomatous melanotic schwannomas**. Atrial myxomas
- Multiple tumors: Pituitary adenoma = acromegaly, Sertoli cell/Leydig cell tumors, pheochromocytoma. Pigmented primary adrenocortical nodular hyperplasia (= Cushing)

MNEMONIC

PARK Your Car

PRKARIA gene in Carney

MNEMONIC

LAMB syndrome

Lentigines
Atrial myxomas
Mucocutaneous myxomas
Blue nevi

NAME syndrome

Nevi
Atrial myxomas
Myxoid tumors
Ephelides

CAFÉ AU LAIT MACULES

- Uniformly pigmented tan to brown macules
- At birth or acquired
- Multiple café au lait macules are associated with many genodermatoses
- Syndromes associated with multiple café au lait macules
  - Albright syndrome
  - Bannayan-Riley-Ruvalcaba syndrome
  - Bloom syndrome
  - Cardiofaciocutaneous syndrome
  - Ectrodactyly-ectodermal dysplasia
  - Clefting syndrome
  - Epidermal nevus syndrome
  - Fanconi aplastic anemia
  - Johanson-Blizzard syndrome
    - VBR1 gene, nasal alar hypoplasia, hypothyroidism, congenital deafness, pancreatic achylia
  - Legius syndrome*
    - AD mutation in SPRED1
  - Maffucci syndrome
  - McCune-Albright syndrome*
  - Morquio syndrome
  - Mucosal neuroma syndrome
  - Neurofibromatosis*
  - Niemann-Pick syndrome
  - Proteus syndrome
  - Ring chromosome syndrome*
  - Russell-Silver syndrome
  - Watson syndrome*
    - Pulmonic stenosis, CALM, perineal freckling
  - Westerhof syndrome
    - Hereditary congenital hypopigmented and hyperpigmented macules

**Known to be associated. The rest are possibly associated.*

TABLE 3.19.2 NEUROFIBROMATOSIS

Type	Defect/Inheritance	Clinical Findings	Other
Neurofibromatosis type 1 (von Recklinghausen disease)	Neurofibromin/AD	2 major criteria needed: ≥6 café au lait spots, axillary or inguinal freckling (Crowe's sign), ≥2 neurofibromas or 1 plexiform neurofibroma, ≥2 Lisch nodules (iris hamartomas), optic glioma, bony lesions (pseudarthrosis osseous lesions, sphenoid dysplasia, scoliosis), 1st-degree relative with NF-1 Minor criteria: CNF macrocephaly, variable MR, pheochromocytoma	50% new mutations NF + JXG = increased risk juvenile myelomonocytic leukemia (JMML)
Neurofibromatosis type 2	Neurofibromin 2 (Merlin)/AD	Acoustic neuromas, deafness, meningiomas, schwannomas of the dorsal roots of the spinal cord. Juvenile posterior subcapsular cataracts. Occasional café-au-lait spots and neurofibromas. No Lisch nodules	Diagnosis requires either: (1) bilateral 8th nerve mass; (2) 1st-degree relative with NF-2 and either unilateral 8th nerve mass or 2 of the following: neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular cataract
Neurofibromatosis type 3 (mixed central and peripheral NF)	AD	Bilateral acoustic neuromas, meningiomas, spinal/paraspinal neurofibromas. Larger pale café au lait spots, palmar neurofibromas. No Lisch nodules	Early death from CNS tumors appearing in 2nd and 3rd decades
Neurofibromatosis type 4 (atypical NF)	AD	Clinically heterogeneous, Lisch nodules usually absent, diffuse NF CALS without other features of NF	
Neurofibromatosis type 5 (segmental NF)	Genetic mosaicism	Segmental distribution of neurofibromas	
Neurofibromatosis type 6		>6 café au lait spots with no other signs of NF (only CALS)	
Neurofibromatosis type 7		Late-onset neurofibromas in decades 50-60	

AD = autosomal dominant; CALS = café-au-lait spots; JXG = juvenile xanthogranuloma; MR = mental retardation; NF = neurofibromatosis.

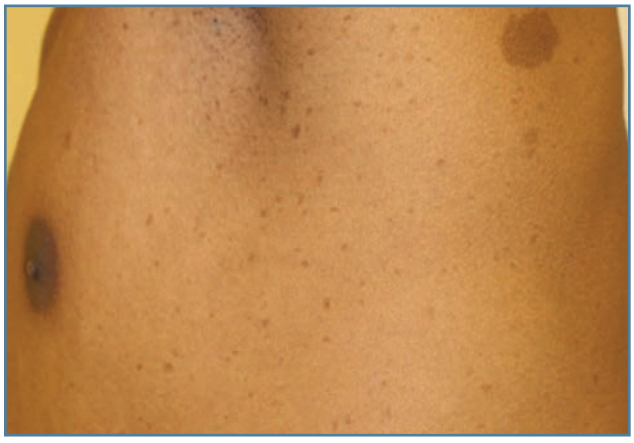

Figure 3.19.2 Neurofibromatosis type 1.

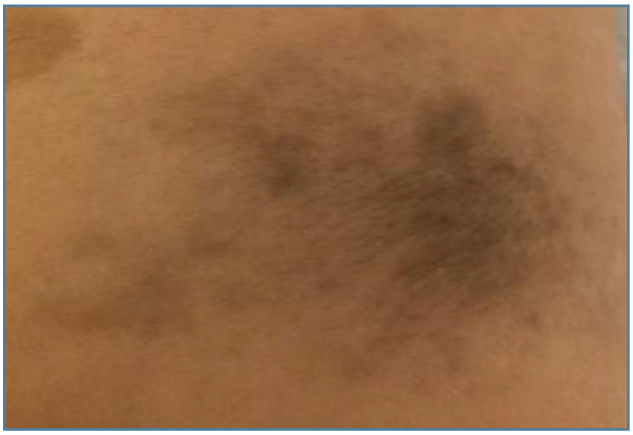

Figure 3.19.3 Neurofibromatosis type 1-plexiform NF and CALM.

MCCUNE-ALBRIGHT SYNDROME (POLYOSTOTIC FIBROUS DYSPLASIA)

- Somatic mosaicism
- *GNAS* gene defect (stimulates G protein, increasing cyclic AMP [cAMP])
- **Large café au lait macules with characteristic "coast of Maine" borders**, may follow lines of Blaschko or in segmental distribution following areas of bony fibrous dysplasia. Pathological fractures may result, i.e., shepherd's crook deformity of proximal femur. Multiple endocrine abnormalities including precocious puberty, hyperthyroidism, hyperparathyroidism, acromegaly, and Cushing syndrome
- Allelic disorder: Albright hereditary osteodystrophy: GNAS G_s subunit of adenylate cyclase. Calcification/ossification, pseudohypoparathyroidism/pseudopseudohypoparathyroidism, brachydactyly, absent 4th knuckle, hypogonadism

TIP

Precocious puberty may be presenting sign

NEUROFIBROMATOSIS

- I: AD, neurofibromin (NF1)
- Two or more of:
  - >6 café-au-lait spots (CALS) that are >5 mm in a prepubertal person or >15 mm in a postpubertal person
  - >1 neurofibroma or 1 plexiform neurofibroma
  - Axillary/inguinal freckling (Crowe's sign)
  - Optic glioma
  - >1 Lisch nodule (iris hamartoma)
  - Sphenoid wing dysplasia/other classic bony abnormality
  - 1st-degree relative

WATSON SYNDROME

- AD, neurofibromin
- Pulmonary stenosis + CALMs

LEGIUS SYNDROME

- AD, *SPRED1* mutation
- Noonan-like facies, CALMs, axillary freckling, ± learning disabilities, no neurofibromas

RUSSELL-SILVER SYNDROME

- Sporadic
- CALMs, short stature, musculoskeletal and craniofacial defects including asymmetry, clinodactyly and syndactyly, precocious puberty, and cryptorchidism

CONGENITAL DERMAL MELANOCYTOSIS (MONGOLIAN SPOT)

- See Section 3.7

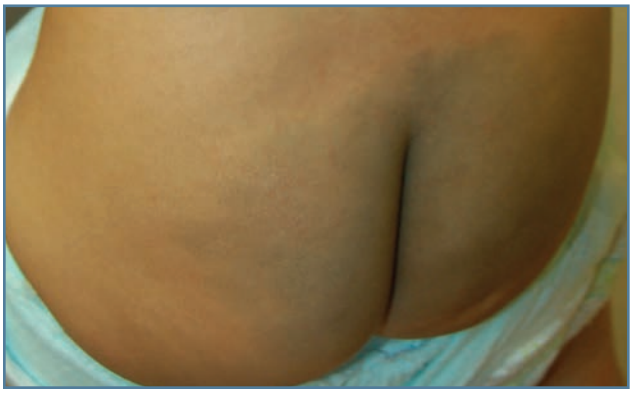

Figure 3.19.4 Dermal melanocytosis.

NEVUS OF OTA (OCULODERMAL MELANOCYTOSIS/ NEVUS FUSCOCERULEUS OPHTHALMAXILLARIS)

- See Section 3.7

NEVUS OF ITO (NEVUS FUSCOCERULEUS ACROMIODELTOIDEUS)

- See Section 3.7

BLUE NEVUS

- See Section 3.7

DOWLING-DEGOS DISEASE

- AD; keratin 5
- Reticulated hyperpigmentation of axilla, groin, inframammary, and antecubital fossa; starts in adulthood

3.20 Vascular Disorders

- Beckwith-Wiedemann syndrome (EMG) syndrome: Exophthalmos, macroglossia, gigantism: Sporadic 85%, 15% AD p57 (*KIP2*) gene (inhibitor of G1 cyclin/Cdk complexes), hyperinsulinemia, neonatal hypoglycemia. Nevus simplex facial capillary malformations, macroglossia, visceromegaly with omphalocele, hemihypertrophy associated with tumors (especially Wilms), linear ear lobe creases
- Von Hippel—Lindau syndrome: AD, *VHL* gene (tumor suppressor gene). Bilateral retinal hemangioblastomas, cerebellar and other CNS hemangioblastomas, renal cysts and renal cell carcinoma, pheochromocytomas, pancreatic cysts and carcinoma, capillary malformations, pulmonary and liver hemangiomas
- Proteus syndrome: Sporadic, somatic mutation in *AKT1*. Subcutaneous lymphovenous malformations, capillary malformations, lipomas, **connective tissue nevi of palms/soles**, hemihypertrophy, frontal bossing, hyperostoses of epiphyses and skull (especially external auditory canal), scoliosis, bilateral ovarian cystadenomas, parotid monomorphic adenoma
- Rubinstein-Taybi syndrome: AD, sporadic contiguous gene syndrome affecting transcriptional coactivator CREB-binding protein. Capillary malformation, short stature, **broad thumbs**, craniofacial abnormalities including beaked nose, mental retardation, congenital heart defects, cryptorchidism
- Ataxia telangiectasia (Louis-Bar syndrome): AR, *ATM* gene (chromosomal strand break repair enzyme) and *MREII* gene (milder form). **Cerebellar ataxia (1st sign), telangiectasias of conjunctiva (peribulbar) and skin**, thymic hypoplasia with increased infections, **respiratory failure**. Increases sensitivity to ionizing radiation with **increased risk leukemia/lymphoma and breast cancer.** Female carriers have increased risk of breast cancer. Increased α-fetoprotein and decreased or absent IgG2, IgE, and IgA

TIP

Avoid X-rays in Ataxia Telangiectasia patients

- Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia): AD, endoglin (transforming growth factor [TGF]-β binding protein), activin-receptor kinase 1 (binds TGF-β_1 and activin A), and bone morphogenetic protein receptor type II (TGF-β family receptor) mutations. **Epistaxis (1st sign),** telangiectasias of skin (hands/feet), mucous membranes **(lips, tongue), under the nails,** and gastrointestinal tract with bleeding, pulmonary arteriovenous fistulas with cerebral emboli. *ALK1* gene mutation associated with increased hepatic AVMs
- Cornelia de Lange syndrome: Sporadic (some AD due to nipped-β-like gene *NIPBL*; X-linked form due to structural maintenance of chromosomes 1-like *SMC1L1* gene). Cutis marmorata, hirsutism, synophrys, trichomegaly, numerous craniofacial abnormalities, severe mental retardation, deafness, low-pitched cry, short stature, clinodactyly and other abnormalities of the hands and feet, genitourinary abnormalities including cryptorchidism, congenital heart defects, and deafness
- Maffucci syndrome: See Section 3.8
- Blue rubber bleb nevus syndrome: See Section 3.8
- Hereditary lymphedema (Nonne-Milroy disease): AD, type 1, *FLT4* gene (VEGF receptor-3). Congenital lymphedema, chylous ascites, scrotal swelling, intestinal tract protein loss with hypoproteinemia, and persistent bilateral pleural effusions
- Lymphedema-distichiasis syndrome: AD, FOXC2 (forkhead family transcription factor gene *MFH1*). Late-onset lymphedema, distichiasis (double row of eyelashes), corneal irritation, ectropion, webbed neck, congenital heart defect
- Late-onset hereditary lymphedema (type 2)—Meige lymphedema, lymphedema ptosis, can have renal disease and diabetes
- Hypotrichosis-lymphedema-telangiectasia: *SOX18* mutation
- Familial glomangioma: *GLMN* mutation
- CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy): *NOTCH3* mutation

ACUTE HEMORRHAGIC EDEMA OF INFANCY (FINKELSTEIN DISEASE)

- Leukocytoclastic vasculitis; 30% IgA
- Infants around 6 months of age (up to 3 years)
- Hypersensitivity reaction thought to be a response to infection (vaccination or medication less common)
- Large round, red-purpuric plaques involving the ears, cheeks, and extremities
- Associated with fever and tender edema of the hands, feet, ears, and face
- Self-limited in 4-20 days
- No treatment

HENOCH-SCHONLEIN PURPURA

- Leukocytoclastic vasculitis
- Palpable purpura in dependent areas
- Etiology unknown
- IgA immune complex deposition
- May have associated edema
- Glomerulonephritis in 40-50%, usually self-limited
- GI pain, arthritis, proteinuria can be associated
- Observation, NSAIDs for joint pain, corticosteroids for severe disease
- Can last 4-6 weeks

3.21 Connective Tissue Disorders

EHLERS-DANLOS SYNDROME (EDS)

- Type 1 (gravis): AD, collagen V. Hyperextensible skin, **gaping wounds, "fishmouth"** cigarette-paper-like atrophic scars, **molluscoid pseudotumors,** calcified subcutaneous nodules, bruises, hypermobile joints with dislocation, hernias, mitral valve prolapse, blue sclerae, **Gorlin's sign (tongue reaches nose), absence of lingual frenulum**
- Type 2 (mitis): AD, collagen V. Milder form of type 1
- Type 3 (benign hypermobile): AD, *TNXB*. **Recurrent joint dislocations**
- Type 4 (vascular): AD/AR, collagen III. Translucent skin with visible venous network, **arterial and visceral rupture resulting in early death**
- Type 5 (X-linked): XLR. Lysyl oxidase deficiency. Relatively mild, similar to type 2
- Type 6 (ocular-scoliotic): AR, *PLOD* gene, lysyl hydroxylase deficiency. Severe kyphoscoliosis, retinal detachment, and other eye abnormalities
- Type 7 (arthrochalasis multiplex congenita): AD/AR, *COL1A/2*, mutations in procollagen amino terminals (AD) or in procollagen aminopeptidase (AR), which cleaves the amino terminals. **Congenital hip dislocation**, severe joint hypermobility (EDS arthrochalasia type)
- Type 8 (periodontitis): Type III collagen. Mild symptoms of EDS with periodontitis and resulting tooth loss
- Type 9 (occipital horn syndrome): XLR, lysyl oxidase. Mild symptoms of EDS with occipital exostoses and hernias
- Type 10 (fibronectin): AR, fibronectin. Ecchymoses and petechiae
- Type 11 (large joint hypermobile): AD; dislocation of large joints

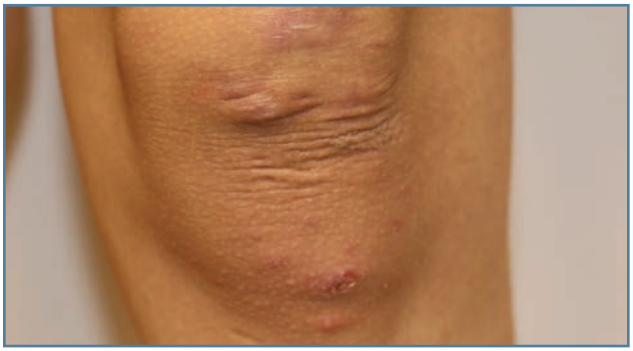

Figure 3.21.1 Ehlers-Danlos syndrome.

MARFAN SYNDROME

- AD, fibrillin 1 and 2
- Tall stature, arachnodactyly, pectus excavatum, high-arched palate, joint laxity, **ectopia lentis with upward dislocation,** aortic dilatation with rupture, mitral valve prolapse, striae, elastosis perforans serpiginosa

CONGENITAL CONTRACTURAL ARACHNODACTYLY

- AD, fibrillin 2
- Long limbs, arachnodactyly, scoliosis, crumpled ear

CUTIS LAXA

- AR, fibulin 4 gene, AD (elastin gene), acquired (Marshall syndrome). AD = mainly skin limited
- Loose, pendulous, inelastic skin, deep voice, lung abnormalities (**emphysema**), arterial rupture, visceral diverticulae and hernias, and joint dislocation. Fibulin 5 (both AD and AR)

PSEUDOXANTHOMA ELASTICUM

- AR, AD, sporadic, *ABCC6* gene (anthracycline resistance protein, ATP-using cell transporter)
- Fragmented and calcified elastin of skin, eyes, and arteries
- Plucked-chicken skin on flexures, yellow papules on mucous membranes, **angioid streaks (rupture in Bruch's membrane)**, gastric hemorrhage, cardiovascular disease, peripheral vascular disease

BUSCHKE-OLLENDORFF SYNDROME

- AD
- Dermatofibrosis lenticularis disseminata **(elastomas)** and **osteopoikilosis** (round opacities in bones)
- Caused by a loss-of-function mutation in *LEMD3* (also called *MAN1*), which encodes an inner nuclear membrane protein. LEMD3 normally interacts with bone morphogenetic protein and activin-TGF-β receptor-activated Smads and antagonizes both signaling pathways

FOCAL DERMAL HYPOPLASIA (GOLTZ SYNDROME)

- X-linked dominant, male lethal, *PORCN* gene
- **Linear atrophy following Blaschko's lines with areas of fat herniation, mucocutaneous papillomas and pits,** alopecia, nail dystrophy, tooth abnormalities, musculoskeletal defects: Lobster claw deformity, **osteopathia striata (vertical striations in metaphyses on X-ray), colobomas, notched nasal ala**

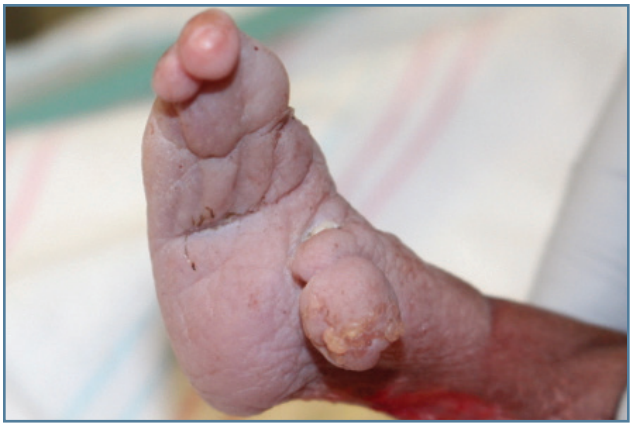

Figure 3.21.2 Ectrodactyly in Goltz syndrome.

LIPOID PROTEINOSIS

- AR, extracellular matrix protein 1 gene (*ECM1*)
- Scars and yellow papules of the face and oropharynx, **eyelid string of pearls, hoarse voice,** verrucous nodules of elbows and knees, bean-shaped temporal and hippocampal calcification with occasional seizures
- Periodic acid—Schiff (PAS)$^{+}$ deposits histologically

RESTRICTIVE DERMOPATHY

- AR
- *LMNA* gene defect or *ZMPSTE24* gene defect
- Tight, restrictive adherent skin at birth associated with fixed, pinched facies. Skeletal anomalies and flexion contractures are present along with pulmonary hypoplasia and cardiac defect. Universally lethal
- Histology: Markedly thin dermis with decreased/absent elastin and collagen

STIFF SKIN SYNDROME

- AD mutations in *FBN1* gene leading to defective fibrillin 1 and increased TGF-β signaling
- Progressive, symmetric, bilateral scleroderma-like presentation starting in infancy or early childhood with expanding "rock hard" hyperpigmented plaques
- Can lead to joint contractures, impaired mobility, and restrictive lung disease
- Segmental form has been described, with onset later in childhood and better prognosis; may be misdiagnosed as linear morphea
- Histology: Horizontally oriented thickened collagen bundles; classic finding = adipocyte entrapment

HYALINE FIBROMATOSIS SYNDROME (INFANTILE SYSTEMIC HYALINOSIS [ISH] AND JUVENILE HYALINE FIBROMATOSIS [JHF])

- AR mutations in *ANTXR2* gene encoding anthrax toxin receptor-2
- Accumulation of abnormal hyalinized tissue in skin, mucosa, bones, joints, and visceral organs
- Subcutaneous nodules, gum hypertrophy
- Previous classification—ISH: Systemic involvement, early lethality from recurrent infections, diarrhea, organ failure vs JHF: More benign course
- Reclassified as grade 1-4 depending on areas of involvement and severity

BEARE-STEVENSON CUTIS GYRATA SYNDROME

- Mutations in fibroblast growth factor receptor 2
- Craniosynostosis, cutis gyrata, acanthosis nigricans, anogenital anomalies, skin tags, prominent umbilical stump, furrowed palms/soles

APERT SYNDROME

- Apert syndrome (same gene): Cranial synostosis, syndactyly, severe acne. Nevus comedonicus (same gene)
- Skeletal dysplasia syndrome with acanthosis nigricans:
- *FGFR3* mutation

PACHYDERMOPERIOSTOSIS

- AR, *HPGD* gene, *SLC2A*; mostly males
- Clubbing of digits, soft tissue hyperplasia, periosteal proliferation of arms and legs, **cutis vertices gyrata on scalp**
- Loeys-Dietz syndrome: AD, TGF-β receptors 1 and 2
- Translucent skin, aortic aneurism, arterial tortuosity, craniofacial and skeletal anomalies, joint hypermobility

OSTEOGENESIS IMPERFECTA

- *COL1A1* gene defect. Types I and IV (AD), types II and III (AD/AR)—most severe, with fractures in utero
- Thin skin, easy bruising, **blue sclera** (except type III), **multiple fractures** with Wormian bones, mitral valve prolapse (especially type I)

3.22 Diseases with Malignant Potential and Related Conditions

BASAL CELL NEVUS SYNDROME (GORLIN SYNDROME)

- AD, patched gene (inhibits hedgehog signaling pathway). Patched inhibits smoothened. Mutated patched → uncontrolled cell proliferation through Gli1-3 transcription factors. Innumerable BCCs, palmoplantar pits, painful odontogenic jaw keratocysts, frontal bossing, bifid ribs, calcification of falx cerebri, medulloblastoma, hypertelorism, and ovarian fibromas and fibrosarcomas

BAZEX SYNDROME

- X-linked dominant > AD. Follicular atrophoderma on backs of hands, hypohidrosis, hypotrichosis, **multiple BCCs**

ROMBO SYNDROME

- AD, vermicular atrophoderma, **multiple BCCs,** trichoepitheliomas, hypotrichosis, acrocyanosis. No follicular atrophoderma or hypohidrosis as seen in Bazex syndrome

NICOLAU-BALUS SYNDROME

- Micropapular eruptive syringomas, milia, atrophoderma vermiculata

BRAUN-FALCO-MARGHESCU SYNDROME

- Atrophoderma vermiculata, PPK, keratosis pilaris

TÜZÜN SYNDROME

- Atrophoderma vermiculata and scrotal tongue

RASMUSSEN SYNDROME

- Milia, trichoepitheliomas, and cylindromas

FAMILIAL CYLINDROMATOSIS

- AD, *CYLD* gene (protein binds organelles to microtubules). Numerous cylindromas (formerly "turban tumors"), eccrine spiradenomas

BROOKE-SPIEGLER SYNDROME

- Multiple trichoepithioliomas, cylindromas, and spiradenomas in addition to **BCC** and **salivary gland tumors**

BIRT-HOGG-DUBÉ SYNDROME

- AD; multiple fibrofolliculomas, trichodiscomas, achrocordons, lipomas, oral fibromas, **renal cell carcinoma, medullary thyroid carcinoma, and colon cancer.** Mutation *FLCN* (folliculin gene)

MYOTONIC DYSTROPHY WITH MULTIPLE PILOMATRICOMAS

- Activating β-catenin mutations (encoded by *CTNNB1*)

GARDNER SYNDROME

- AD, *APC* gene (β-catenin-mediated transcription). **Colonic polyposis with cancer** (100% by age 50), epidermoid cysts with foci of pilomatricoma and calcification, **congenital hypertrophy of retinal pigment epithelium,** facial/skull osteomas, supernumerary teeth, desmoid tumors

CRONKHITE-CANADA SYNDROME

- Sporadic. Gastrointestinal polyposis, nail atrophy, alopecia, generalized pigmentation of skin, **melanotic macules on fingers,** malabsorption with hypoalbuminemia

PEUTZ-JEGHERS SYNDROME

- AD, *STK11/LKB1* (serine threonine kinase tumor suppressor gene). Pigmented macules of the mouth, fingers, and mucosae, gastrointestinal hamartomatous polyps (especially small bowel) with bleeding and **intussusception, gastrointestinal adenocarcinomas, ovarian sex cord tumor, and breast, pancreatic, and endometrial cancers.** Laugier-Hunziker syndrome looks similar, without malignancy

PTEN HAMARTOMA TUMOR SYNDROME

- Umbrella term, disease presents on a spectrum, associated with macrocephaly and autism spectrum disorder
- AD, *PTEN* (encodes a phosphatase that dephosphorylates tyrosine, serine, and threonine)
  - Cowden syndrome: Facial trichilemmomas, oral papillomas, acral keratotic papules, sclerotic fibromas, breast fibroadenomas and **adenocarcinomas**, thyroid adenomas and **adenocarcinomas**, and hamartomatous polyps of the gastrointestinal tract
  - Lhermitte-Duclos syndrome: Cowden syndrome plus dysplastic gangliocytoma of the cerebellum
  - Bannayan-Riley-Ruvalcaba syndrome: AD, *PTEN*. Genital lentigines, hamartomas, lipomas, hemangiomas, trichilemmomas, café-au-lait macules, and angiokeratomas are cutaneous findings. Macrocephaly, mental retardation. and intestinal polyposis are features. Lipid storage myopathy and Hashimoto's thyroiditis can occur

MULTIPLE ENDOCRINE NEOPLASIA TYPE I (WERMER SYNDROME)

- AD, *MEN1* (encodes menin). **Parathyroid, pancreatic,** and **pituitary tumors**. Angiofibromas, collagenomas, CALMs, lipomas, hypopigmented macules, gingival macules. **Tuberous sclerosis—like cutaneous findings**

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2A (SIPPLE SYNDROME)

AD, *RET* proto-oncogene. Parathyroid tumors, pheochromocytomas, **medullary thyroid cancer**. Familial **macular/lichen amyloidosis,** Hirschsprung

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2B (MULTIPLE MUCOSAL NEUROMAS)

- AD, *RET* proto-oncogene. Pheochromocytoma, medullary thyroid cancer, rare parathyroid carcinoma. Mucosal neuromas, marfanoid habitus, GI ganglioneuromatosis

DYSKERATOSIS CONGENITA

- X-linked recessive—dyskerin gene (ribosomal RNA synthesis); AD—*TERC* gene (telomerase). Reticulate pigmentation of skin, poikiloderma, alopecia, nail atrophy, **premalignant oral leukoplakia,** Fanconi-type pancytopenia resulting in early death. Allelic to Hoyeraal-Hreidarsson syndrome (+ posterior fossa malformations), lacrimal duct atresia with constant tearing, absent fingerprints, Mental retardation, deafness, testicular atrophy; thrombocytopenia and anemia; increased infection
- Female carriers may have limited skin involvement and pulmonary complications; increased risk of malignancy

FAMILIAL DYSPLASTIC NEVI/MELANOMA

- AD, *CDKN2A* (p16 tumor suppressor gene that inhibits cyclin-dependent kinase 4), *CDK4* (cyclin-dependent kinase 4, proto-oncogene). **Dysplastic nevi, melanoma, pancreatic cancer, and astrocytomas.** Mutation in *BRAF* in common melanocytic nevi (ex: dermal) and in malignant melanoma

FAMILIAL MULTIPLE CUTANEOUS LEIOMYOMATOSIS (REED SYNDROME)

- AD, fumarate hydratase. Multiple cutaneous leiomyomas, uterine leiomyomas and **leiomyosarcoma, type II papillary renal cell carcinoma**

LI-FRAUMENI SYNDROME

- AD, *p53* mutation; breast carcinoma, brain carcinoma, osteosarcoma, leukemia; skin cancers not classic but **some increased risk of melanoma/SCC**

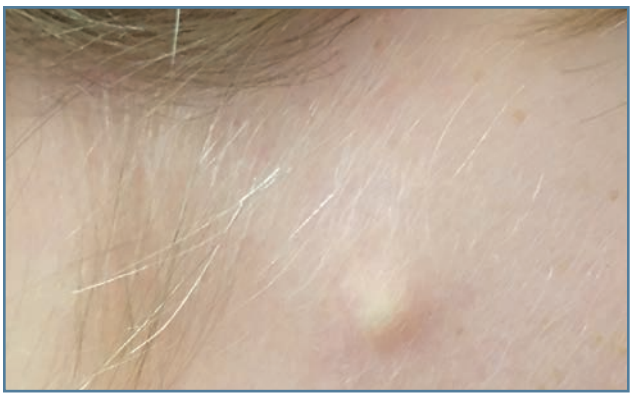

Figure 3.22.1 Pilomatricoma.

3.23 Disorders with Immunodeficiency

WISKOTT-ALDRICH SYNDROME

- X-linked recessive, *WASP* gene, an Arp2/3 complex—interacting protein, atopic dermatitis on face, scalp, flexures, thrombocytopenia with petechiae, purpura, epistaxis, bloody diarrhea, hematemesis, intracranial hemorrhage, recurrent bacterial infections, otitis media, pneumonia, meningitis, sepsis; increased susceptibility to herpes simplex virus (HSV), *Pneumocystis carinii* pneumonia (PCP), human papillomavirus (HPV); increased IgA, IgD, IgE; **decreased IgM**; impaired cell-mediated and humoral immune response; 20% risk of lymphoreticular malignancy in adolescence/young adulthood

CHRONIC GRANULOMATOUS DISEASE

- AR: Mutation in *CYBA* (cytochrome subunit). XLR: Mutation in *CYBB* (cytochrome subunit). AR: *NCF1* and *NCF2* (encoding neutrophil cytosolic factors 1 and 2). Diagnosed by **nitroblue tetrazolium reduction assay:** Abnormal WBCs cannot reduce the dye, showing inability to produce respiratory burst needed to kill catalase-positive organisms after phagocytosis. **Recurrent pyoderma (*S. aureus,* most commonly), periorificial dermatitis,** ulcerative stomatitis and

chronic gingivitis in mouth, suppurative lymphadenitis with abscesses and fistulas, pneumonia with empyema, hepatosplenomegaly with granulomas, abscesses, chronic diarrhea, osteomyelitis, increased risk of lupus in carriers/adults with mild disease

HYPER-IgE SYNDROME (JOB SYNDROME)

- Autosomal dominant (AD) HIES
  - *STAT3* gene mutation
  - Atypical atopic dermatitis, abscesses/paronychia/candidiasis. Coarse facial features, broad nasal bridge. Retention of primary teeth. Skeletal anomalies/osteoporosis
  - Elevated IgE (>2,000 IU/mL) with eosinophilia and abnormal neutrophil chemotaxis
- Autosomal recessive (AR) HIES
  - *Dock8* gene mutation
  - Severe viral infection and early malignancy
  - No connective tissue/skeletal abnormalities

SEVERE COMBINED IMMUNODEFICIENCY (SCID)

- X-linked recessive: Most common, γ chain, IL-2 receptor gene (*IL2RG*). AR: From Janus kinase 3 gene (*JAK3*). AD: *IL7R* gene mutation. Mixed group of disorders, all sharing defect in cell-mediated and humoral immunity; 20% secondary to adenosine deaminase deficiency (*ADA* and *PNP* genes mutated), **associated with dermatofibrosarcoma protuberans (DFSP),** candidal infections, mucocutaneous, bacterial pyodermas, seborrheic-like dermatitis/lichen planus–like sclerodermatous changes, aplastic thymus, pneumonia, chronic diarrhea

OMENN SYNDROME

- AR form of SCID with erythroderma, *RAG1* and *RAG2* genes

CHRONIC MUCOCUTANEOUS CANDIDIASIS

- AR or AD (*ICAM1*) or AD with thyroid disease. *Candida*, severe, of skin, mouth, nails; deep dermatophytes

GATA2 DEFICIENCY

- AD; HPV infection with progression to dysplasia, high risk of **myelodysplasia**/acute myeloid leukemia (AML)

PLAID (PLCG2-ASSOCIATED ANTIBODY DEFICIENCY AND IMMUNE DYSREGULATION)

- AD; cold (evaporative cooling) urticaria, granulomas, neonatal nasal and acral inflammatory lesions

DOCK8 DEFICIENCY

- AR. Increased IgE, multiple allergies, eczematous dermatitis, **severe HPV, molluscum, herpes infections**

PGM3 DEFICIENCY

- AR. Increased IgE, dermatitis, multiple allergies, asthma, **neurologic abnormalities**

APECED

- AR, *AIRE* gene (autoimmune regulator gene). Autoimmune polyendocrinopathy, candidiasis, ectodermal dysplasia. Addison's hypoparathyroidism, candidiasis (severe bullous chronic paronychia)

X-LINKED AGAMMAGLOBULINEMIA (BRUTON)

- X-linked recessive; *BTK* gene. All Igs decreased; also AR, AD forms

COMMON VARIABLE IMMUNODEFICIENCY

- *ICOS, TNFRSF13, TNFRSF13C, CD19* genes; IgG and IgA decreased; ± decrease in IgM

X-LINKED HYPER-IGM SYNDROME

- AR, *CD40LG*. Increased IgM; decreased IgA, IgE, and IgG

IPEX

- X-linked recessive, *FOXP3* mutation. Immune dysregulation, polyendocrinopathy, **enteropathy,** multiorgan autoimmune disease

3.24 DNA Repair Disorders and Chromosomal Disorders

XERODERMA PIGMENTOSUM (XP)

- The genes implicated in XP are involved in the repair of UV-induced DNA damage (nucleotide excision repair). UV irradiation induces specific types of DNA damage, primarily, **cyclobutane pyrimidine dimers (CPDs) and 6—4 photoproducts.** These are associated with skin cancer. The defects in nucleotide excision repair seen in XP involve all aspects of DNA repair, including recognizing damaged DNA (XPA and XPE), unwinding the coiled DNA to allow repair (helicases; XPB and XPD), and repairing the localized damaged DNA (endonucleases; XPF and XPG)
- **Acute photosensitivity/sunburns from infancy, numerous lentigines in young children,** 1,000× skin cancer risk, premalignant and malignant skin cancers including BCCs, SCCs, and melanomas, SCCs of distal tongue, cataracts, ectropion with vascularization, and mental retardation (some subtypes)

TABLE 3.24.1 XERODERMA PIGMENTOSUM COMPLEMENTATION GROUPS

Group	Gene Function	Inheritance	Syndrome/Comments	Physical Findings
A	Defective nucleotide excision repair: Initial step of binding defective DNA encodes DNA damage binding protein (DDB1)	AR	DeSanctis-Cacchione syndrome	Most severe variant. Photosensitivity with variable to severe neurologic abnormalities/growth delay/deafness
B	DNA helicase DNA excision repair cross-complementing (*ERCC3*) gene defect	AD	Overlap with Cockayne syndrome XP/CS and trichothiodystrophy	Photosensitivity (XP) with pigmentary retinopathy and basal ganglia calcification (CS)
C	Defective nucleotide (endonuclease) excision repair: Binding to ssDNA to allow stable repair		Most common in Europeans/worldwide	At great risk for skin cancer (melanoma). Rare neurological symptoms

TABLE 3.24.1 XERODERMA PIGMENTOSUM COMPLEMENTATION GROUPS CONTINUED

Group	Gene Function	Inheritance	Syndrome/Comments	Physical Findings
D	DNA helicase; *ERCC2* DNA repair gene	AR	Overlap with trichothiodystrophy (PIBIDS) and XP/CS	Poikiloderma, early skin cancer, photo-ocular damage, decreased intelligence, neurological impairment (later onset)
E	Defective nucleotide excision repair: Enzyme that cleaves pyrimidine	AR		Mildest skin/eye photosensitivity. No neurologic changes
F	Endonuclease *ERCC4* gene	AR	Occurs primarily in Japanese patients, although rare	Mild photosensitivity, freckling, rare skin cancer. No neuro/ocular abnormalities
G	Endonuclease human homolog of the yeast *RAD2* gene	AR	Overlap with XP/CS	Mild skin changes. No skin cancer. Neuro/ocular abnormalities with XP/CS only
Variant	*POLH* gene: Normal DNA repair rate, but defective postreplication repair	AR?	About 1/3 of all patients with XP. Most common in Japan	Variable photosensitivity with no neurological abnormality

AD = autosomal dominant; AR = autosomal recessive; CS = Cockayne syndrome; XP = xeroderma pigmentosum.

COCKAYNE SYNDROME (CS)

- AR
- Defective excision repair, cross-complementing group 8 gene (*ERCC8*)
- CS group A: *ERCC8*, defective excision repair
- CS group B: *ERCC6*
- **Photosensitivity without poikiloderma,** mental retardation and cachectic dwarfism, sunken face
- "Wizened" appearance, "bird-headed" facies, "Mickey Mouse" ears
- Cataracts, deafness, pigmentary retinopathy (salt and pepper), dental caries. Skeletal, GU, and endocrine abnormalities as well
- Diffuse CNS demyelination, peripheral neuropathy, mental retardation, intracranial calcification, death from neurodegenerative disease
- **CS is not associated with skin cancer**

ROTHMUND-THOMSON SYNDROME (POIKILODERMA CONGENITALE)

- Compound heterozygous mutation in *RECQL4* gene defect (encodes DNA helicase)
- **Poikiloderma, photosensitivity,** sparse hair, atrophic nails
- Short stature, juvenile zonular cataracts, annular pancreas, abnormal dentition, cryptorchidism, hypogonadism, osteoporosis
- Increased malignancy: Basal cell carcinoma, squamous cell carcinoma, **osteogenic sarcoma**

TIP

Hypoplastic or absent thumbs, has only 4 fingers, RECQL-"4"

MNEMONIC

ROTHMUND
Radius absent
Osteosarcoma
Thumb ray absent
Hypogonadism
Mottled skin
j**U**venile cataracts
Nail dystrophy
DNA helicase

BLOOM SYNDROME (BLM)

- AR
- BLM gene defect (*RECQL3;* RecQ protein-like-3 DNA helicase). Increased sister chromatid exchange and increased spontaneous chromosomal breakage/rearrangement
- Prenatal-onset growth deficiency, hypogonadism, **photosensitivity, midfacial telangiectasia (lupus like), dyspigmentation,** prominent ears and nose, café-au-lait macules, hypertrichosis
- Increased malignancy: Leukemia, lymphoma, SCC, adenocarcinoma
- Hypogammaglobulinemia with **recurrent respiratory infections leading to chronic lung disease** and gastrointestinal infections
- Skeletal/GU abnormalities. Non-insulin-dependent diabetes mellitus (NIDDM), acanthosis nigricans

MNEMONIC

BLOOM
Butterfly rash
Lymphoma/leukemia
Hyp**O**gonadism
Infertility IgM, IgA (low)

WERNER SYNDROME

- AR, *RECQL2* (DNA helicase). **Sclerodermoid skin**, chronic leg ulcers, alopecia and graying of hair, beaked nose, short stature, osteoporosis, hypogonadism, atherosclerotic disease, sarcomas and other tumors

PROGERIA (HUTCHINSON-GILFORD SYNDROME)

- AD, AR mutation in lamin A (nuclear envelope protein)
- Lipoatrophic sclerodermoid skin, alopecia, nail atrophy, **craniomegaly with dilated scalp veins** and small face, muscle/bone wasting, **severe premature atherosclerosis with early death**

MUIR-TORRE SYNDROME

- AD, *HMSH2* and *MLH1* (DNA mismatch repair gene)
- **Sebaceous adenomas, epitheliomas, and carcinomas; keratoacanthomas (esp. w/sebaceous differentiation)**
- Gastrointestinal, genitourinary, breast cancers (variant of hereditary nonpolyposis colorectal cancer [HNPCC; Lynch syndrome)

DOWN SYNDROME

- Trisomy 21 (1:700 births, risk increased with maternal age)
- Single palmar crease, nuchal folds, syringomas, **elastosis perforans serpiginosa**, epicanthic folds with up-slanting palpebral fissures, **Brushfield spots,** scrotal tongue, obesity, skin infections, hidradenitis suppurativa, mental retardation, atrioventricular septal defects, ventricular septal defects, numerous other defects
- Prenatal diagnosis by low α-fetoprotein in maternal serum and amniocentesis
- Trisomy 8
- Short nails, no patella (similar to nail-patella syndrome)

KLINEFELTER SYNDROME

- X-aneuploidy (47,XXY, 48,XXYY, etc.) from X-chromosome nondisjunction during maternal or paternal meiosis
- Tall stature, varicose veins, arterial and venous leg ulcers, scant androgenic hair (body, pubis), gynecomastia, testicular hypoplasia, and antisocial behavior

TURNER SYNDROME

- X-aneuploidy (XO), 1:2,500, partial or total loss of one X chromosome from nondisjunction during gametogenesis. Webbed neck (remnant of cystic hygroma), keloids, hypoplastic nails, low-set ears with low posterior hairline, short stature, short 4th and 5th metacarpals, congenital lymphedema of hands and feet, primary amenorrhea from gonadal dysgenesis, cardiovascular abnormalities including coarctation of the aorta, and horseshoe kidneys

3.25 Disorders of Metabolism

ALKAPTONURIA

- AR, *HGD* gene (encodes homogentisic acid oxidase)
- Ochronosis: Blue-gray pigmentation of face, **ears, cartilage,** tendons, acral surfaces, cerumen, sweat, sclera, cartilage of pubic symphysis, ear, nose, dark urine (pH > 7.0)
- Arthropathy, intervertebral disk calcification

FABRY DISEASE (ANGIOKERATOMA CORPORIS DIFFUSUM)

- X-linked recessive, GLA gene encoding α-galactosidase A
- Accumulation of glycosphingolipids in vascular endothelium—ischemia and **cerebrovascular infarction**
- **Angiokeratomas between umbilicus and knees (bathing suit distribution)—may see in female carriers, urine "Maltese crosses,"** mulberry cells, **renal insufficiency with proteinuria,** painful crises, paresthesias of hands and knees relieved by phenytoin, angina, myocardial infarction (MI), cerebrovascular accidents (CVAs), peripheral neuropathy, corneal opacities ("whorl-like" configuration)
- Fucosidosis (α-L-fucosidase) and sialidosis are indistinguishable from Fabry's on cutaneous exam; β-galactosidase deficiency and aspartylglucosaminuria show angiokeratomas, too

GAUCHER DISEASE

- AR, acid β-glucosidase (*GBA*) gene; type I—adult; type II—infants
- Gaucher cells: Glucocerebroside in histiocytes in spleen, liver, bone marrow, lymph nodes, brain. Erlenmeyer flask deformity in bone, **collodion type fatal in perinatal period**

MUCOPOLYSACCHARIDOSES

- AR (except Hunter syndrome—X-linked recessive), deficiency of lysosomal enzymes responsible for breakdown of mucopolysaccharides
- Skin findings: Firm, **ivory-colored papules between angles of scapula (Hunter),** all patients have thick skin, increased dermatan and heparan sulfate (Hunter), all patients have generalized hirsutism, coarse facies with thick nose and depressed nasal bridge, thick lips and tongue, short neck, broad hands, short fingers, mental retardation, short stature, corneal clouding and retinitis pigmentosa, cardiac failure and valvular disease, bronchopneumonia, hepatosplenomegaly, dysostosis multiplex, osteoporosis, joint laxity, **dermal melanocytosis (Hurler)**
- Hurler and Scheie (type IH/S): α-L-Iduronidase
- Hunter (type II): Iduronate sulfatase
- Sanfilippo (type IIIC): Multiple enzymes can be deficient
- Maroteaux-Lamy (type VI): Arylsulfatase B
- Morquio (types IVA, IVB): Either *N*-acetylgalactosamine-6-sulfatase (type IVA) or β-galactosidase (type IVB)
- Multiple carboxylase deficiency

BIOTINIDASE DEFICIENCY OR HOLOCARBOXYLASE SYNTHETASE DEFICIENCY

- AR, *BTD* gene
- Decreased free serum biotin, **periorificial/acral/generalized dermatitis (as in zinc deficiency),** *Candida* infection, **alopecia,** hypotonia, seizures, vomiting, optic atrophy, hearing loss, metabolic acidosis with hyperammonemia; treat with biotin 10 mg/day

PHENYLKETONURIA

- AR, *PAH* gene (encodes phenylalanine hydroxylase; protein requires cofactor tetrahydrobiopterin)
- Increased phenylalanine inhibits tyrosine in melanogenesis and toxic to CNS, generalized **hypopigmentation**, eczema, **sclerodermoid changes to skin,** blond hair, blue eyes, mental retardation, urine with "mousy" odor

HOMOCYSTINURIA

- AR, *CBS* gene (encodes cystathionine β-synthase); mutation leads to increased homocystine and methionine levels in blood/urine
- **Malar flush, deep vein thromboses (DVTs) and emboli,** cardiovascular disease, **livedo reticularis,** leg ulcers, blond hair, fair complexion, downward lens dislocation (ectopia lentis), glaucoma, **marfanoid habitus,** mental retardation, seizures, psychiatric disorders

ACRODERMATITIS ENTEROPATHICA

- AR (intestinal zinc-specific transporter encoded by *SLC39A4*)
- Defect in zinc absorption, appearing earliest in bottle-fed infants; after weaning, in breast-fed older infants
- **Periorificial, scalp, and acral dermatitis,** scaling, vesicles/bullae, erosions, **alopecia, diarrhea,** stomatitis, glossitis, irritability, photophobia; treat with lifelong zinc supplementation

WILSON DISEASE

- AR (*ATP7B* gene, encoding ATPase copper-transporting β polypeptide)
- Defect in biliary excretion of copper, leading to copper accumulation in liver
- Hepatolenticular degeneration: Accumulation of copper in liver, brain, cornea; pretibial hyperpigmentation, blue lunulae, hepatomegaly, cirrhosis, Kayser-Fleischer ring (yellow-brown copper deposition in Descemet's membrane of cornea), ataxia, dysarthria, dementia

HEMOCHROMATOSIS

- Type 1: AR (*HFE* gene, encoding homeostatic iron regulator)
- Type 2A: AR (*HJV* gene, encoding hemojuvelin)
- Type 2B: AR (*HAMP* gene, encoding hepcidin antimicrobial peptide)
- Type 3: AR (*TFR2* gene, encoding transferrin receptor 2)
- Type 4: AD (*SCL40A1* gene, encoding ferroportin)
- Increased intestinal iron absorption—iron overload, generalized metallic-gray hyperpigmentation, koilonychia, alopecia (scant pubic/axillary hair), cardiac failure, arrhythmias, heart block, hepatomegaly with cirrhosis, diabetes ("bronze diabetes"), polyarthritis with chondrocalcinosis, susceptible to *Vibrio vulnificus* and *Yersinia* infections; screen with ferritin
- Linked to porphyrias

TABLE 3.25.1 METABOLIC DISORDERS

Disorder	Defect	Clinical Findings
Gaucher	β-Glucocerebrosidase; AR	Hyperpigmentation, multiorgan infiltration Type 1: Adult, no neurological deterioration, bronze hyperpigmentation Type 2: Infantile, rapid neurological deterioration, bronchopneumonia Type 3: Juvenile, chronic neuropathy
Fabry	α-Galactosidase A; X-linked recessive	Angiokeratomas, cardiovascular disease, neurological deterioration, "Maltese-cross" urine, corneal verticillata
Fucosidosis	α-L-Fucosidase; AR	Angiokeratomas, coarse features, neurological deterioration
Hartnup	AR; tryptophan	Photosensitivity, ataxia, psychosis, atrophic glossitis
Prolidase deficiency	Prolidase	Telangiectasias, crusted dermatitis, **severe lower leg ulceration,** increased infections/SLE, MR
Phenylketonuria	Phenylalanine hydroxylase deficiency; auto-recessive	Fair complexion. Neurologic deterioration if untreated. Occasional sclerodermatous skin changes, mousy urine odor
Alkaptonuria	Homogentisic acid oxidase; AR	Blue-gray pigmentation of face, groin, axillae. Blue sclera (Osler's sign). Severe arthropathy, dark urine with pH > 7
Wilson (hepatolenticu-lar degeneration)	*ATP7B* gene defect (copper-transporting ATPase; low ceruloplasmin); AR	Accumulation of copper: Blue lunulae, copper-colored ring around cornea (Kayser-Fleischer ring), neurologic sequelae, liver failure. Rx: Penicillamine
Tyrosinemia II (Richner-Hanhart)	Tyrosine aminotransferase; AR	Painful PPK, keratitis, MR, blindness
Hurler	α-L-Iduronidase; AR	Dermal melanocytosis, coarse facies, HSM, corneal clouding, dysostosis multiplex, and MR

TABLE 3.25.1 METABOLIC DISORDERS CONTINUED

Disorder	Defect	Clinical Findings
Hunter	Iduronate sulfatase; XLR	Pebbly skin lesions on scapula and hypertrichosis. Less severe than Hurler
Lesch-Nyhan	HGPRT; XLR	Self-mutilation, MR, choreoathetosis
Lipoid proteinosis of Urbach-Wiethe (hyalinosis cutis et muco-sae)	*ECM1* gene defect; AR	**Hyaline papules along eyelid margin ("string of pearls"),** both acral and in axillae; early hoarseness, blisters in infancy; drusen-like lesions on fundus; temporal lobe, hippocampal calcification; wooden tongue
Niemann-Pick	Types A and B: Acid sphingomyelinase deficiency; AR Type C: Cholesterol esterification defect; AR	Type A: Infancy, xanthomas, progressive CNS deterioration, FTT, HSM, cherry red spots, blindness, deafness Type B: Infancy to childhood, like type A except CNS spared Type C: Childhood, HSM, developmental delay, psychomotor deterioration

AR = autosomal recessive; FTT = failure to thrive; HGPRT = hypoxanthine-guanine phosphoribosyltransferase; HSM = hepatosplenomegaly; MR = mental retardation; PPK = palmoplantar keratodermas; SLE = systemic lupus erythematosus; XLR = X-linked recessive.

3.26 Lipodystrophy

CONGENITAL GENERALIZED LIPODYSTROPHY (BERARDINELLI-SEIP)

- *BSCL2* gene (encodes nuclear lamins). Generalized lipodystrophy
- Lack both subcutaneous fat and extracutaneous adipose tissue
- Often, acanthosis nigricans, hypertrichosis, generalized hyperpigmentation, and thick, curly scalp hair
- Patients have voracious appetites, perspire excessively, and may be heat-intolerant despite normal thyroid function (elevated basic metabolic rate)
- Muscles, genitalia appear hypertrophic
- Mental retardation is common
  - Laboratory and internal disease
    - Glucose intolerance (lipoatrophic diabetes); insulin resistance detected earlier than diabetes
    - Hepatomegaly resulting from increased fat; cirrhosis may develop
    - Renal, retinal, and neuropathic diabetic changes
    - CT and ultrasound show reduced fat around viscera
    - Eruptive xanthomas may appear
  - Treatment
    - No effective treatment

ACQUIRED GENERALIZED LIPODYSTROPHY (LAWRENCE SYNDROME)

- AR; type I (*AGPAT* gene). Type II (*BSCL2* gene)
- Onset in childhood/adolescence/early adulthood ± preceding panniculitis/autoimmune connective tissue disorder; features similar to Bernardinelli-Seip

FAMILIAL PARTIAL LIPODYSTROPHY (DUNNIGAN)

- Type 1: Kobberling. Type 2: Dunnigan, AD, *LMNA* (nuclear lamins A/C). Type 3: *PPARG* gene mutation
- Symmetric lipoatrophy of trunk and limbs (sparing neck, shoulders, buffalo hump area, genitalia), tuberoeruptive xanthomas, acanthosis nigricans, hypertriglyceridemia

ACQUIRED PARTIAL LIPODYSTROPHY (BARRAQUER-SIMONS SYNDROME)

- Sporadic or AD; *LMNB2* gene mutation
- Loss of subcutaneous fat in clearly demarcated, generally symmetric areas

- **Begins on face,** spreads downward, stopping at any level → face become cachectic, with disappearance of buccal fat pads; **premature aged expression;** sunken eyes; easy visualization of veins
- Lower part of body may be affected without upper part being affected
- **Excess fat deposition over hips and thighs frequently in women**
- 80% female, and usually begins before age 15 years
  - Laboratory
    - Hypertriglyceridemia and insulin resistance
    - Clinically apparent diabetes in 20%
    - **Decreased serum complement (C3)**
    - **Increased C3 nephritic factor → immunoglobulin that binds factor H, an inhibitor of C3, allowing uncontrolled C3 activation**
    - **Glomerulonephritis (unknown frequency)**
  - Treatment
    - No effective therapy

LEPRECHAUNISM (DONOHUE SYNDROME)

- AR, insulin receptor gene mutation; generalized lipodystrophy and elfin facies; death in infancy

FAMILIAL MULTIPLE LIPOMATOSIS

- AD. Multiple lipomas of the upper and lower extremities

3.27 Hyperlipoproteinemias

TYPE I

- Familial lipoprotein lipase deficiency (AR) or apolipoprotein CII deficiency
- **Increased chylomicrons**
- Eruptive xanthomas, lipemia retinalis
- Associated with hepatomegaly, pancreatitis, abdominal pain ("horrible, screaming pain")

TYPE IIA

- Familial hypercholesterolemia, common hypercholesterolemia (AD)
- Increased low-density lipoprotein (LDL)
- **Tendinous,** tuberous xanthelasmas; arcus juvenilis; planar, eruptive xanthomas
- Secondarily caused by hepatoma, obstructive biliary disease, porphyria, hypothyroidism, anorexia, nephrotic syndrome, Cushing's
- Atherosclerosis

TYPE IIB

- Familial hypercholesterolemia (AD)
- Increased LDL and very low-density lipoprotein (VLDL)
- **Tendinous,** tuberous xanthelasmas; arcus juvenilis; planar xanthomas
- Secondarily caused by nephrotic syndrome and Cushing's syndrome
- Atherosclerosis

TYPE III

- Familial dysbetalipoproteinemia (AR)
- Increased intermediate-density lipoprotein (IDL)
- **Palmar,** planar, tendinous, tuberous, eruptive, intertriginous xanthomas
- Secondarily caused by paraproteinemia
- Atherosclerosis
- Associated with diabetes, gout, and obesity

TYPE IV

- Familial hypertriglyceridemia (AD)
- Increased VLDL
- Eruptive, tendinous, tuberous xanthomas
- Secondarily caused by diabetes, uremia, paraproteinemia, alcoholism, lipodystrophy, obesity
- Atherosclerosis

TYPE V

- Familial type V hyperlipoproteinemia, familial lipoprotein lipase deficiency (AD)
- Increased chylomicrons and VLDL
- Eruptive xanthomas, lipemia retinalis
- Secondarily caused by diabetes, obesity, and pancreatitis
- Associated with hepatomegaly

3.28 Disorders of the Hair And Nails

HAIR SHAFT ABNORMALITIES WITH FRAGILITY

- Trichorrhexis nodosa
- Monilethrix
- Pseudomonilethrix
- Trichorrhexis invaginata
- Pili torti
  - Menkes kinky hair syndrome
    - XLR
    - Mutations in gene encoding Cu^{2+}-transporting ATPase, α-polypeptide
    - Pili torti (occasionally trichorrhexis nodosa) with pigmentary dilution of skin and hair
    - Progressive, severe neurological deterioration secondary to copper accumulation, intracranial hemorrhage, growth retardation, and Wormian bones
    - Serum copper

TIP

Tyrosinase is a copper-dependent enzyme

  - Bazex
  - Rombo
  - Crandall
  - Björnstad
- Pili bifurcati
- Trichothiodystrophy (Tay syndrome)
  - Defective DNA repair involving *ERCC2*/xeroderma pigmentosum complement group D (XPD) (and rarely *ERCC3*/XPB)
  - AR
  - Variable clinical features (BIDS, IBIDS, PIBIDS):
    - Photosensitivity (±), overlap with XPD (XPB)
    - Ichthyosis (±), erythrodermic or eczematous, may present as collodion baby
    - Brittle hair, sulfur-deficient trichoschisis ("tiger tail" alternating bands of light and dark)
    - Intellectual impairment
    - Decreased fertility
    - Short stature
  - Variable nail abnormalities, cataracts, recurrent infection, microcephaly, hypogammaglobulinemia, and hypogonadism
- Marie-Unna hypotrichosis
- Hypotrichosis simplex

HAIR SHAFT ABNORMALITIES WITHOUT FRAGILITY

- Pili annulati
- Woolly hair
- Uncombable hair
- Loose anagen syndrome

NONSCARRING ALOPECIAS WITHOUT HAIR SHAFT ABNORMALITIES

- Congenital triangular alopecia
- Papular atrichia
  - AR
  - Defect in human homolog of mouse hairless gene
  - Generalized atrichia following loss of natal hair, cysts on elbows and knees with generalized papillary lesions

Figure 3.28.1 Congenital triangular alopecia.

ECTODERMAL DYSPLASIAS

- Anhidrotic ectodermal dysplasia (Christ-Siemens-Touraine syndrome)
  - XLR
  - Defect in ectodysplasin-A (*EDA*) gene
  - Sparse hair, periorbital wrinkling and hyperpigmentation, decreased sweat glands with heat intolerance, absent or conical teeth, normal nails, characteristic saddle nose facies and prominent lips
  - Impaired mucosal secretions with decreased tearing, ozena, otitis, pharyngitis
  - AD form with clinical features similar to X-linked recessive form secondary to a defect in ectodysplasin anhidrotic receptor (*EDAR*) gene
  - May have collodion membrane
- Hypohidrotic ectodermal dysplasia with immune deficiency
  - AD/AR
  - Defect in IKK-γ (*NEMO*) gene
  - Decreased eccrine glands with hair and teeth abnormalities, dysgammaglobulinemia with recurrent infections

p63 ECTODERMAL DYSPLASIAS

- Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome (EEC)
  - AD
  - Defect in *p63* gene
  - **Lobster claw deformity** (ectrodactyly), sparse hair and eyebrows/lashes, hypodontia, and micronychia associated with clefting. Kidney, eye, and endocrine abnormalities may coexist
- Ankyloblepharon, ectodermal defects, cleft lip/palate syndrome (AEC syndrome, Hay-Wells syndrome)
  - AD
  - Defect in *p63* gene
  - Ankyloblepharon filiforme adnatum, decreased sweating with abnormal teeth/nails and sparse hair, cleft lip/palate, collodion membrane or erosions at birth
  - **Erosive scalp dermatitis,** hypospadias, cup-shaped ears
- Anhidrotic ectodermal dysplasia, cleft lip, and cleft palate (Rapp-Hodgkin syndrome)
  - AD
  - Defect in *TP63* (*p63*) gene
  - Hypohidrosis, hypodontia, alopecia, small nails with cleft lip/palate, short stature
  - Characteristic facies with **maxillary hypoplasia** and high forehead, atretic ear canals, absent 1/3 lateral eyebrow
- Hidrotic ectodermal dysplasia (Clouston syndrome)
  - AD
  - Defect in *GJB6* gene encoding connexin-30
  - Decreased to absent hair with variable hair shaft abnormalities, palmoplantar keratoderma, nail dystrophy, normal teeth and sweating, mental retardation and eye abnormalities, tufting of terminal phalanges, and thickened skin/bones can occur
  - Oculo-dental-digital dysplasia

DISORDERS OF FOLLICULAR PLUGGING

- Keratosis pilaris
- Keratosis pilaris atrophicans
- Keratosis follicularis spinulosa decalvans (KFSD)
- IFAP (ichthyosis follicularis, atrichia, photophobia) syndrome

NAILS

- Congenital malalignment of the great toenail
  - Lateral deviation of first toenail nail plate (usually bilateral)
  - May resolve spontaneously
- Nail-patella syndrome
  - AD
  - *LMX1B* gene defect
  - Hypoplastic or aplastic nails (elbow and iliac horn abnormalities), triangular or absent lunulae
  - Hypoplastic or absent patella, elbow abnormalities, small joint hyperextensibility, renal disease, glaucoma, and other ophthalmologic abnormalities
- Congenital onychodysplasia of the index fingers (COIF)
  - Characterized by various types of dystrophy of the second fingernails
  - May be associated with underlying bony anomalies

- Pachyonychia congenita
  - AD
    - Type I (Jadassohn-Lewandowsky) caused by defect in keratins 6a and 16
    - Type II (Jackson-Lawler) caused by defect in keratins 6b and 17
  - Thick hyperkeratotic nails, palmoplantar keratoderma, hyperhidrosis, keratotic papules (intraoral and on extremities)
  - Type 1 is associated with **benign oral leukokeratosis,** not premalignant
  - Type 2 is associated with **steatocystoma multiplex,** epidermal inclusion cysts and amyloid deposition, cataracts, microphthalmia, and natal teeth
- Dyskeratosis congenita (Zinsser-Cole-Engman syndrome): See Section 3.22

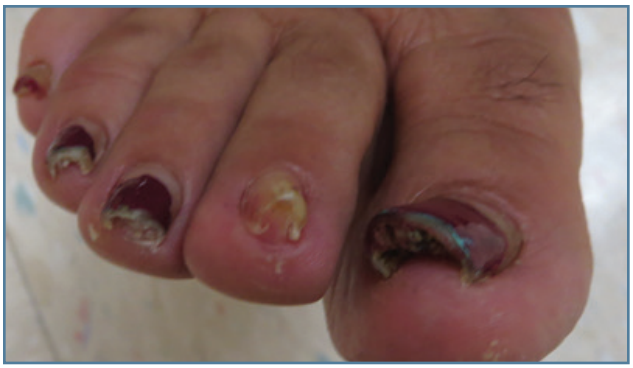

Figure 3.28.2 Pachyonychia congenita.

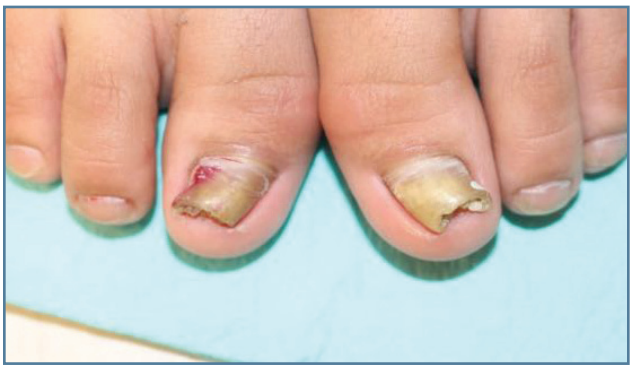

Figure 3.28.3 Congenital malalignment of the toenail.

3.29 Porphyrias

PORPHYRINOGENS

- Building blocks of hemoglobin and cytochrome enzymes
- In porphyrias, intermediate metabolites of hemoglobin synthesis are increased
- Photosensitivity in porphyria caused by absorption of UVR in Soret band (400-410 nm) by increased porphyrins → activated porphyrins unstable and transfer energy to oxygen, creating reactive oxygen species
- Pathway:
  - δ-Aminolevulinic acid (ALA) made in mitochondria via ALA synthetase
  - From ALA are formed (successively) porphobilinogen, uroporphyrin III, coproporphyrin III, and protoporphyrin IX, which enters mitochondrion and is converted to heme by ferrochelatase
  - Heme, by negative feedback, represses activity of ALA synthetase
  - If heme inadequate, ALA synthetase activity increases
  - Medications that increase cytochrome drug-metabolizing system in the liver exacerbate porphyrias by increasing production of porphyrin intermediates

PORPHYRIA CUTANEA TARDA (PCT)

- Uroporphyrinogen decarboxylase deficiency (sporadic in 80%), enzymatic activity abnormal only in liver and without mutations in the gene
- Familial PCT shows decrease in activity and amount of enzyme and presents earlier in life (before age of 20)
- **Most common type of porphyria**
- **Photosensitivity resulting in bullae, especially on sun-exposed parts (dorsal hands)**
- Bullae not surrounded by erythema
- Bullae heal with scarring, milia, and dyspigmentation
- Hypertrichosis on the face
- Sclerodermatous thickenings may develop on the back of the neck, preauricular areas, thorax, fingers, and scalp
- Direct relationship between levels of uroporphyrins in the urine and sclerodermatous
- changes
- **Liver disease frequently present:** Alcoholism, hepatitis C; iron overload in the liver of hemochromatosis carriers

- Associated diseases: Diabetes in 15%, lupus erythematosus, HIV; treatment with estrogens
- **Histology: Minimal inflammatory infiltrate, fibrin cuffing (PAS$^+$) of vessels is type IV collagen, caterpillar bodies in epidermis, festooning of papillary dermis at base of blister**
- **Direct immunofluorescence (DIF): Linear IgG, IgM, IgA, C3, fibrinogen at basement membrane and around vessels**
- **Indirect immunofluorescence (IIF): Negative**
- Test
  - Urine: Pink/coral-red under Wood's lamp
  - 4-hr urine: Elevated porphyrins → uroporphyrins: coproporphyrins 3:1 or greater
  - Low coproporphyrin in stool
- Treatment
  - Removal of all precipitating environmental agents such as alcohol and medications
  - Sun protection; chemical sunscreens help little as they don't absorb at necessary wavelengths; physical sunscreens may be more helpful
  - Phlebotomy (2-week intervals), to reduce iron levels
  - Low-dose antimalarials
  - Treatment of hepatitis C virus (HCV)

PSEUDOPORPHYRIA

- Normal urine and serum porphyrins
- No hypertrichosis, dyspigmentation, and sclerodermoid changes
- **Most commonly caused by medications:** Naproxen (and other nonsteroidal antiinflammatory drugs [NSAIDs]), nalidixic acid, tetracycline, furosemide (Lasix), thiazides, furosemide, cyclosporine, etretinate, isotretinoin, amiodarone, pyridoxine, dapsone
- Sunbeds, patients on hemodialysis
- Treat by discontinuation of medication

MNEMONIC

Pseudoporphyria Drugs

Not Till After Last Night's Party Dude

Nalidixic **A**cid
Tetracycline
Lasix
Naproxen
Pyridoxine
Dapsone

CONGENITAL ERYTHROPOIETIC PORPHYRIA (CEP)

- Gunther's
- **Uroporphyrinogen III synthase** homozygous defect
- Presents soon after birth, with red urine
- Severe photosensitivity
- Redness, swelling, and blistering in sun-exposed areas with resultant scarring and **significant mutilation**
- **Erythrodontia** of both deciduous and permanent teeth, and teeth fluoresce coral-red in Wood's lamp
- Hypertrichosis (werewolf)
- Other features: Growth retardation, hemolytic anemia, thrombocytopenia, porphyrin gallstones, osteopenia, and increased bone fractures
- Test
  - Dark urine and severe photosensitivity
  - **Elevated uroporphyrin I and coproporphyrin I in urine, stool, and red cells → distinguish from hepatoerythropoietic porphyria**
  - Stable red fluorescence of erythrocytes

HEPATOERYTHROPOIETIC PORPHYRIA (HEP)

- Autosomal recessive
- **Homozygous form of PCT**
- Homozygous or compound heterozygous deficiency of **uroporphyrinogen decarboxylase**
- **Clinically similar to congenital erythropoietic porphyria**
- Dark, red urine at birth
- Vesicles at **infancy,** followed by sclerodermoid scarring, hypertrichosis, pigmentation, red fluorescence of teeth under Wood's lamp, nail damage
- No treatment except sunscreen/sun avoidance
- Test
  - **CEP has elevated uroporphyrins in the RBCs, and HEP doesn't, but HEP has elevated RBC protoporphyrins**
  - Abnormal urinary uroporphyrins as in PCT
  - Elevated erythrocyte protoporphyrins
  - Increased coproporphyrins in feces

ACUTE INTERMITTENT PORPHYRIA (AIP)

- Deficiency in porphobilinogen deaminase, which has 50% activity in affected individuals
- Second most common form of porphyria

- Periodic attacks of colic, paralyses (motor neuropathy), and psychiatric disorders
- Attacks precipitated by drugs: Barbiturates, estrogen, griseofulvin, sulfonamides
- Attacks also precipitated by infection, fever, decreased caloric intake, alcohol, pregnancy, and menses
- **No skin lesions**
- Only 10% of those with genetic defect develop the disease, but all at risk for primary liver cancer
- Test
  - Elevated urinary porphobilinogen (Watson-Schwartz test)
  - Increased ALA in plasma and urine during attacks (levels only increased during attacks)
- Treatment
  - Avoid precipitating medications, starvation
  - Glucose loading
  - Oral contraceptives
  - Pain medications like phenothiazines, opiates, propoxyphene

VARIEGATE PORPHYRIA AND HEREDITARY COPROPORPHYRIA

- Clinical: Skin manifestations like PCT, with acute abdominal attacks like AIP
- Coproporphyrinogen oxidase deficiency (hereditary coproporphyria), protoporphyrin oxidase (variegate porphyria)
- Photosensitivity in 1/3
- Attacks of neurological and GI symptoms like AIP
- Acute attacks precipitated by same factors as AIP and VP
- Autosomal dominant
- Test
  - Fecal coproporphyrin always increased
  - Urinary coproporphyrins, δ-aminolevulinic acid (ALA), and porphobilinogen (PBG) increased only during attacks

TIP

Disease: Inheritance	Enzyme Defect
Acute intermittent porphyria: AD	Porphobilinogen deaminase
Congenital erythropoietic porphyria: AR	Uroporphyrinogen synthetase III
Porphyria cutanea tarda: sporadic and AD	Uroporphyrinogen decarboxylase
Hepatoerythropoietic porphyria: AR	Uroporphyrinogen decarboxylase
Hereditary coproporphyria: AD	Coproporphyrinogen oxidase
Variegate porphyria: AD	Protoporphyrinogen oxidase
Erythropoietic protoporphyria: AD and AR	Ferrochelatase

TIP

DDx of Noninflammatory Bullae

- PCT
- Pseudoporphyria
- Noninflammatory Epidermolysis bullosa acquista (EBA)
- Bullous diabeticorum
- Suction or friction bullae
- Epidermolysis bullosa (EB)
- Patient on dialysis

TIP

- Variegate porphyria has a characteristic emission peak at 626 nm
- Gallstones associated with erythropoietic protoporphyria
- No porphyrins in urine in erythropoietic protoporphyria
- No skin changes in acute intermittent porphyria

TIP

Distinguish variegate and hereditary coproporphyria by porphyrin profile: The latter should have much more coproporphyrin in urine and stool than the former

VARIEGATE PORPHYRIA

- Protoporphyrinogen oxidase decreased in activity
- Autosomal dominant with high penetrance
- Most people have silent disease
- Combination of skin lesions of PCT and GI/neurological disease of AIP, must be compared with PCT
- South African ancestry
- Attacks life-threatening
- Aggravated by drugs: Barbiturates, estrogen, griseofulvin, sulfonamides
- Aggravated by infection, alcohol, pregnancy, and decreased caloric intake
- Treat with glucose loading, hematin infusion during attack, avoidance of drug precipitators, and sunscreen/sun avoidance
- Test
  - Fecal coproporphyrins and protoporphyrins are always elevated, with proto > copro
  - Urinary coproporphyrins increased over uroporphyrins, distinguishing disease from PCT
  - Plasma fluoresces at 626 nm → diagnostic (seen only in active disease)

ERYTHROPOIETIC PROTOPORPHYRIA

- Ferrochelatase deficiency
- Usually presents in early childhood
- AD and AR inheritance
- **Immediate burning/stinging/pruritus of skin within minutes of sun exposure** → elevated protoporphyrin IX, absorbs in the Soret band and at 500-600 nm, and thus visible light through window glass can precipitate symptoms; protoporphyrin IX is the only oxidized porphyrin in the heme pathway
- Erythema, plaque-like edema, wheals, crust, and purpura can be seen in photodistribution
- Repeated exposure gives skin "weather-beaten" look
- Excessive porphyrins deposited in the liver, porphyrin gallstones are found, and livers are cirrhotic—may require liver transplantation
- Test
  - Urine porphyrins normal
  - Erythrocyte protoporphyrin elevated
  - DDx:
    - **Hydroa vacciniforme**
    - XP
    - Solar urticaria
- Treatment
  - Sun protection with barriers
  - β-Carotene
  - Psoralen-UVA (**PUVA**) photochemotherapy or narrow-band UVB (NB-UVB) to increase skin thickness and epidermal melanin

MNEMONIC

EPP **E**mpty **P**ee **P**ee

TRANSIENT ERYTHROPORPHYRIA OF INFANCY

- Occurs in infants exposed to blue lights for treatment of hyperbilirubinemia
- Symptom: Marked purpura in exposed skin
- All affected infants had received blood transfusions

THE BASIC HEME SYNTHESIS PATHWAY (DISTILLED DOWN)

1. Glycine + succinyl-CoA
2. δ-Aminolevulinic acid (via ALA synthase)
3. Porphobilinogen (via ALA dehydratase)
4. Hydroxymethylbilane (via porphobilinogen deaminase)
5. Coproporphyrinogen III (via uro decarboxylase)
6. Protoporphyrinogen (via copro oxidase)
7. Protoporphyrin IX (via proto oxidase)
8. Heme (via ferrochelatase)

TABLE 3.29.1 RADIOLOGIC FINDINGS IN GENODERMATOSES AND OTHER SYNDROMES

Findings	Associated Disease
Accordion hand	Multicentric reticulohistiocytosis
Asymptomatic dural calcification and choroid attachments	Papillon-Lefèvre
Bifid ribs	Nevoid basal cell carcinoma syndrome
Bilateral bean-shaped calcification of hippocampus	Lipoid proteinosis
Bilateral posterior iliac horns, radial head subluxation, hyperextensible joints, thickened scapula, absent patella, bilateral 1st rib hypoplasia	Nail-patella
Broad thumbs	Rubinstein-Taybi

TABLE 3.29.1 RADIOLOGIC FINDINGS IN GENODERMATOSES AND OTHER SYNDROMES CONTINUED

Findings	Associated Disease
Calcification of falx cerebri and basal ganglia	Nevoid basal cell carcinoma syndrome
Calcification of ligament, intracranial calcification (dura, falx, pineal, choroids)	Pseudoxanthoma elasticum
Calcification of tubers in basal ganglia	Tuberous sclerosis
Cerebellar, spinal, medullary hemangioblastomas	Von Hippel—Lindau
Chondrodysplasia punctata	Conradi-Hünermann
Clinodactyly	Down's, Cornelia de Lange, Russell-Silver
Congenital hip dislocation	EDS 7
Cystic defects in end of long bones and skull	Infantile fibromatosis
Double-contoured railroad tram-track calcification (meningeal angiomas)	Sturge-Weber
Dysostosis multiplex	Mucopolysaccharidosis
Erlenmeyer flask deformity	Gaucher
Enchondromas, metacarpals with phleboliths, chondrosarcomas	Maffucci
Hyperostosis of external auditory canal	Proteus syndrome
Hypoplastic thumbs, radii, ulnae	Rothmund-Thomson
Intracranial calcification	Cockayne, TORCH infections, dyskeratosis congenita
Lytic bone cysts of hands with honeycombed pattern	Sarcoid
Medulloblastoma	Nevoid basal cell carcinoma syndrome
Melorheostosis (linear hyperostosis under affected skin)	Linear scleroderma
Occipital horns (exostoses)	EDS 9, Menkes kinky hair disease
Osteomas in maxilla, mandible	Gardner
Osteomyelitis-like	Sweet's syndrome
Osteopathia striata (stripes on metaphases of long bones)	Focal dermal hypoplasia (Goltz syndrome)
Osteopoikilosis (round densities in long bones)	Buschke-Ollendorff syndrome
Phalangeal thickening with periosteal cysts	Tuberous sclerosis
Polyostotic fibrous dysplasia	McCune-Albright syndrome
Resorption of distal phalanges	Scleroderma
Sclerotic bone lesions	POEMS syndrome
Sphenoid wing dysplasia	Neurofibromatosis type 1
Supernumerary vertebrae with extra ribs	Incontinentia pigmenti
Thickening of calvarium	Clouston
Tufted phalanges	Clouston
Wafer-like calcification of cartilage (spine, pubis, ear, nose)	Alkaptonuria
Wormian bodies in sagittal suture and metaphyseal widening with spurs in long bones	Menkes kinky hair disease

EDS = Ehlers-Danlos syndrome; POEMS = polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; TORCH = toxoplasmosis, other agents, rubella, cytomegalovirus, herpes simplex.

TABLE 3.29.2 TOOTH FINDINGS IN GENODERMATOSES

Tooth Finding	Associated Disease
Anodontia	Hypomelanosis of Ito
Anodontia/pegged teeth	Incontinentia pigmenti
Dental pits	Tuberous sclerosis
Enamel dysplasia	Sjögren-Larsson, Herlitz JEB
Natal teeth	Pachyonychia congenita type II (Jackson-Lawler)
Odontogenic cysts	Nevoid basal cell nevus syndrome, Gardner syndrome
Odontoid hypoplasia	Down's and Hurler's syndromes
Odontomas and supernumerary teeth	Gardner syndrome
Peg-shaped conical incisors/canines, molars with hooked cusps	Anhidrotic ectodermal dysplasia
Periodontitis	Papillon-Lefèvre, Haim-Munk, Ehlers-Danlos type 8
Resorption of alveolar ridge (floating teeth)	Letterer-Siwe
Retention of primary teeth	Hyper-IgE syndrome

JEB = junctional epidermolysis bullosa.

MNEMONIC

Blue Sclerae

All DEMON Fly Past

Alkaptonuria
Downs
Ehlers-Danlos
Marfan
Osteogenesis imperfecta
Nevus of Ota

Fanconi's

Pseudoxanthoma elasticum

MNEMONIC

Angioid Streaks

APPLES

Anemia, sickle cell
Pseudoxanthoma elasticum
Paget's disease of the bone
Lead poisoning
Ehlers-Danlos
Sclerosis, tuberous

TABLE 3.29.3 EYE FINDINGS IN GENODERMATOSES

Eye Finding	Associated Disease
Angioid streaks (rupture of Bruch's membrane)	Pseudoxanthoma elasticum
Ankyloblepharon	CHANDS, Hay-Wells syndrome
Atypical retinitis pigmentosa (glistening dot)	Sjögren-Larsson
Blue sclerae	Osteogenesis imperfecta types 1, 2, and 3; Ehlers-Danlos syndrome
Blue sclerae, retinal detachment, ruptured globe, keratoconus	Ehlers-Danlos syndrome type 6
Blue to gray-blue eyes, prominent red reflex	Tyrosinase-negative albinism

TABLE 3.29.3 EYE FINDINGS IN GENODERMATOSES CONTINUED

Eye Finding	Associated Disease
Blue to yellow-brown eyes	Tyrosinase-positive albinism
Brushfield spots	Down syndrome
Cherry red spot	Niemann-Pick, Tay-Sachs, generalized sialidosis, Sandhoff syndrome
Choroid malformation	Sturge-Weber syndrome
Coloboma	Focal dermal hypoplasia
Comma-shaped corneal opacities	X-linked ichthyosis
Congenital hypertrophy of retinal pigment epithelium	Gardner syndrome
Corneal clouding, retinitis pigmentosa	Mucopolysaccharidosis
Corneal opacities, lipodermoid tumors	Epidermal nevus syndrome
Decreased corneal sensation to tear flow	Riley-Day syndrome
Dystopia canthorum with heterochromia iridis	Waardenburg syndrome
Ectopia lentis (downward)	Homocystinuria
Ectopia lentis (upward)	Marfan syndrome
Eyelid papillomas	Xeroderma pigmentosum
Eyelid string of pearls	Lipoid proteinosis
Glaucoma	Neurofibromatosis type 1, Sturge-Weber syndrome
Juvenile posterior subcapsular lenticular opacity	Neurofibromatosis type 2
Lester sign (hyperpigmentation of pupillary margin of iris)	Nail-patella syndrome
Lisch nodules, optic gliomas	Neurofibromatosis type 1
Optic atrophy	Biotinidase deficiency
Phakomas (astrocytic hamartomas of optic nerve)	Tuberous sclerosis
Pingueculae	Gaucher syndrome
Pseudoherpetic keratitis with blindness	Richner-Hanhart syndrome
Retinal hemangioblastomas	Von Hippel—Lindau syndrome
Retinitis pigmentosa (salt and pepper)	Refsum
Salt and pepper retina	Cockayne syndrome, Refsum syndrome

CHANDS = curly hair-ankyloblepharon-nail dysplasia syndrome.

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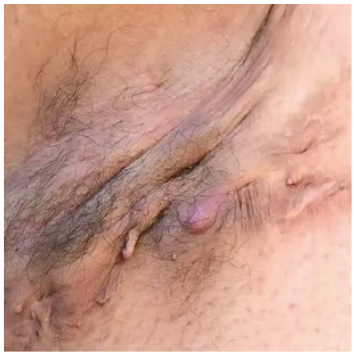
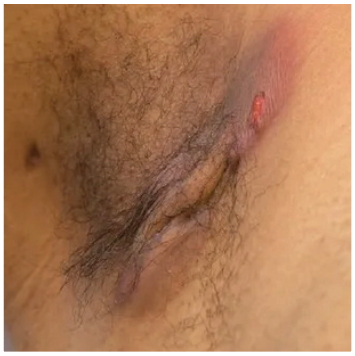
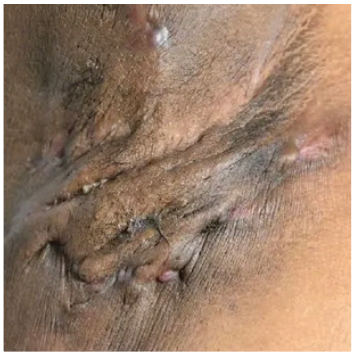
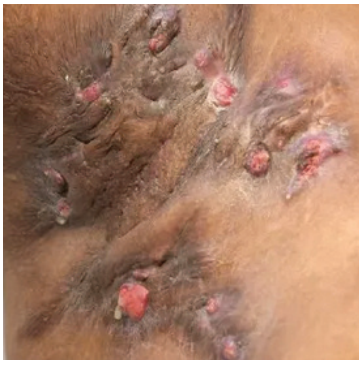
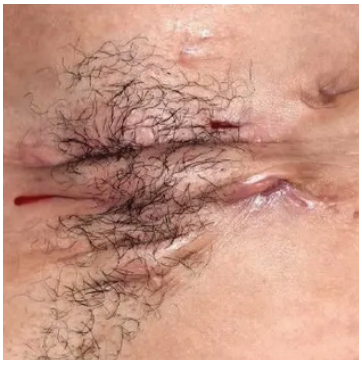

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SURGICAL DERMATOLOGY

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4.1 Procedural Dermatology

ANATOMY

Head and Neck

- Superficial musculoaponeurotic system (SMAS): Discrete fibromuscular layer enveloping and interlinking muscles of facial expression
  - **Large sensory nerves and blood vessels that supply the face lie within the SMAS or between the SMAS and subcutaneous fat**
  - Contribute to relaxed skin tension lines (RSTLs) perpendicular to muscle action
  - Role in facial expression
  - Galea aponeurotica of scalp and superficial temporal fascia: Thick SMAS
  - Rejuvenation procedures, such as facelifts, rely on redistribution and plication of SMAS
  - It extends from the temporalis muscles laterally to the platysma inferiorly, the trapezius posteriorly, and the frontalis superiorly
- Cranial nerve V (trigeminal nerve)
  - 3 branches, primarily sensory, but motor supply to muscles of mastication
    - Ophthalmic (V1)
      - Supratrochlear
      - Infratrochlear
      - Supraorbital
      - External nasal
      - Lacrimal
    - Maxillary (V2)
      - Infraorbital
      - Zygomaticotemporal
      - Zygomaticofacial
    - Mandibular (V3): Emerges from foramen ovale
      - Mental
      - Auriculotemporal
    - Damage = Frey's syndrome (see below)
      - Buccal
  - **Danger zones for the trigeminal nerve (CN V) during surgery**
    - Supraorbital rim in the mid-pupillary line
      - Injury to the supraorbital branch of V1
      - Lies anterior to the SMAS
      - Results in numbness of the forehead, upper eyelid, nasal dorsum, and scalp
    - 1 cm below the infraorbital rim in the mid-pupillary line
      - Injury to the infraorbital branch of V2, which lies anterior to the SMAS
      - Results in numbness of the nasal sidewall, cheek, upper lip, and lower eyelid
    - Mid-mandible below the second premolar injury to the mental branch of V3
      - Lies anterior to the SMAS
      - Results in numbness of ipsilateral lower lip and chin
  - Clinical correlation
    - Trigeminal trophic syndrome causes anesthesia, paresthesia, and erosion of the nasal ala (APE); results from injury or surgery that damages CN V at the gasserian ganglion, or due to encephalitis or leprosy (nasal alar erosion may clinically mimic basal cell carcinoma)
    - Frey's syndrome (auriculotemporal syndrome): Pain, vasodilation, and hyperhidrosis of the cheeks when eating (gustatory sweating); occurs following parotid gland surgery; thought to involve haphazard nerve regeneration whereby parasympathetic fibers rather than sympathetic fibers innervate the sweat glands and blood vessels of the skin
- Cranial nerve VII (facial nerve)
  - The facial nerve exits the stylomastoid foramen and courses through the parotid gland and bifurcates
  - **Provides motor innervation to the muscles of facial expression and sensory innervation to the conchal bowl and the anterior tongue; taste through chorda tympani branch; and tactile sensation through lingual nerve branch**

MNEMONIC

SCALP

Skin
Connective tissue
Aponeurosis (galea)
Loose connective tissue
Periosteum

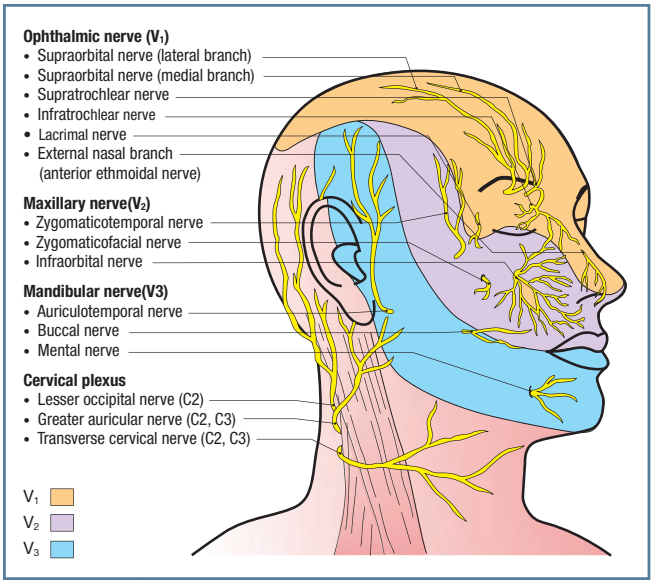

Figure 4.1.1 Sensory innervation of the face.

- The temporal and marginal mandibular are the branches most at risk during surgery because they have very superficial rami
  - Undermine in the superficial fat above the SMAS to avoid injury to the temporal branch
- The nerves innervate the facial muscles deeply at their undersurfaces, except for the buccinator, which is innervated at its superficial surface
- **Danger zones for the facial nerve (CN VII) during surgery**
  - Injury to temporal branch of CN VII
    - Rectangular box 2 cm in height extending from the lateral eyebrow to the anterior hairline contains temporal branch of CN VII
    - Lies beneath the SMAS
    - Results in inability to raise eyebrow or completely close the eye, flattening of the forehead

MNEMONIC

To remember the branches of the facial nerve: To Zanzibar By Motor Car

Temporal
Zygomatic
Buccal
Marginal mandibular
Cervical

  - Injury to the marginal mandibular branch of CN VII
    - Mid-mandible 2 cm posterior to the oral commissure
    - Lies beneath the SMAS
    - **Injury results in inability to pull the ipsilateral lower lip downward and laterally or evert the corresponding vermilion border → "crooked" smile, appreciated on smiling, but is not as apparent when the patient is at rest. Most at risk during liposuction and Kybella treatments**
  - Injury to zygomatic branch of CN VII
    - Causes eyelid ectropion and inability to close eyelid
  - Injury to buccal branch of CN VII
    - Inability to smile

TIP

Kybella (deoxycholic acid) is a novel agent approved for the treatment of submental fat, and cases of asymmetric smile or facial muscle weakness have been reported as a result of marginal mandibular nerve injury

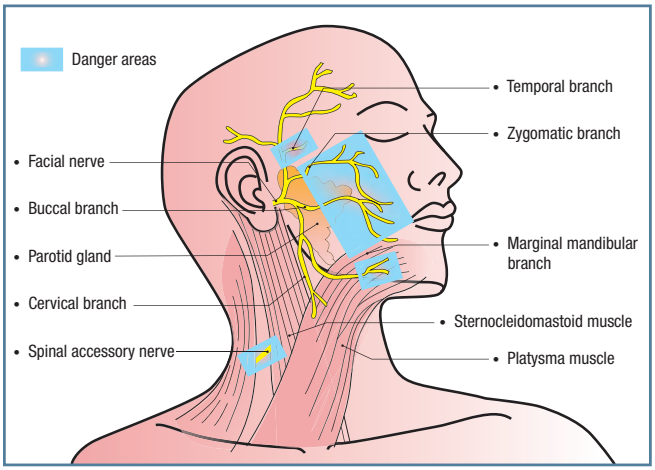

Figure 4.1.2 Facial nerve (CN7) branches and danger zones.

TABLE 4.1.1 CRANIAL NERVE VII BRANCHES AND MUSCLES SUPPLIED

Temporal Branch
• Frontalis muscle m. • Corrugator supercilii m. • Orbicularis oculi m. (superior portion) • Auricular m. (anterior and superior; also known as the temporoparietalis m.)
Posterior Auricular Branch
• Occipitalis m. • Auricular m. (posterior)
Zygomatic Branch

• Orbicularis oculi m. (inferior portion)
• Nasalis m. (alar portion)
• Procerus m.
• Upper lip muscles
  ▸ Levator anguli oris m.
  ▸ Zygomaticus major m.

Buccal Branch

• Buccinator m. (muscle of mastication)
• Depressor septi nasi m.
• Nasalis m. (transverse portion)
• Upper lip muscles
  ▸ Zygomaticus major and minor m.
  ▸ Levator labii superioris m.
  ▸ Orbicularis oris m.
  ▸ Levator anguli oris m.
• Lower lip muscles (orbicularis oris m.)

Marginal Mandibular Branch

• Lower lip muscles
  ▸ Orbicularis oris m.
  ▸ Depressor anguli oris m.
  ▸ Depressor labii inferioris m.
  ▸ Mentalis m.
• Risorius m.
• Platysma m. (upper portion)

Cervical Branch
• Platysma m.

- Sensory innervation of the ear
  - Posterior ear: Great auricular nerve
  - Conchal bowl: Vagus nerve
  - Cervical nerve 2 (C2) (lesser occipital) supplies sensory innervation to the scalp posterior to the ear and the superior portion of the posterior auricle
  - C2, C3 (great auricular) supplies sensory innervation to the skin overlying the parotid, the lower anterior ear, the lower posterior ear, and the mastoid process

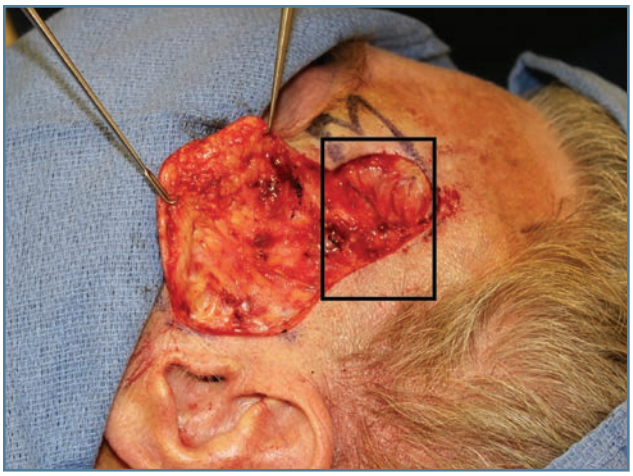

Figure 4.1.3 Temporal nerve danger zone in vivo. (Courtesy of Jesse M. Lewin, MD)

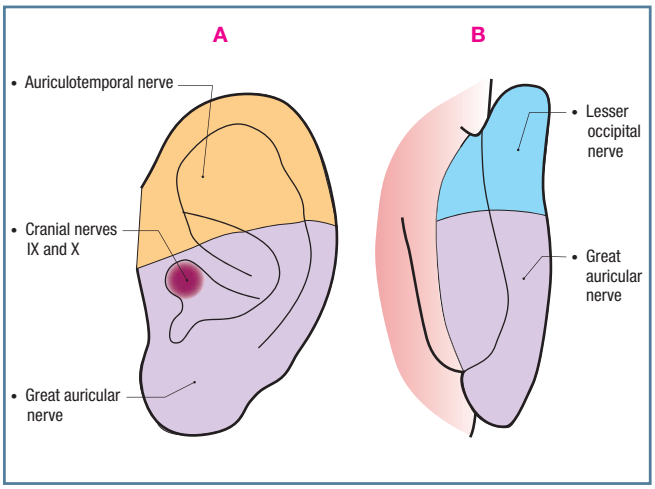

Figure 4.1.4 Sensory innervation of the ear.

- Sensory nerves of the neck and posterior scalp
  - Great auricular (C2, C3), lesser occipital (C2), greater occipital (C2), transverse cervical (C2, C3), supraclavicular (C3, C4)
  - The nerve supply to the lateral neck and posterior scalp is from the cervical plexus
  - C2 (greater occipital) supplies sensory innervation to the occipital scalp
  - C2, C3 (transverse cervical) supplies sensory innervation to the anterior portion of the neck
    - **Danger zones during surgery: Approximately 6.5 cm below the external auditory canal along the posterior border of the sternocleidomastoid muscle; injury to the great auricular nerve (C2, C3); lies posterior to the SMAS; results in numbness of the inferior two-thirds of the ear and the adjacent cheek and neck**

- C3, C4 (supraclavicular) supplies sensory innervation to the lower neck, clavicle, and shoulder

- Arterial blood supply of the face
  - Internal carotid artery (ICA) supplies eyelids, upper nose, nasal dorsum, forehead, scalp via ophthalmic branch
  - External carotid artery (ECA) supplies rest of face
  - The six major arteries supplying the face:
    - Facial: Angular artery anastomoses with dorsal nasal branch of ophthalmic artery in periocular region **(connection between the internal and external carotid arteries)**
    - Superficial temporal: Comes off the ECA, and palpable at the superior pole of the parotid gland; branches into the transverse facial and frontal arteries
    - Maxillary: Comes off the ECA, and branches into the infraorbital, buccal, and inferior alveolar (mental) arteries
    - Posterior auricular: Off the ECA
    - Occipital: Off the ECA
    - Ophthalmic: Comes off the ICA, and branches into the supraorbital, supratrochlear, palpebral, dorsal nasal, and lacrimal arteries; **this network anastomoses with the ECA, specifically, the angular artery anastomosis with the dorsal nasal branch**
  - Facial veins lack valves
  - Drain into cavernous sinus

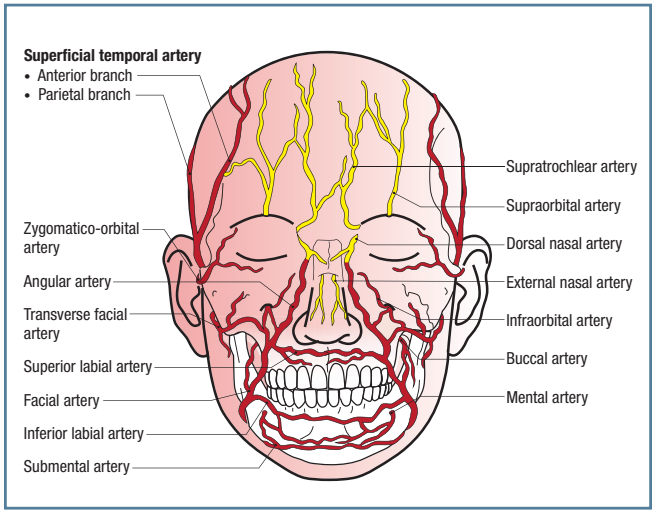

Figure 4.1.5 Arterial supply of the face and scalp.

Relevant Anatomy of the Trunk

- **Erb's point** near the mid-posterior sternocleidomastoid muscle helps locate the great auricular, lesser occipital, and spinal accessory nerve
- Spinal accessory nerve
  - Injury results in the inability to elevate the shoulder on the affected side, winged scapula, and the inability to initiate arm abduction
  - Spinal accessory nerve approx. 1 cm above Erb's point: Intersection of a line drawn 6 cm below mastoid process and posterior border of sternocleidomastoid muscle. Injury results in winged scapula decreased abduction (injury to C5/C6)

Anatomy of the Upper and Lower Extremities

- Legs and feet
  - Sural nerve: Innervates the posterolateral sole
  - Posterior tibial nerve: Innervates the anteromedial sole
  - Deep peroneal nerve: Innervates the great toe and toe cleft between 1st and 2nd toes
  - Superficial peroneal nerve: Innervates the dorsum of the foot
  - Nerve blocks of the posterior tibial and sural nerves may be performed prior to excisional surgery on the feet (Figure 4.1.7)

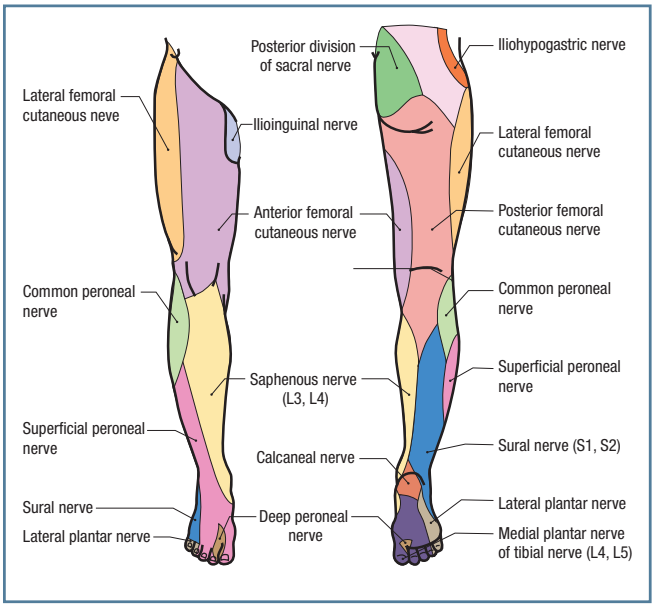

Figure 4.1.6 Sensory innervation of the leg and foot.

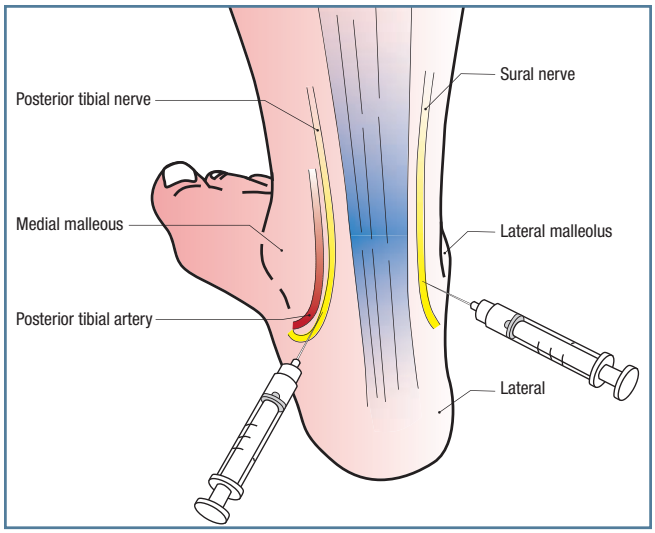

Figure 4.1.7 Nerve block for the foot.

- Hands
  - Median nerve: Originates from brachial plexus, medial to the brachial artery and the biceps tendon, passes through carpal tunnel. Innervates thenar muscles
  - Radial nerve: Originates from brachial plexus, provides motor innervation to the dorsal arm muscles and the extensor muscles of the wrists and hands; cutaneous sensory innervation to dorsal hand, except for the 4th and 5th digits (innervated by the ulnar nerve)
  - Ulnar nerve: Originates from brachial plexus, provides cutaneous sensory innervation to the 4th and 5th fingers, motor innervation to hypothenar muscles

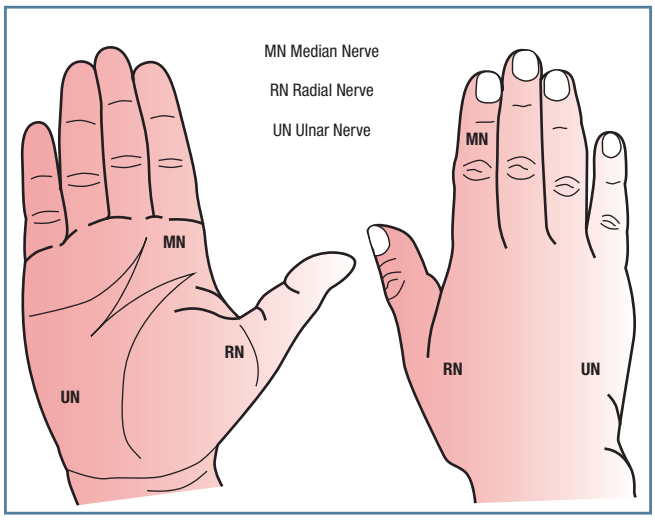

Figure 4.1.8 Motor innervation of the hand.

Genitals: External Topographic Anatomy

Melanoma and nonmelanoma skin cancers occur on the genitals, and it is important to have an understanding of the anatomy of these regions for surgical planning and execution of Moh's micrographic surgery (MMS) or excisional surgery.

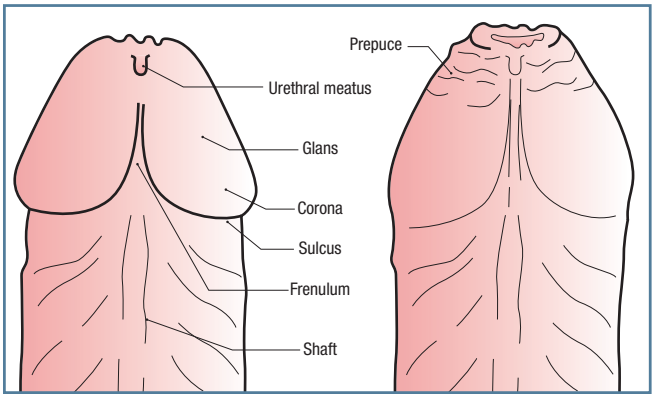

Figure 4.1.9 External anatomy of the penis.

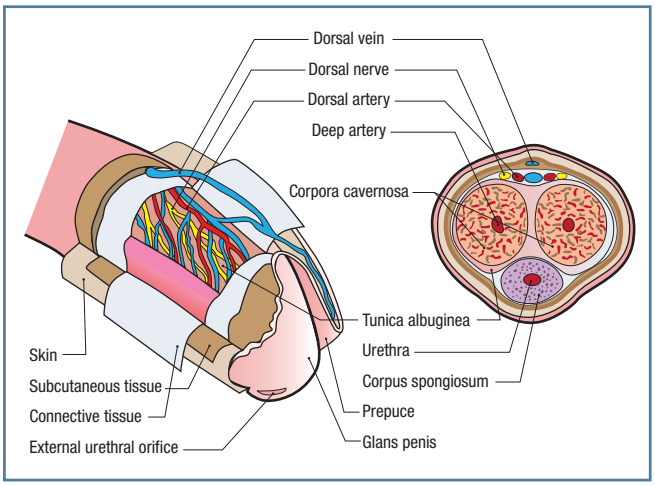

Figure 4.1.10 Internal anatomy of the penis.

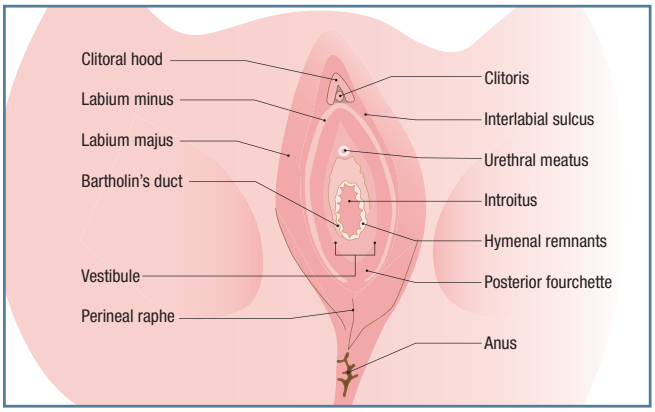

Figure 4.1.11 External anatomy of the vulva.

Nail Unit

The anatomy of the nail unit is important to understand in order to define the location of pathology based on clinical finding; and in order to perform nail biopsies (matrix, bed) and nail plate avulsions.

- The nail is composed of 5 major anatomic regions
  - Nail plate: Actual nail made up of tightly packed onychocytes
  - Proximal nail fold: Dorsal part of digit that lies adjacent to nail
  - Nail matrix: Epithelium that starts mid-distal phalanx, which generates the nail plate and determines the thickness of the nail plate; **keratinizes without a granular layer**
  - Nail bed: Thin epithelium immediately beneath nail plate; **absent granular layer**
  - Hyponychium: Epithelium that lies on the volar surface of digit
- **The nail plate grows distally after it emerges from the proximal nail fold**
- **Nail matrix keratinization occurs along an oblique and upward direction so that the proximal portion of the nail matrix gives rise to the dorsal nail plate while the distal portion produces the ventral nail plate. The distal portion of the nail matrix is visible as the lunula**

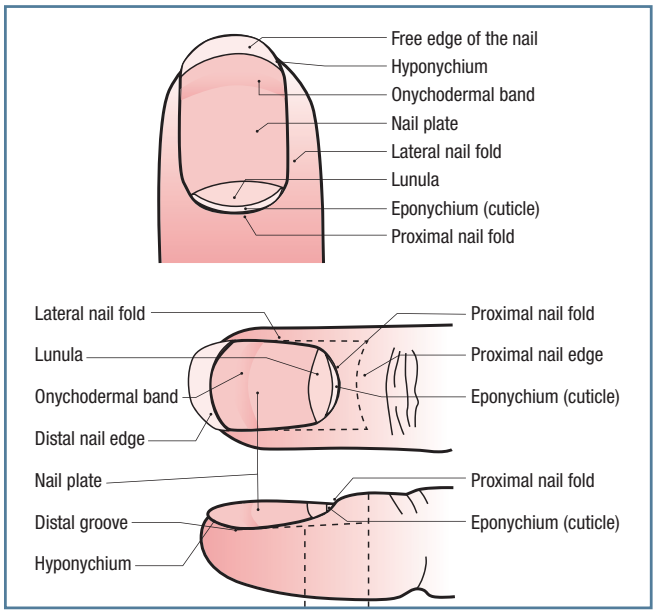

Figure 4.1.12 Topographic nail unit anatomy.

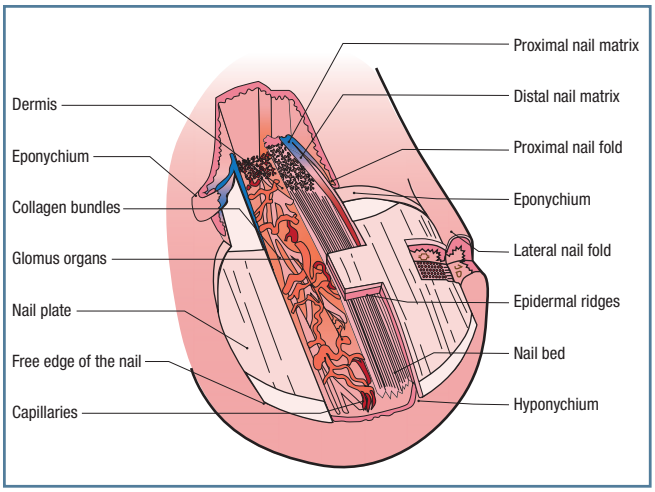

Figure 4.1.13 Subcutaneous nail unit anatomy.

INSTRUMENTS

Surgical Instruments

- Surgical scissors
  - Gradle: Delicate sharp tips, i.e., skin tag removal
  - Iris scissor: Tissue cutting
  - Baby Metzenbaum: Sharp or blunt undermining
  - Westcott and Castroviejo scissors: Delicate, spring-loaded tissue scissors with sharp tips, ideal for small delicate sites, e.g., eyelid

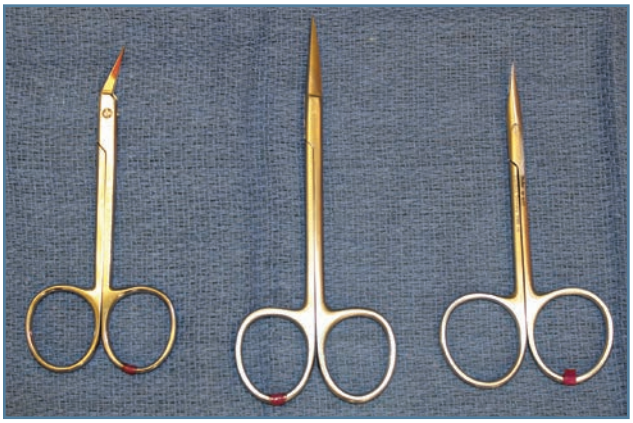

Figure 4.1.14 Surgical scissors (left to right): O'Brien, straight suture, Gradle.

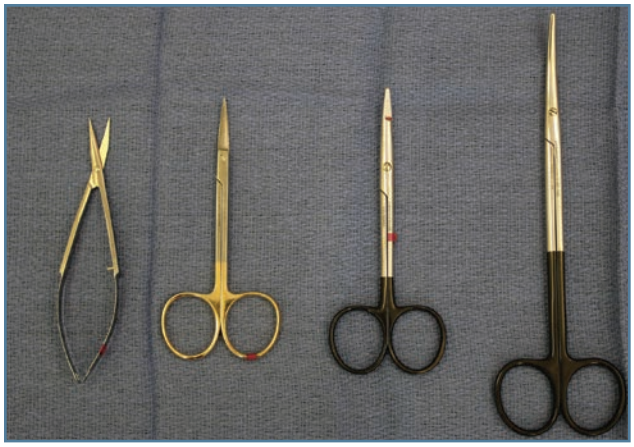

Figure 4.1.15 Surgical scissors (left to right): Westcott, iris (tungsten carbide), baby Metzenbaum, Metzenbaum.

Figure 4.1.16 Bandage scissor.

- Needle holders
  - Webster and Halsey needle holders: Either smooth or serrated jaws, ideal for small needles and fine suture material, e.g., facial reconstruction
  - Baumgartner and Mayo-Hegar holders: Larger, more durable needle holders for larger needles and suture material, e.g., trunk reconstruction

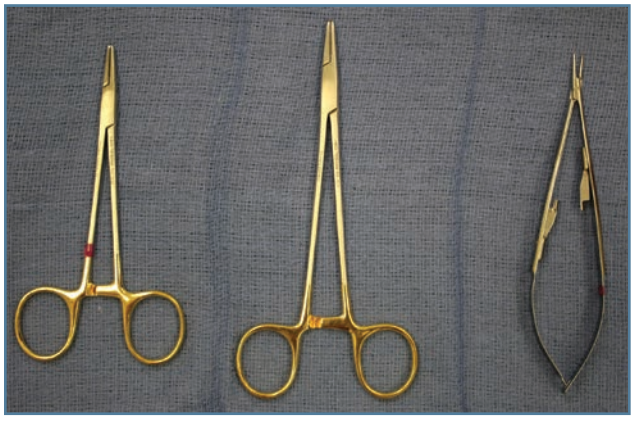

Figure 4.1.17 Needle holders (left to right): Halsey, Mayo-Hegar, Castroviejo.

- Scalpel handles and blades
  - Beaver blade handle: Can be rolled with one's fingertips, providing greater precision and control
  - #7 handle: Textured handle → better control and comfort because the cutting angle may be changed by rolling the handle with the fingers
  - #3 handle: Most frequently used in dermatologic surgery
  - Blades
    - #15 blade: Curved, used for most dermatologic surgery
    - #15c: Curved with finer tip, more delicate areas
    - #11 blade: Tapered sharp tip, for incision and drainage
    - #10 blade: Wide curved blade for larger excisions (e.g., back)

Figure 4.1.18 Scalpel handles (left to right): Round knurled handle, Beaver blade handle, #3 handle.

Figure 4.1.19 Blades used in dermatologic surgery (left to right): #10, #15, #15c, #11.

- Forceps
  - Adson forceps: Standard large forceps used for excisional surgery on the trunk and proximal extremities. Toothed or serrated
  - Bishop-Harmon and Foerster forceps are very lightweight, fine-tipped, and ideal for delicate work on the face and hand
  - Jeweler's forceps: Sharp tip, used for suture removal

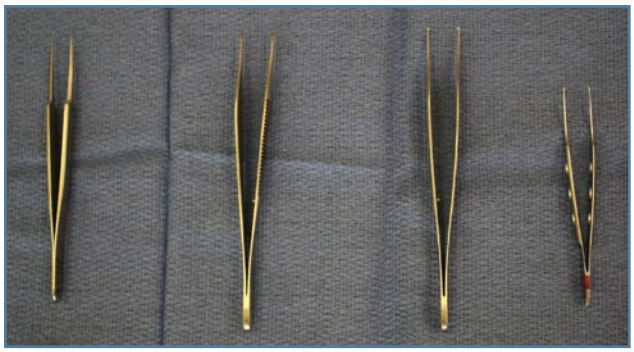

Figure 4.1.20 Forceps (left to right): Jeweler's forceps, Adson forceps without teeth, Adson forceps with teeth, Bishop-Harmon forceps.

- Nail surgery instruments
  - Freer septum elevator (nail elevator): Thin curved blades that facilitate atraumatic nail avulsion
  - English nail splitter: Cutting blade opposed to a flat anvil-like surface used for partial longitudinal nail avulsion
  - Double-action nail clipper: Cuts nail plates

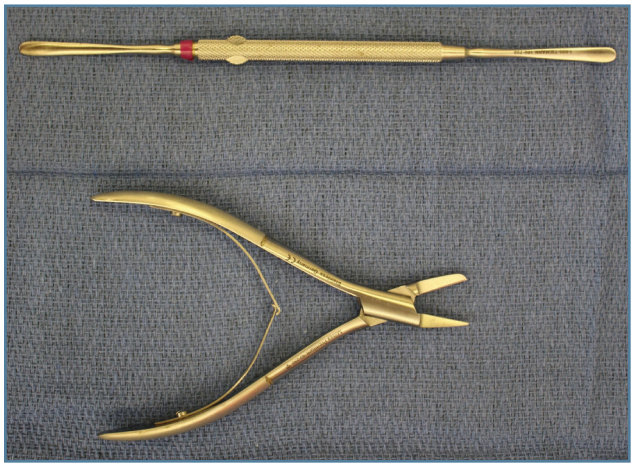

Figure 4.1.21 Nail surgery instruments (top to bottom): Nail elevator and English nail splitter.

- Other instruments used in dermatologic surgery
  - Skin hooks: Single or double pronged, used for elevating tissue atraumatically (e.g., undermining, elevating flaps)
  - Curette: Labeled by size, used for tumor removal and debulking (EDC, Mohs surgery)
  - Chalazion clamp: Immobilizing structures during procedures (ear, lip, eyelid)
  - Hemostats: Clamping vessels

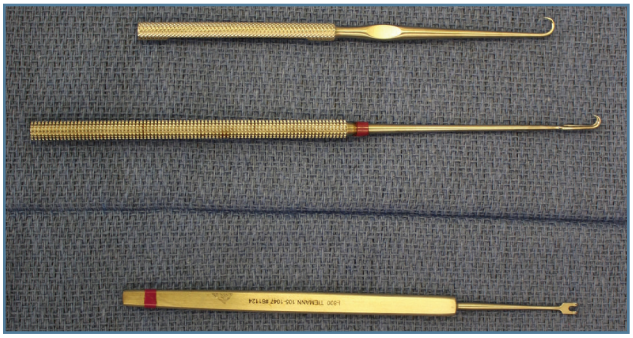

Figure 4.1.22 Single- and double-pronged skin hooks.

Figure 4.1.23 Fox dermal curette.

Figure 4.1.24 Chalazion clamp.

Figure 4.1.25 Mosquito hemostat.

Sutures

- Suture properties
  - Memory: Propensity of suture to maintain its natural configuration defines stiffness
  - Capillarity: Capacity of suture to absorb and transfer fluid
  - Elasticity: Ability of suture to regain its original form and length after deformation
  - Plasticity: Ability to stretch and maintain its new length
- Suture needles: Composed of stainless steel; the needle is divided into the **point, body, and shank;** the largest diameter of the needle determines the size of the suture track
  - Three types of needle points: Cutting, reverse cutting, round with tapered point
  - Most common shape for dermatologic surgery is 3/8 circle
  - Reverse cutting used most frequently in cutaneous surgery as the outside cutting edge is directed away from the wound edge, thereby minimizing the potential of the suture to tear through tissue
  - The number used to classify a suture specifies the diameter of that suture material that is required to produce a certain tensile strength; the smaller the cross-sectional diameter of a suture material, the higher the U.S. Pharmacopeia (USP) number that is assigned

TABLE 4.1.2 ABSORBABLE SUTURES

Suture	Origin	Filament	Absorption	Reactivity	Tensile Strength
Surgical gut	Animal collagen	Twisted	80 d	Moderate	Poor
Vicryl (polyglactin 910)	Copolymer of 90% glycolide and 10% L-lactide	Braided	50-80 d	Low	Good
Dexon (polyglycolic acid)	Polymer of glycolic acid	Braided	90 d	Low	Good
PDS (polydioxanone)	Polymer of polydioxanone	Monofilament	180 d	Low	Greatest; lasts longest
Maxon (glycolic acid)	Copolymer of glycolic acid and trimethylene carbonate	Monofilament	180 d	Low	Good
Monocryl (poliglecaprone 25)	Copolymer of glycolide and ε-caprolactone	Monofilament	90-120 d	Low	High memory or coil

TABLE 4.1.3 NONABSORBABLE SUTURES

Suture	Origin	Filament	Reactivity	Tensile Strength	Handling
Silk	Silk	Braided or twisted	High	0-50% at 1 yr	Mucosal/periocular; good
Ethilon	Nylon	Monofilament	Low	High	Poor
Dermalon	Nylon	Monofilament	Low	High	Poor
Prolene	Polypropylene	Monofilament	Least	Good	Poor
Dacron	Polyester	Braided	Low	High	Good
Ethibond	Polyester	Braided	Low	High	Good
Novafil	Polybutester	Monofilament	Low	High	Good

TABLE 4.1.4 IDENTIFYING VARIOUS TYPES OF NEEDLES

Needle Angle of Curvature	Body Type	Point Type
S: 1/8 circle	R: Round body	T: Trocar point
V: 1/4 circle	S: Cutting needle	N: Blunt point
D: 3/8 circle	L: Lancet needle	S: Sternum point
H: 1/2 circle		C: Short cutting point
F: 5/8 circle		M: Micropoint

Antiseptics and Instrument Sterilization

TABLE 4.1.5 ANTISEPTICS

Group	Spectrum	Class	Onset	Sustained Activity	Comments
Alcohol	$Gram^+$	Ethanol (ethyl alcohol), isopropanol (isopropyl alcohol)	Fast	None	No killing of spores, fungi, virus; antibacterial only; defats skin
Iodine	$Gram^+$, $Gram^-$	Halogen	Fast	None	May sensitize patient, allergic contact dermatitis (ACD)
Iodophor (Betadine)	$Gram^+$, $Gram^-$	Halogen	Moderate	Up to 1 hr	Absorbed through skin, must be dry to be effective, tissue damaging, inactivated by blood, ACD
Hexachlorophene (pHisoHex)	$Gram^+$	Phenol	Slow	Yes	Teratogen, neurotoxic
Chlorohexidine (Hibiclens)	$Gram^+$, $Gram^-$	Biguanide	Fast	Yes	Low skin absorption, irritates eyes, ototoxic
Benzalkonium	$Gram^+$, $Gram^-$	Cationic surfactant	Slow	None	Nonirritating to tissues

TABLE 4.1.6 INSTRUMENT STERILIZATION METHODS

Method	Advantages	Disadvantages
Steam autoclave	Most popular in office; easiest; safest	Must use 20-30 min at 2 atm pressure and 121°C; corrosive; may dull sharp instruments
Chemiclave	Lower humidity than steam; less dulling of sharp instruments; instruments are drier	Special chemical needed (mixture of formaldehyde, methyl ethyl ketone, acetone, and alcohols)
Dry heat (oven)	Inexpensive; no corrosion or dulling	High temperature, longer time (1 hr at 171°C; 6 hr at 121°C); cannot use cloth, paper, or plastic
Gas sterilization	Good for large volumes (mostly used in hospitals)	Expensive equipment; prolonged times (1 day for paper, 7 days for polyvinyl chloride); toxic, mutagenic gas
Cold sterilization (alcohol, detergent, quaternary ammonium, or more effective glutaraldehyde solutions)	Simple, inexpensive	Irritating to skin, not always effective against bacterial spores or hepatitis B virus

Dressings

TABLE 4.1.7 WOUND DRESSINGS

Dressing	Characteristics
Alginate (calcium alginate, seaweed)	Most absorptive, exudate turns into gel
Hydrocolloids (DuoDERM)	Fibrinolytic, promote angiogenesis, inhibit keratinocyte migration, antibacterial, increase healing rate, can cause surrounding maceration
Hydrofilms	Occlusive, allow gas and water vapor
Hydrogels	Good for dry, painful wounds
Foams	Absorptive

PREOPERATIVE CONSIDERATIONS

Prophylactic Antibiotics

- Infection rates in dermatologic surgery are low (0.07—4.25%)
- **Absolute indications: Artificial heart valve (mechanical, bioprosthetic, and homograft valves), artificial joint within 2 years, history of endocarditis, history of rheumatic fever (RF), mitral valve prolapse (MVP) with holosystolic murmur**
- Discretionary: Surgery on mucous membranes, open wounds greater than 24 hr, immunosuppression
- Prevention of surgical site infection includes oral antibiotic prophylaxis for procedures in sites at increased risk for infection
- High risk for surgical site infection: Lower extremity, groin, oral, wedge excision (lip or ear), flap surgery (nose or ear), skin graft anywhere on the body, extensive inflammatory skin disease, infected surgical site
- For prevention of infective endocarditis and hematogenous total joint infection
  - High-risk cardiac:
    - Prosthetic cardiac valve
    - Previous infective endocarditis
    - Cardiac transplant with cardiac valvulopathy
    - Congenital heart disease (unrepaired cyanotic defect, completely repaired defect with prosthesis within 6 months of placement, repaired defect with residual defect)
  - Low-risk cardiac:
    - Pacemaker, defibrillator
    - Mitral valve prolapse
    - Rheumatic heart disease
    - Aortic stenosis
    - Cardiac stent
  - High-risk joint:
    - Joint replacement within first 2 years
    - Previous prosthetic joint infection
    - Immunocompromised patients with prosthetic joints (inflammatory arthropathies like systemic lupus erythematosus [SLE] or rheumatoid arthritis [RA], diabetes mellitus [DM], HIV, malignancy, malnourishment, external beam radiation therapy [XRT]—induced immunosuppression, bone marrow transplant [BMT] recipients, chronic steroid users, after organ transplants)
  - Low-risk joint:
    - Orthopedic pins, plates, screws, total joint prostheses

TABLE 4.1.8 ANTIBIOTIC PROPHYLAXIS IN DERMATOLOGIC SURGERY GUIDELINES

Clinical Scenarios for Antibiotic Prophylaxis Recommended
1. High risk for prosthetic joint infection in a high-risk surgical site
2. High risk for infective endocarditis in a high-risk surgical site
3. High risk for infective endocarditis and breach of oral mucosa
Clinical Scenarios for Antibiotic Prophylaxis Considered
1. High risk surgical site
2. High risk for prosthetic join infection and breach of oral mucosa
High Risk Surgical Site
• Lesions below the knee • Lesions in the groin • Skin graft at any site • Wedge excision on the ear and lip • Flap surgery on the nose and ear
High Risk for Prosthetic Join Infection
• First 2 years following joint placement • Previous prosthetic joint infections • Immunocompromised/immunosuppressed patients • Diabetes (Type 1 and 2) • Patients on chemotherapy • Obesity • Tobacco exposure • HIV infection • Active malignancy • Malnourishment
High Risk for Infective Endocarditis
• Prosthetic cardiac valve • Previous infective endocarditis • Unrepaired cyanotic congenital heart disease • Completely repaired congenital heart defects <6 months after procedure • Repaired congenital heart disease with residual defects • Cardiac transplant patients with subsequent cardiac valvopathy
Prophylaxis Antibiotic Regimens
• Cephalexin 2G PO **OR** Amoxicillin 2G PO (if breach of oral mucosa) • If PCN Allergic: Clindamycin 600mg PO **OR** Azithromycin / Clarithromycin 500mg PO **OR** Levofloxacin 500mg PO (if below knee or in groin)

Anticoagulation in Dermatologic Surgery

- Retrospective review of 20,000 Mohs micrographic surgeries → bleeding complications occurred in 15.4% of cases
- Thrombotic complications occur in patients who discontinue anticoagulants for Mohs surgery (stroke, transient ischemic attack, myocardial infarction, unstable angina, deep vein thrombosis, pulmonary embolus, and death)
- Consensus guidelines are to continue medically necessary anticoagulant and antiplatelet medications, as bleeding complications are more easily corrected than thrombotic complications
- Many surgeons will check international normalized ratio (INR) in patients on warfarin

Antimicrobial Agents

- Postoperative wounds can be effectively and safely cared for with petrolatum-based ointment with equivalent efficacy for wound healing as a combination antibiotic first-aid ointment by creating a moist occlusive environment
- No difference in infection rates between postoperative wounds treated with topical antibiotics versus those treated with white petrolatum
- Topical antibiotics not necessary to achieve satisfactory wound healing and may cause allergic contact dermatitis
- Topical antibiotics may be used to treat bacterial wound infections not requiring systemic treatment

TABLE 4.1.9 TOPICAL ANTIBACTERIAL AGENTS

Type	Composed of:	Spectrum	Comments
Gentamicin		Gram$^-$	Resistance
Neomycin		Gram$^-$	No *Pseudomonas* coverage
Polymyxin B		Gram$^-$	*Pseudomonas* coverage
Bacitracin		Gram$^+$	Allergic contact dermatitis
Neosporin	Neomycin/bacitracin/polymyxin B	Broad	Allergic contact dermatitis
Polysporin	Bacitracin/polymyxin B	Broad	Allergic contact dermatitis
Bactroban	Mupirocin	Gram$^+$	Allergic contact dermatitis
Silvadene	Silver sulfadiazine	Broad	Reports of neutropenia and kernicterus; contact dermatitis in those with sulfa allergy

Anesthetics

- **Classified into two main classes, amides and esters, based on the linkage in the intermediate chain**
- Three portions of the chemical structure:
  - Aromatic ring: Responsible for onset of action
  - Intermediate (middle) chain: Determines class (amide vs. ester)
  - Terminal amine: Determines duration of action
- The amides are metabolized in the liver by the cytochrome P450 system
- Esters may cross-react with STPP (sulfa, thiazides, *para*-aminobenzoic acid, *para*-phenylenediamine)
- Block neural transmission by displacing calcium ions from receptor and control sodium permeability

TIP

- Prilocaine: Risk of methemoglobinemia (treat with methylene blue)
  - Methemoglobinemia also seen in patients on dapsone and with glucose-6-phosphate dehydrogenase (G6PD) deficiency—can use cimetidine with dapsone to decrease risk
- Bupivacaine: Cardiotoxicity
- Benzocaine: Safe in liver disease patients
  - Avoid benzocaine in patients allergic to *para*-phenylenediamine
- Tetracaine/bupivacaine: Longest acting
- Procaine: Shortest acting

TIP

- Bupivacaine, etidocaine, tetracaine (BET) have the longest durations of action
- Cocaine is the most vasoconstrictive anesthetic
- Digital tourniquets can be safely left on for 10-15 min

TIP

Esters are metabolized in the plasma by pseudocholinesterase and therefore should not be used in patients with pseudocholinesterase deficiency

TABLE 4.1.10 LOCAL ANESTHETICS

Name	Type	Metabolism	Onset	Duration without Epinephrine	Duration with Epinephrine	Pregnancy Category
Cocaine	Ester	Plasma	Rapid	45 min	n/a	C: Only vasoconstrictor
Procaine	Ester	Plasma	Rapid	15-30 min	30-90 min	B: Shortest duration of action
Tetracaine	Ester	Plasma	Slow	120-240 min	240-480 min	C
Lidocaine	Amide	Hepatic	Rapid	30-130 min	60-400 min	B
Bupivacaine	Amide	Hepatic	Slow	120-240 min	240-480 min	C: Most toxic
Mepivacaine	Amide	Hepatic	Rapid	30-120 min	60-400 min	C
Prilocaine	Amide	Hepatic	Slow	30-120 min	60-400 min	B
Etidocaine	Amide	Hepatic	Rapid	200 min	300 min	B

n/a = data not available.

- Symptoms of lidocaine toxicity are directly related to the serum lidocaine level
  - Signs and symptoms: Circumoral paresthesia; tinnitus; visual disturbances; metallic taste; seizures; coma; cardiopulmonary arrest
  - First sign is perioral tingling
  - Treatment of lidocaine toxicity depends on severity: Observation, airway support/oxygen, activate 911 system, CPR/life support for cardiopulmonary arrest
- Recommended maximum dose of lidocaine in adults:
  - 4.5 mg/kg without epinephrine; 7.0 mg/kg with epinephrine; 55 mg/kg used in tumescent anesthesia for liposuction
  - A 70-kg man can have ~50 ml max of 1% lido with epi (1:100,000). Calculations: 7mg/kg (max dose lidocaine with epi) X 70 kg (weight) / 10 mg/ml (concentration of 1% lidocaine) = 49ml
  - Recommended maximum dose of lidocaine in children is 1.5-2 mg/kg without epi; 3-4.5 mg/kg with epi
- Anesthetics work by blocking sodium influx in unmyelinated C-fibers
- On administration of anesthesia, the loss of sensation or function occurs in the following order: Temperature, pain, touch, pressure, vibration, proprioception, motor function
- Peak epinephrine activity: 5-10 min
- Epinephrine
  - Toxicity manifested by tremor, increased heart rate, diaphoresis, palpitations, headache, increase in blood pressure, and chest pain
  - Epinephrine drug interactions: Monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, phenothiazines, propranolol, amphetamines, digitalis
  - Epinephrine contraindications: Peripheral vascular disease, acute angle glaucoma, hyperthyroidism, pregnancy, severe hypertension, or cardiovascular disease
  - Local infiltrative anesthesia with epinephrine may be used in small amounts in women who are pregnant, but elective procedures and those not of urgent medical necessity requiring lidocaine with epinephrine should be postponed until after delivery
  - Procedures of urgent medical necessity should be delayed until the second trimester when possible. In case of doubt, consult with the patient's obstetrician. Strength of recommendation: Level of evidence: II-B
- Epinephrine prolongs duration of anesthesia and decreases lidocaine absorption, allowing higher amounts to be used
  - Max time to blanching: 5-30 min
- Parabens in an anesthetic can cause allergic contact dermatitis

- Allergy to lidocaine is rare (immunologic reaction represents only 1% of all adverse reactions)
  - True allergy to lidocaine → switch to an ester type of local anesthetic
- Anesthetic alternatives (can be used for small procedures such as shave biopsies)
  - Injection of 1% diphenhydramine (longer onset of action: 5 min vs. 1 min for lidocaine and limited efficacy)
  - Injection of bacteriostatic saline (0.9% benzyl alcohol in normal saline)
- Buffered lidocaine contains one part 8.4% sodium bicarbonate solution and 10 parts lidocaine with epinephrine (less painful since less acidic)
  - Anesthetics work better in alkaline pH and increase onset of action
- Topical anesthesia: EMLA is a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine; ELA- Max is composed of 4% lidocaine; unlike EMLA, ELA-Max does not need to be applied under occlusion to be effective. EMLA should not be used on infants younger than 3 months old because metabolites of prilocaine can form methemoglobin
- Nerve blocks
  - Regional cutaneous nerve block anesthesia is recommended for ablative laser resurfacing of the face and botulinum toxin injection of the palm
  - Nerve block should be considered as an alternative or in addition to infiltrative anesthesia for procedures on the face, hands, feet, and digits, and may provide the benefit of decreased tissue swelling/distortion, prolong anesthesia, and reduce postoperative discomfort for the patient

WOUND HEALING

- Wound healing involves the following phases, which occur as a continuum
  - Vascular phase: Occurs when the integrity of the skin is compromised. Involves an initial vasoconstriction followed by vasodilation. Net result is the formation of a hemostatic plug. Platelets are the first cells to appear after wounding. Platelets release fibrinogen, fibronectin, platelet-derived growth factor (PDGF)
  - Inflammatory phase (6 hr-10 days): Macrophages are the most important inflammatory cell in the wound-healing process. They are the only cells that can tolerate low oxygen tension. They secrete factors that stimulate angiogenesis, wound debridement, and collagen synthesis. Fibronectin is vital to healing. Produced by fibroblasts and endothelial cells. 6 hr-3 days: Polymorphonuclear cells (PMNs) infiltrate the wound and stimulate wound debridement and bacterial ingestion. Day 6: Lymphocytes infiltrate the wound.
  - Proliferative phase (24 hr- 14 days): Cells from the wound margin and the adnexa begin reepithelialization within the first 24 hr of injury. Fibronectin is believed to be important in this process. Occluded wounds will heal more rapidly because occlusion facilitates keratinocyte migration. Type III collagen is the first collagen to be synthesized in a wound. Then type I later on. Fibroblasts synthesize collagen, elastin, proteoglycans (PGs). Newly formed connective tissue consists of type I/III collagen and PGs (decorin, biglycan)/glycosaminoglycans
  - Wound contraction and remodeling (maturation phase): 10 days → 1 year. Tensile strength increases with time but never reaches more than 70-80% of the original strength of the skin prior to injury. Tensile strength is approximately 5% of its original strength at 1 week postoperatively and reaches 70% approximately 8 weeks after wounding. Contraction of wound greatest from 5 to 15 days mediated by myofibroblasts
  - Factors affecting wound healing: Poor surgical technique (excess tension), vascular disorders, tissue ischemia, infection, topical meds (steroids), hemostatic agents (aluminum chloride), dry wounds, malnutrition, systemic disease

TABLE 4.1.11 CHEMICAL MEDIATORS OF INFLAMMATION THAT PLAY A ROLE IN WOUND HEALING

Chemical Mediator	Action
Histamine	Increase vascular permeability
Serotonin	Stimulate fibroblast proliferation
Kinins	Increase vascular permeability
Prostaglandins	Increase vascular permeability, sensitize pain receptors, increase glycosaminoglycans (GAGs)
Complement	Increase vascular permeability, increase phagocytosis, mast cells, and basophil activity

FLAPS AND GRAFTS

Suturing and Wound Repair

- Basic principles of wound repair
  - Undermine tissue in order to minimize and/or eliminate wound tension
  - Meticulous hemostasis to avoid hematoma formation and other bleeding
  - Place incisions parallel to relaxed skin tension lines (RSTLs are created by the "tension vectors" of underlying muscle movement that is perpendicular to these lines), and in aesthetic junction lines (e.g., nasolabial fold, nasofacial sulcus, cheek-eyelid junction)
  - Length-to-width ratio of 3:1 for linear repairs (appropriate removal of standing cones) to facilitate tension-free closure

TIP

Endogenous factors that are crucial to wound healing, such as fibrin degradation products and PDGF, may be more available in moist environments such as moist dressed wounds

Figure 4.1.26 Relaxed skin tension lines (RSTLs) of the face.

Figure 4.1.27 Relaxed skin tension lines (RSTLs) of anterior trunk and extremities.

Figure 4.1.28 Relaxed skin tension lines (RSTLs) of posterior trunk and extremities.

- Apposition of the dermis with absorbable buried mattress sutures → tissue approximation and eversion, closes dead space
- Apposition of the epidermis with "top sutures"
  - **Simple interrupted or running sutures**
  - **Running locked stitch is used for wounds under tension and to provide hemostasis**
  - **Vertical mattress suture produces eversion and approximation of the skin edges, and it eliminates dead space**
  - **Horizontal mattress suture functions mainly to remove tension from the edges of a wound; it also assists with hemostasis**
  - **Running subcuticular suture (misnomer—truly intradermal): Avoids track marks since the suture does not cross the epidermis; best performed with polypropylene (nonabsorbable) or poliglecaprone or PDS (absorbable) due to the low coefficient of friction of these sutures**
- Other suturing techniques
  - Basting stitch anchors tissue to bed of wound; it ensures apposition of a full-thickness skin graft to the recipient bed
  - Suspension or tacking sutures secure skin/subcutis to periosteum or perichondrium to elevate an area, maintain a concavity, or alter the tension vector near a free margin

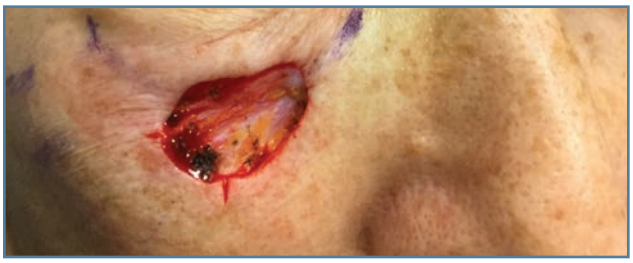

Figure 4.1.29 Post-Mohs defect of the right cheek-lid junction. (Courtesy of Jesse M. Lewin, MD)

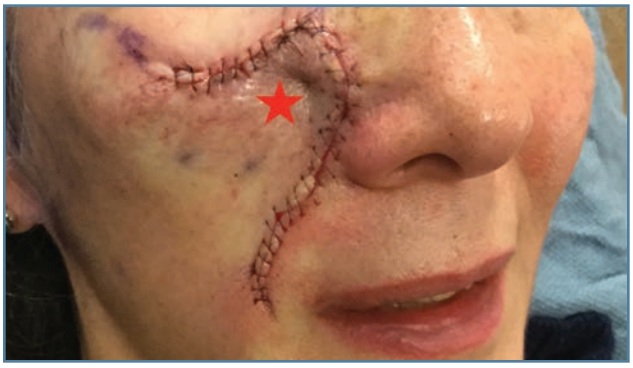

Figure 4.1.30 Inferiorly based rotation flap with dimpling at the site of a periosteal tacking stitch to the maxilla (red star)—used to support the weight of the flap and counteract downward forces. Over time this dimpling becomes imperceptible as the suture is resorbed. (Courtesy of Jesse M. Lewin, MD)

  - Tip stitch (also known as half-buried horizontal mattress suture) designed to align tissue at corner of a flap and prevent vascular compromise (i.e., bringing together more than two skin edges)
  - Deep tension-relieving stitches: Imbrication, plication, subcutaneous corset plication, percutaneous suspension
  - Stitches under extreme tension: Subcutaneous inverted cross mattress (SICM), double-butterfly, pulley stitch (far-near-near-far), modified winch

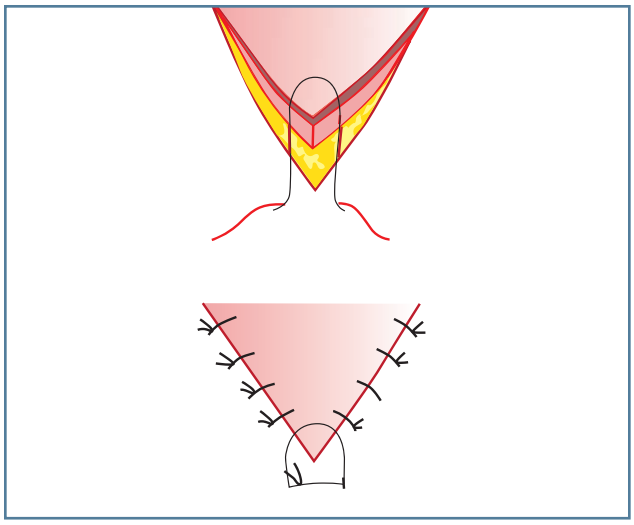

Figure 4.1.31 Tip stitch.

- Timing of suture removal
  - Face: 5-7 days
  - Neck/scalp: 10-14 days
  - Trunk extremities: 10-14 days
  - Legs/feet: 14-21 days
  - If sutures are left in too long they can leave track marks (hyperpigmentation at insertion points)

Flaps: Defined by Mechanism of Tissue Rearrangement

- **Advancement flaps**
  - O-T, A-T
  - Island pedicle flap or V-Y advancement flap
  - Unilateral or bilateral advancement flap
  - H-plasty
  - Burow's advancement flap
  - Anchor flaps
  - Helical rim advancement flap (Antia-Buch flap/chondrocutaneous advancement flap)
  - Crescentic advancement flap
  - East-west advancement flap
  - Mucosal advancement flap
  - Seagull flap
  - Peng flap

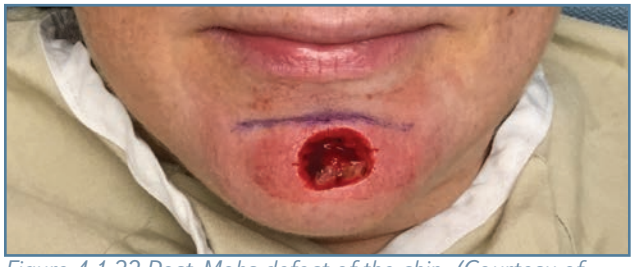

Figure 4.1.32 Post-Mohs defect of the chin. (Courtesy of Jesse M. Lewin, MD)

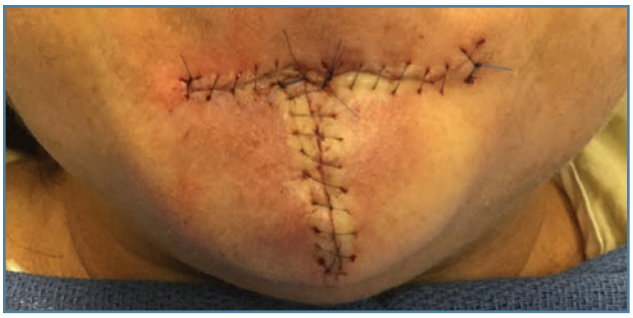

Figure 4.1.33 O-T or A-T advancement flap. (Courtesy of Jesse M. Lewin, MD)

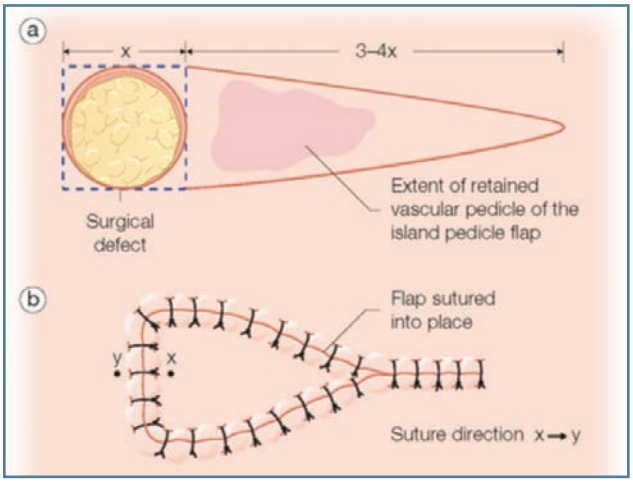

Figure 4.1.34 Schematic of island pedicle/V-Y advancement flap.

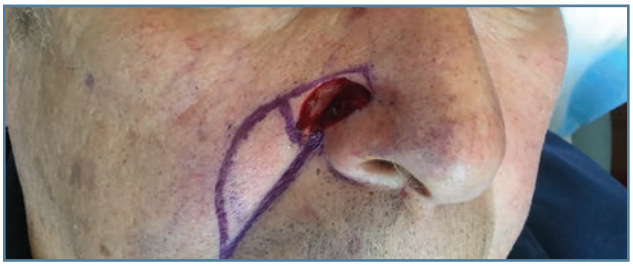

Figure 4.1.35 Post-Mohs defect of the right alar sulcus. (Courtesy of Jesse M. Lewin, MD)

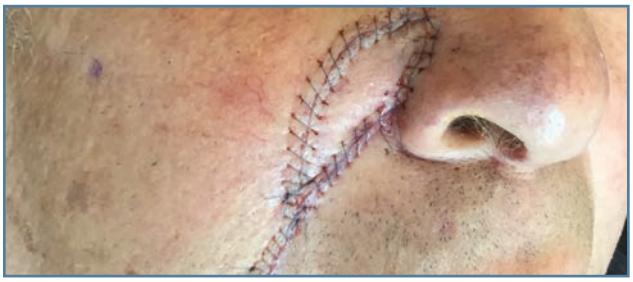

Figure 4.1.36 Island pedicle/V-Y advancement flap. (Courtesy of Jesse M. Lewin, MD)

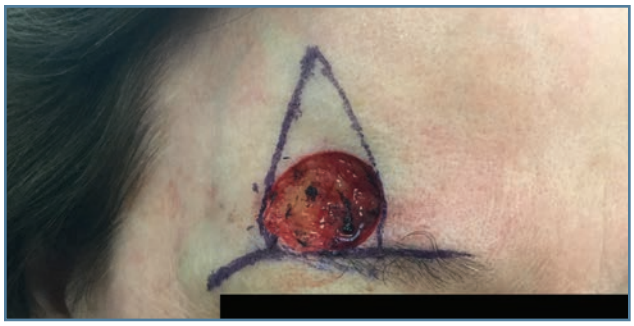

Figure 4.1.37 Post-Mohs defect of the right eyebrow. (Courtesy of Jesse M. Lewin, MD)

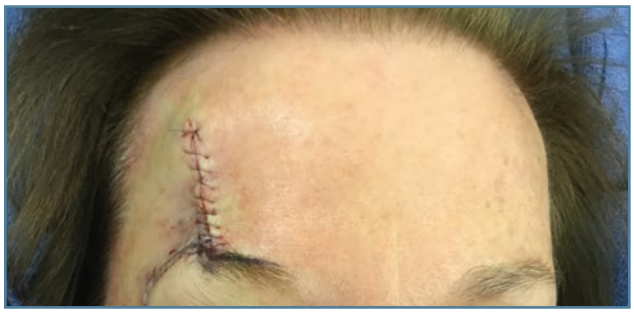

Figure 4.1.38 Unilateral advancement flap (O-L). (Courtesy of Jesse M. Lewin, MD)

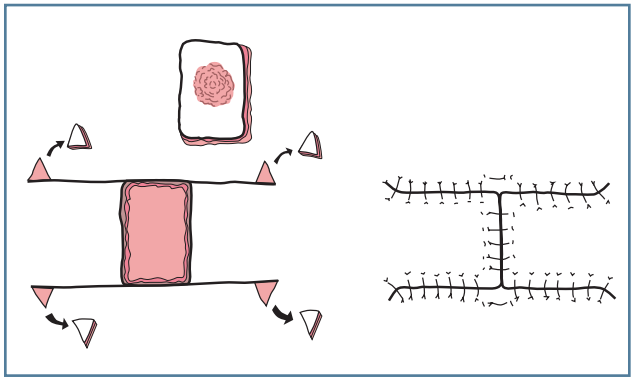

Figure 4.1.39 Schematic of H-plasty.

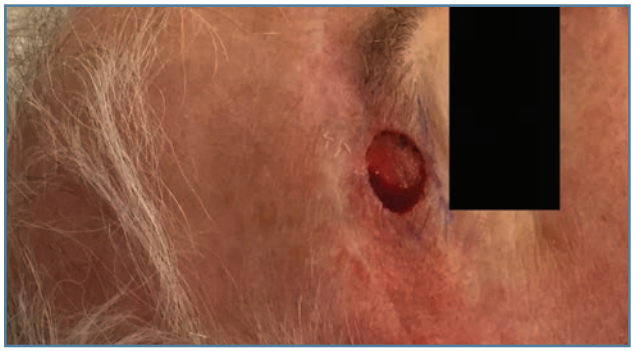

Figure 4.1.40 Post-Mohs defect of the right lateral eyebrow. (Courtesy of Jesse M. Lewin, MD)

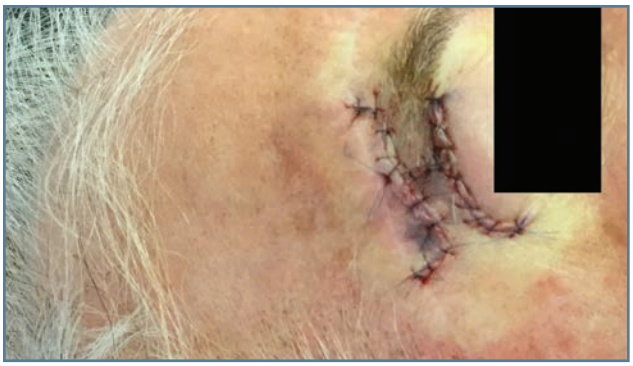

Figure 4.1.41 H-plasty. (Courtesy of Jesse M. Lewin, MD)

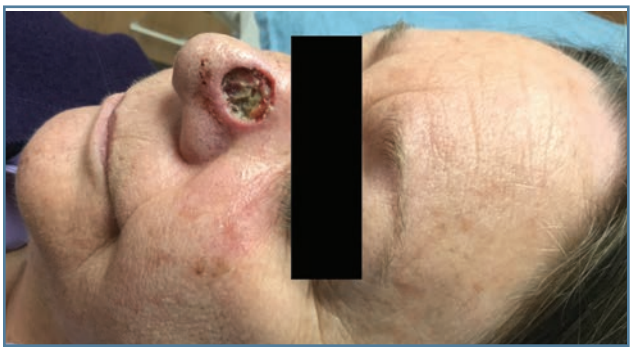

Figure 4.1.42 Post-staged excision defect of the left nasal ala and sidewall. (Courtesy of Jesse M. Lewin, MD)

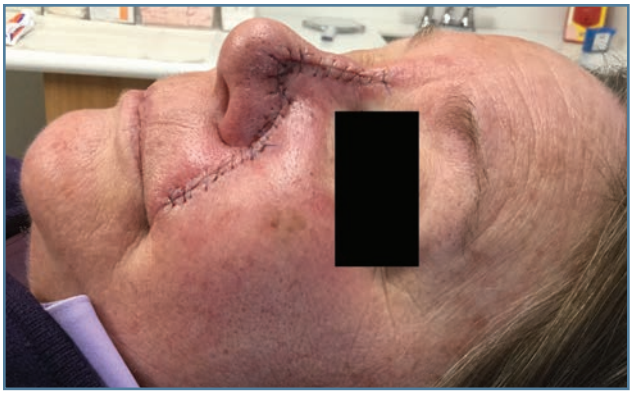

Figure 4.1.43 Crescentic advancement flap. (Courtesy of Jesse M. Lewin, MD)

- **Rotation flaps**
  - O to Z (also known as bilateral rotation flap)
  - Mustarde flap or laterally based cheek rotation
  - Back cut rotation flap
  - Spiral rotation flap
  - Dorsal nasal flap (also known as Rieger flap)
  - Glabella turndown

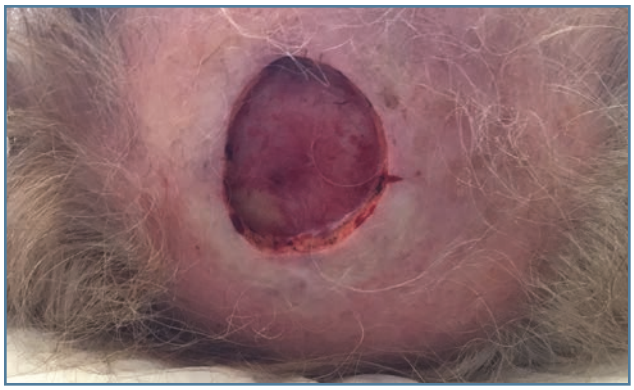

Figure 4.1.44 Post-Mohs defect of the scalp. (Courtesy of Jesse M. Lewin, MD)

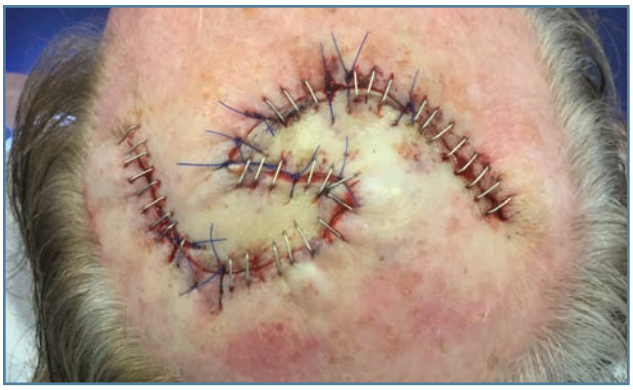

Figure 4.1.47 Bilateral rotation flap sutured and stapled into place. (Courtesy of Jesse M. Lewin, MD)

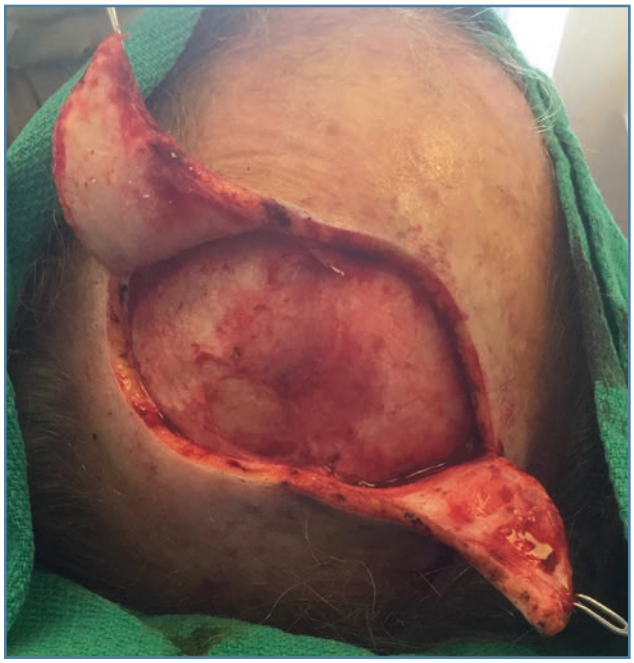

Figure 4.1.45 Bilateral rotation flap (O-Z) elevated at the level of the galea. (Courtesy of Jesse M. Lewin, MD)

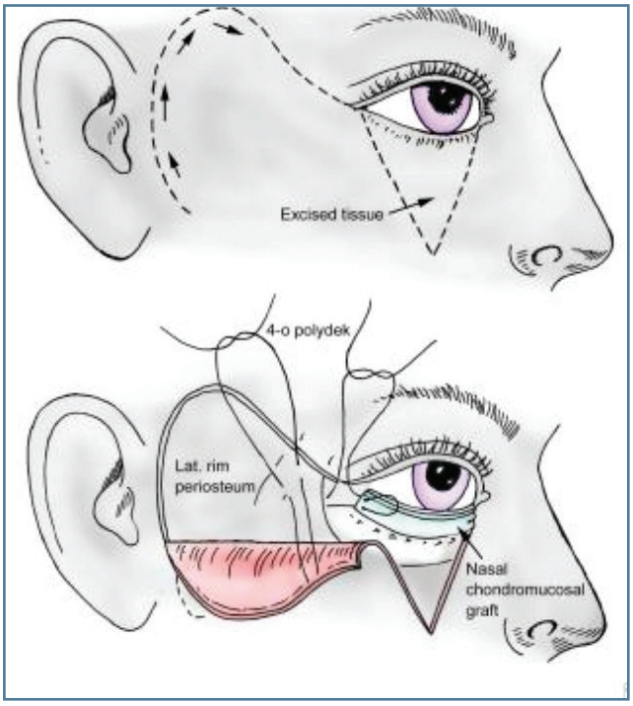

Figure 4.1.48 Schematic of Mustarde (laterally based rotation flap).

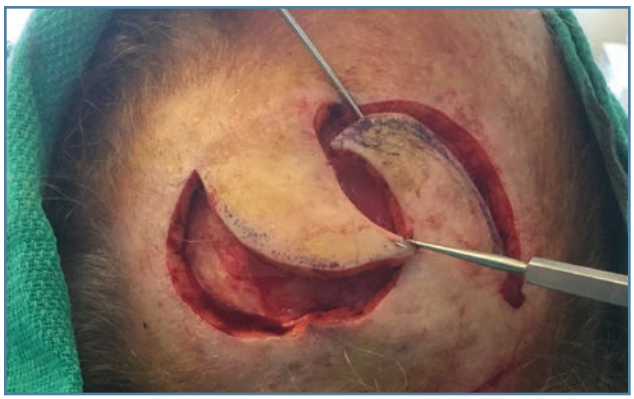

Figure 4.1.46 Bilateral rotation flap limbs moved into position with skin hooks. (Courtesy of Jesse M. Lewin, MD)

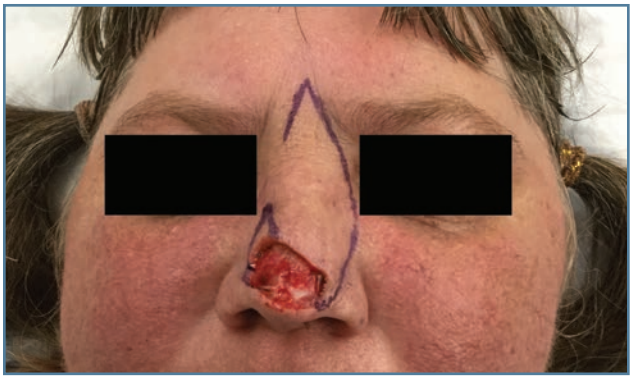

Figure 4.1.49 Post-Mohs defect of the nasal tip and supratip. (Courtesy of Jesse M. Lewin, MD)

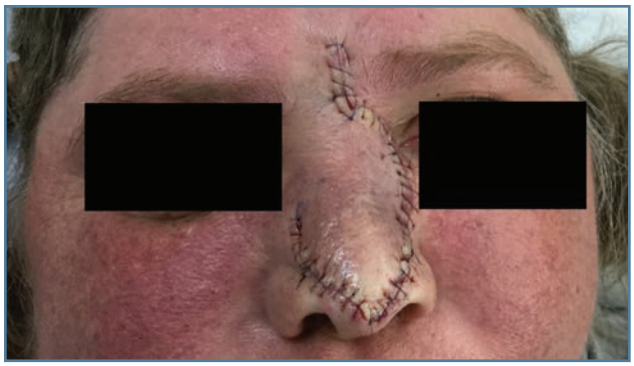

Figure 4.1.50 Dorsal nasal rotation flap (Rieger flap). (Courtesy of Jesse M. Lewin, MD)

- **Transposition flaps**
  - Z-plasty: Transpose two angular flaps, placing them in a complementary fashion into the defects of the other flap
  - Rhombic transposition flap (classical, Dufourmentel, Webster [30-degree angle])
  - Bilobed transposition flap
  - Trilobed transposition flap
  - Note or banner flap
  - Single-staged nasolabial transposition flap

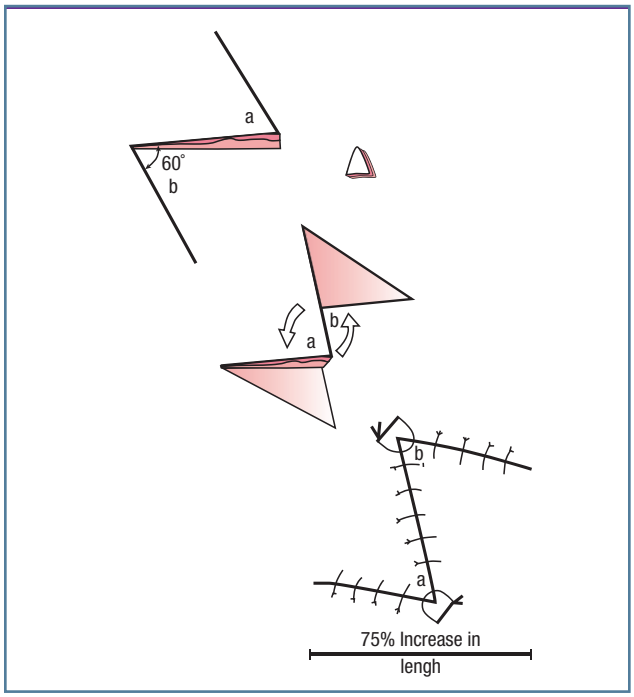

Figure 4.1.51 Z-plasty schematic.

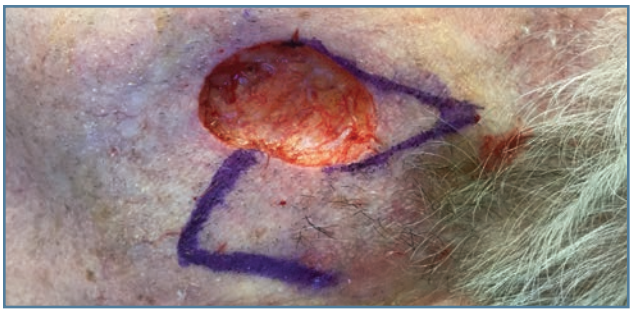

Figure 4.1.52 Post-Mohs defect of the left preauricular region with planned rhombic transposition flap marked. (Courtesy of Jesse M. Lewin, MD)

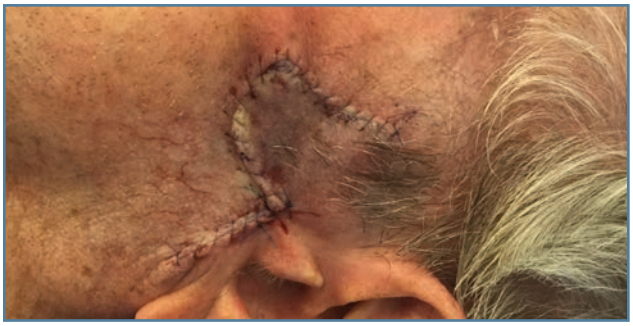

Figure 4.1.53 Rhombic transposition flap sutured into place. (Courtesy of Jesse M. Lewin, MD)

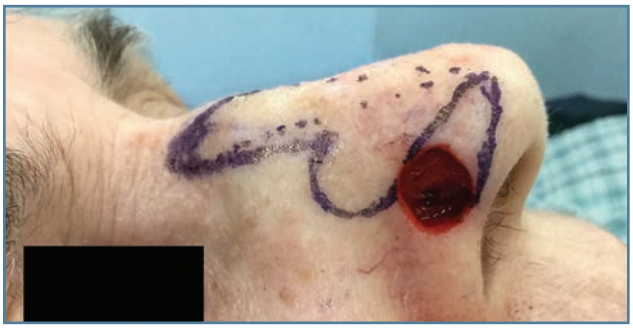

Figure 4.1.54 Post-Mohs defect of the right ala. (Courtesy of Jesse M. Lewin, MD)

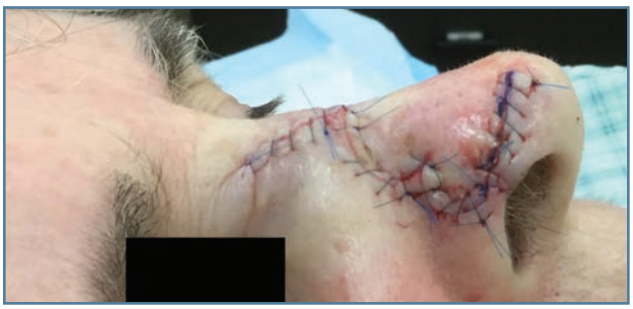

Figure 4.1.55 Medially based bilobed transposition flap. (Courtesy of Jesse M. Lewin, MD)

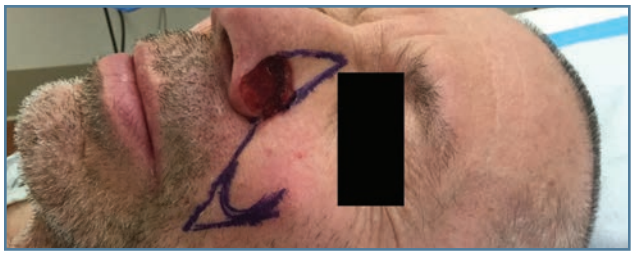

Figure 4.1.56 Defect of the left nasal ala. (Courtesy of Jesse M. Lewin, MD)

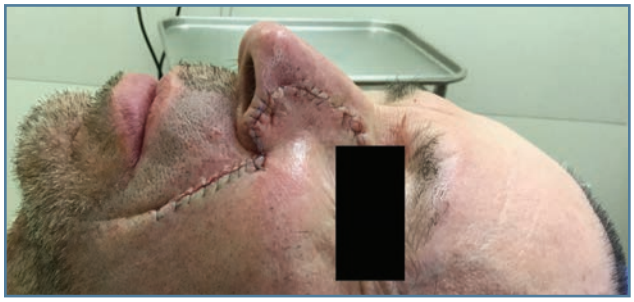

Figure 4.1.57 Nasolabial transposition flap. A cartilage graft from the antihelix was also placed below the flap to support the alar rim. (Courtesy of Jesse M. Lewin, MD)

- **Interpolation flaps: Tissue importation flaps; 2 staged (pedicle division most commonly at week 2**)
  - Paramedian forehead flap: Axial flap, blood supply is supratrochlear artery
  - Abbé flap (lip-switch flap): Axial flap, blood supply is labial artery
  - Staged melolabial interpolation flap: Random-patterned flap with blood supply from perforators of the angular artery
  - Retroauricular pedicled flap/mastoid interpolation flap: Rich random-pattern blood supply from mastoid region

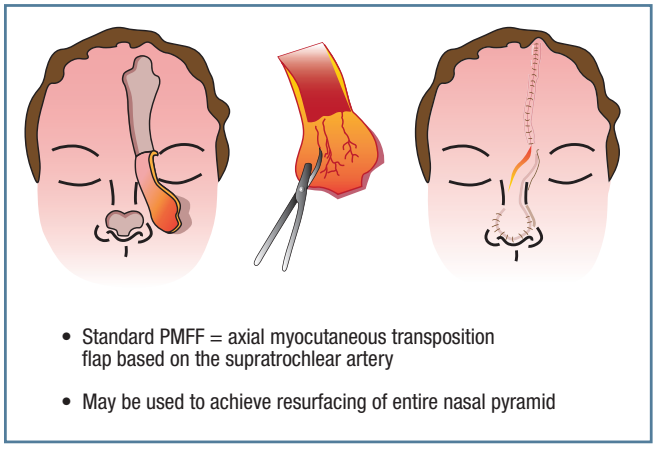

Figure 4.1.58 Schematic of paramedian forehead flap.

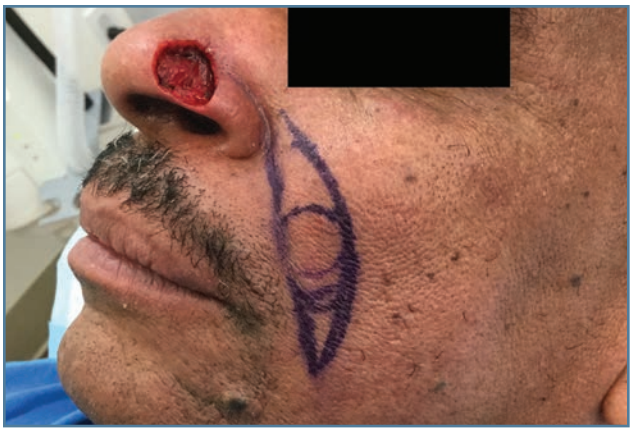

Figure 4.1.59 Post-Mohs defect of the left nasal ala with drawing of planned staged melolabial interpolation flap pedicle. (Courtesy of Jesse M. Lewin, MD)

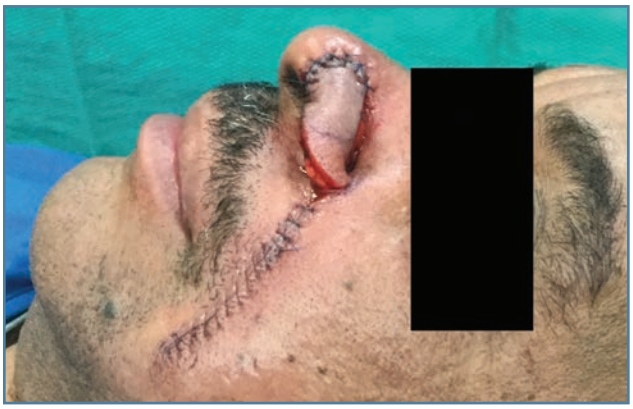

Figure 4.1.60 Staged melolabial interpolation flap with pedicle in place (a cartilage graft/strut from the antihelix was used to support the alar rim)—in 3 weeks this pedicle is divided and the donor cheek area is linearly closed. (Courtesy of Jesse M. Lewin, MD)

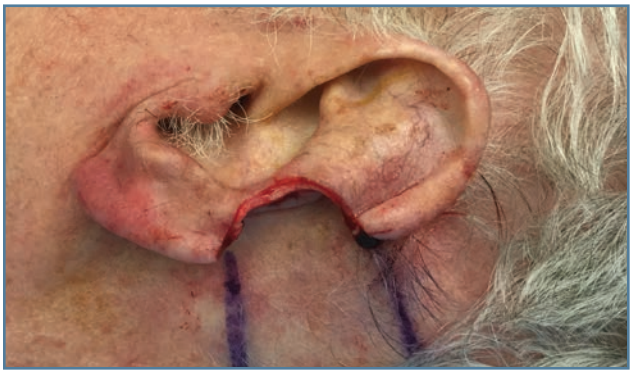

Figure 4.1.61 Through-and-through defect of the left helix and antihelix. (Courtesy of Jesse M. Lewin, MD)

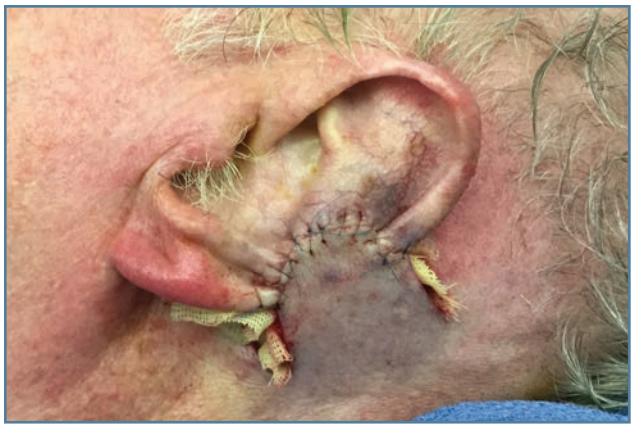

Figure 4.1.62 Mastoid/retroauricular interpolation flap. (Courtesy of Jesse M. Lewin, MD)

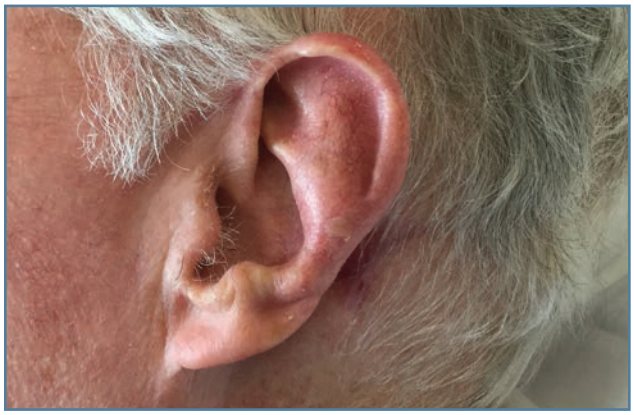

Figure 4.1.63 Follow-up photo after pedicle division. The donor site was allowed to heal by second intent. (Courtesy of Jesse M. Lewin, MD)

Grafts: For Surgical Defects That Cannot Be Closed Primarily or with Adjacent Skin Flap

- A full-thickness skin graft (FTSG) is composed of the entire epidermis and dermis
  - Subcutaneous tissue must be removed since the fat may compromise the viability of the graft. FTSGs may be taken from the head (commonly pre- or postauricular, conchal bowl) or clavicular region, but the size of the tissue needed will dictate where an adequate reservoir exists
  - FTSG contracts by approximately 15% once removed from the donor site. Consideration of the donor and recipient region tissue match in terms of color, and sebaceous nature of the tissues, will lead to better cosmesis
  - Higher metabolic demand than STSG

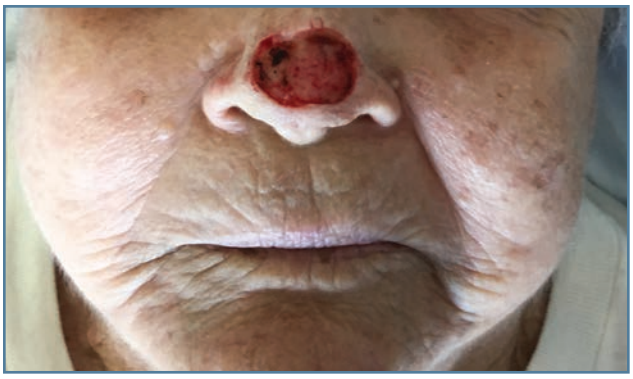

Figure 4.1.64 Post-Mohs defect of the nasal tip and supratip defect. (Courtesy of Jesse M. Lewin, MD)

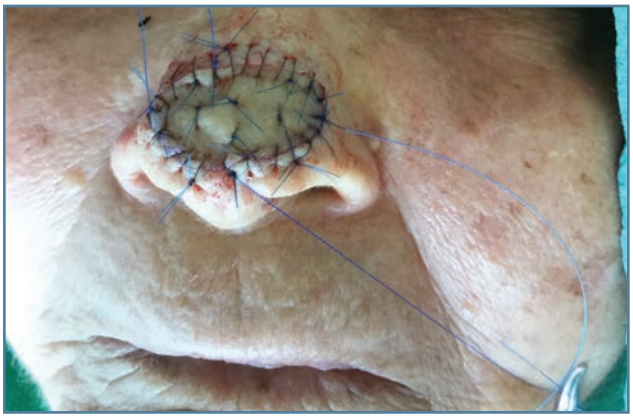

Figure 4.1.65 Full-thickness skin graft harvested from the right preauricular cheek. (Courtesy of Jesse M. Lewin, MD)

- A split-thickness skin graft (STSG) contains epidermis and variable amounts of dermis. The anterolateral thigh is the site most often used for STSGs
  - Thin: 0.008-0.012 in.
  - Medium: 0.012-0.018 in.
  - Thick: 0.018-0.028 in.
  - Lower metabolic demand than FTSG
- Composite grafts are made up of more than one tissue type, typically skin and cartilage. They are commonly used to repair ear and nasal alar defects. Composite grafts have the greatest metabolic demand of all types of grafts and therefore have the highest rates of failure
- Stages of graft healing
  - Imbibition: For the first 48 hr the graft is sustained by plasma from the recipient bed, hyperemia 1-3 days
  - Inosculation: On days 2-3 blood vessels in the graft establish connections with the wound bed

- Neovascularization: Ingrowth of new vessels into the graft occurs at approximately 1 week
- Maturation: Months postgrafting, sensory innervation occurs, and the graft becomes more pale

- **Exposed bone and cartilage are poorly vascularized tissues and are therefore not optimal sites for skin graft survival**

Second Intent

- Healing by second intent is a reasonable option for shallow defects located on concave sites such as the temple, medial canthus, conchal bowl, alar crease
- Avoid second-intent healing near free margins due to risk of contraction leading to anatomic distortion (e.g., ectropion, eclabium) and on exposed bone or cartilage

SURGICAL COMPLICATIONS

Hematoma

- Hematoma formation, or collection of usually clotted blood, will inhibit healing of a wound, prevent graft survival, and serve as a source of potential infection
- In a large, active, or evolving hematoma, the hematoma should be drained
- Small, stable, organized hematomas may be allowed to resorb

Dehiscence

- Dehiscence describes the rupture of a sutured wound along a surgical incision
- Risk factors include increased tension, trauma, age, medical conditions affecting wound healing and/or collagen formation (e.g., obesity, diabetes)
- Hypergranulation tissue: If left in place, this tissue will serve as a physical barrier to epidermal migration. It may be removed mechanically with a curette and chemically with agents such as silver nitrate and trichloroacetic acid

Necrosis

- Necrosis is often the result of hematoma, tension (and resultant vascular compromise), or infection
- **Earliest sign often pallor**
- **Black graft: If the epidermal surface of a graft becomes black and necrotic, it does not necessarily signify graft failure. The epidermal portion of the graft may slough with subsequent reepithelialization. In this situation, the best treatment is observation**
- Injection of anesthesia with epinephrine is safe; and has not been proven to result in vascular compromise

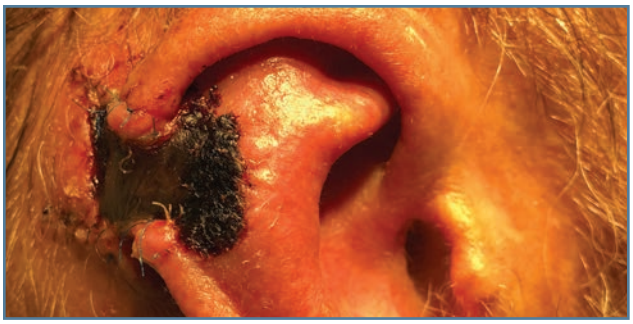

Figure 4.1.66 Flap necrosis in smoker. (Courtesy of Sailesh Konda, MD)

Infection

- Wound classification:
  - Clean: "Perfect" technique; noninflammatory
  - Clean-contaminated: Small imperfections in technique (gastrointestinal [GI]/respiratory/genitourinary [GU] tracts entered without gross contamination)
  - Contaminated: Major imperfections in technique (gross contamination of GI/resp/GU)
  - Dirty: Wound with acute/active infection
- Wound infection: Sutures should be removed as they can serve as a nidus for infection. The wound should be cultured, irrigated, and then allowed to heal by second intention. Antibiotics should be initiated

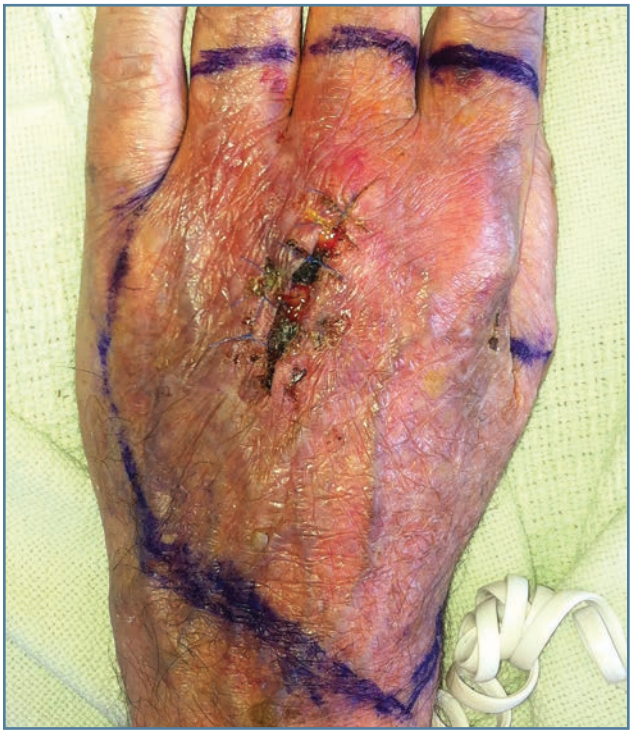

Figure 4.1.67 Wound infection: Methicillin-resistant Staphylococcus aureus (MRSA) cellulitis with wound dehiscence. (Courtesy of Sailesh Konda, MD)

Chondritis

- Can develop when cartilage is exposed
- May be prevented by instituting prophylactic antibiotics postoperatively

Granuloma

- Granuloma formation can occur in response to suture material and result as a reaction to an infection or as an inflammatory response

Trapdoor Deformity

- **Hypothesized to be caused by insufficient undermining**
- **Best prevention is at time of repair**
  - Widely undermine
  - Placement of basting sutures
  - Squaring off corners
- May be treated with intralesional corticosteroids

Figure 4.1.68 Trapdoor deformity.

Scarring Complications

- Track marks result from increased tension, or prolonged placement of sutures
- Hypertrophic scarring: Thickened, often raised lesion that remains within the boundaries of the original surgical incision
  - Some anatomic sites are more prone to formation
- Keloid formation: An aberrant wound-healing response that also results in a thickened, widened, and often raised lesion that can grow outside the boundaries of the original incision
  - Genetics also plays a role in development of keloids
- Treatment with massage in smaller lesions as well as topical and intralesional high-potency corticosteroids is recommended. May also consider occlusion and hydration, with or without silicone sheeting
- Laser treatment with both ablative and nonablative resurfacing lasers, as well as vascular lasers such as the pulsed dye laser, are also appropriate forms of treatment
- Surgical scar revision is also an option, including the use of Z-plasty
- **Contracture: Wound contraction is maximal approximately 2 months after reepithelialization has occurred. Scar relaxation occurs 3 months to 1 year postoperatively and will lessen the final degree of contracture.** Intervention, when appropriate, via surgery, laser, and/or intralesional injections can potentially provide considerable improvement

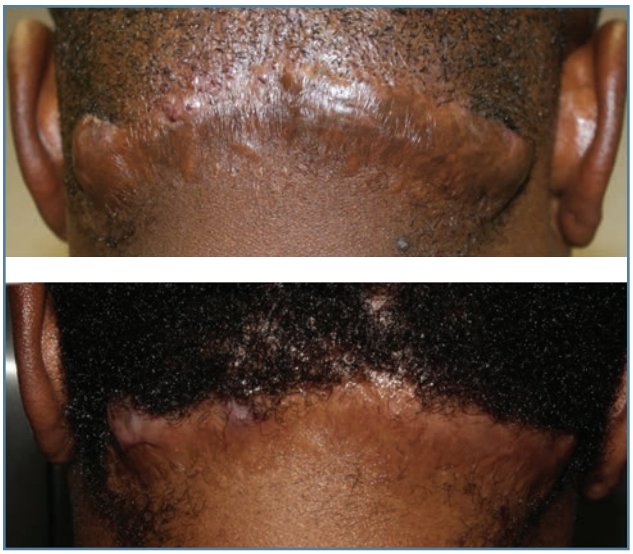

Figure 4.1.69 Keloid.

ELECTROSURGERY AND CRYOSURGERY

Electrosurgery

- Electrocautery: **Direct heat transfer** without current traveling through patient; low-voltage, high-amperage; **works in wet field**
- Electrodesiccation: Superficial ablation with monoterminal device; high-voltage, low-amperage; **electrode contacts the skin**
- Electrofulguration: Superficial ablation with monoterminal device; high-voltage, low-amperage; **no direct contact with skin, results in sparks jumping to skin**
- Electrocoagulation: Biterminal, use of an electrode; low-voltage, high-amperage, damped; dry surgical field required
- Electrosection: Biterminal, use of electrode; low-voltage, high-amperage, undamped current; cutting
- Precautions when using electrosurgery with pacemakers and implantable cardioverter-defibrillators (ICDs): Short bursts of energy (<5 seconds), low power, avoid the cutting current, avoid use on the skin around the pacemaker or ICD. Although recommended in the literature, most dermatologists do not follow specific precautions such as intraoperative monitoring, preoperative cardiology consultation, or postoperative evaluation of the cardiac device by a cardiologist

TABLE 4.1.12 ELECTROSURGERY WAVEFORMS

Eelectrosurgery Type	Circuit	Tissue Contact	Voltage	Amperage	Histology
Electrofulguration	Monoterminal	No	High	Low	Tissue desiccation: Cell outlines preserved but shrunken. Nuclei elongated. Some vessel thrombosis
Electrodesiccation	Monoterminal	Yes	High	Low	Tissue desiccation: Cell outlines preserved but shrunken. Nuclei elongated. Some vessel thrombosis
Electrocoagulation	Biterminal	Yes	Low	High	Tissue coagulation: Cell outlines lost from massive protein denaturation. Homogeneous hyalinized appearance. Vessel thrombosis
Electrosection with coagulation	Biterminal	Yes	Low	High	Cell disintegration forming approximately 0.1-mm incision; adjacent cellular outline elongation and mild coagulation effect
Electrosection	Biterminal	Yes	Low	High	Cell disintegration forming approximately 0.1-mm incision; minimal coagulation effect
Electrocautery	None (hot wire)	Yes	Low	High	Amorphous tissue with charred foci and formation of steam spaces

Cryosurgery

- **Cryosurgery: Very low temperatures to destroy living tissue**
- **Cryotherapy: Very low temperatures to induce physiologic change, not destroy**
- Cryogens:
  - Liquid nitrogen: Boiling point of −196°C (−321°F); most utilized in dermatology
  - Nitrous oxide (N^2O): Used at −88°C
  - Carbon dioxide gas: Used at −78°C
- Lethal temperatures:
  - Melanocyte necrosis: −4°C
  - Keratinocyte treatment: −35°C
  - Nonmelanoma skin cancer (NMSC) treatment: Below −50°C
  - Vascular endothelium: −15 to 40°C

COSMETIC DERMATOLOGY

Injectable Neurotoxins

- Botulinum toxin (BTX) cleaves proteins (collectively called the SNARE complex) in the presynaptic neuron, which are required for the release of acetylcholine
- Additional blocked neurotransmitters: Substance P, noradrenaline, calcitonin gene—related peptide, glutamate

TIP

BTX blocks acetylcholine release

- Botulinum toxin genotypes: A, B, C1, C2, D, E, F, G
- **BTX-A (onabotulinumtoxinA [Botox], abobotulinumtoxinA [Dysport, Azzalure], and incobotulinumtoxinA [Xeomin, Bocouture]) cleave the SNAP-25 protein whereas BTX-B (Myobloc, NeuroBloc) cleaves the synaptobrevin protein of the SNARE complex**
- Injection into the muscles of facial expression results in a **chemical denervation** of striated muscles and thus a temporary paralysis; denervates sweat glands (hyperhidrosis) and can improve symptoms of Raynaud's
- FDA-approved cosmetic indications:
  - Botox: Moderate to severe glabellar and lateral canthal (crow's feet) rhytides; also approved for hyperhidrosis
  - Dysport and Xeomin: Moderate to severe glabellar rhytides
- Potential targets (innervation)
  - Frontalis (temporal branch of facial nerve): Loss of function results in flattening of forehead skin tension lines, drooping eyebrow
  - Corrugator supercilii (temporal branch of facial nerve): "Scowling"—draws eyebrows medially and down, loss of function flattens glabellar lines
  - Procerus (zygomatic branch of facial nerve): Over nasal bone, scowling and parallel glabellar line formation, loss of function flattens glabellar lines
  - Orbicularis oculi (zygomatic branch of facial nerve): Closes eyelid tight, intertwined with procerus, corrugator, and frontalis; loss of complete function → inability to close eyelid tightly, loss of partial function → flattening of crow's feet

- Nasalis (zygomatic and buccal branches of facial nerve): Across nasal dorsum, facilitates alar "flaring" and loss of function softens "rabbit lines" during exaggerated wrinkling of nose
- Orbicularis oris (buccal and marginal mandibular branch of facial nerve): Purses/puckers lips, partial loss of function softens perioral skin tension lines
- Depressor anguli, depressor labii, and mentalis (marginal mandibular branch of the facial nerve): Lip depressors, loss of function elevates corners of lips
- Platysma (marginal mandibular and cervical branches of facial nerve): Provides only a thin cover to the marginal mandibular nerve, loss of function flattens neck bands

Figure 4.1.70 Neurotoxin injection points.

Injectable Fillers

- Various agents used alone or in combination with other agents or modalities to improve appearance of wrinkles, atrophic acne scars; to volumize and recontour the face; and in lip augmentation[7]
- Selection of agent depends on location and depth of volume deficiency, cost, and desired longevity
- Collagen
  - 1981: Bovine collagen first FDA-approved filler (Zyderm I)
  - Zyderm II, Zyplast (not commercially available)
  - **3-5% of the population reacts to bovine collagen, therefore two skin tests are performed at 6 weeks and then at 2 weeks prior to the first collagen treatment**
  - Evolence (2008): Porcine-derived collagen (not commercially available)
  - Human-derived collagen
    - Cadaveric: Dermalogen, Cymetra (not commercially available)
    - Noncadaveric: CosmoDerm I, CosmoDerm II, CosmoPlast (not commercially available)
  - 2007: Artefill (now Bellafill), a product made of microspheres of polymethylmethacrylate (PMMA) and purified bovine collagen gel, received FDA approval for correction of nasolabial folds. **More recently received approval for correction of atrophic acne scars**
- **Hyaluronic acid (HA)**
  - The most abundant GAG in the skin and binds water, creating volume when injected into the skin
  - Hyaluronic acid products can be derived from the combs of domestic fowl (Hylaform/Hylaform Plus [not commercially available], Hydrelle) or by bacterial (streptococcal) fermentation (Captique, Puragen/Puragen Plus)
  - 2003: Restylane—cross-linked non-animal-derived hyaluronic acid product approved by FDA (including Restylane Lyft [formerly Perlane], Restylane-L, Silk, Refyne, Defyne); Lyft also FDA approved for age-related volume loss of hands
  - 2008: Prevelle Silk approved as first HA containing lidocaine, to help reduce pain associated with injection (not commercially available)
  - Additional non-animal-derived HAs with differing cross-linking include Juvéderm (Ultra/Ultra XC, Ultra Plus/Ultra Plus XC, Voluma, Volbella, Vollure), Belotero
- Sculptra
  - A synthetic, biocompatible, biodegradable injectable polymer of poly-L-lactic acid
  - **FDA approved for the treatment of HIV-associated lipoatrophy in addition to facial wrinkles**
  - Results believed to be due to stimulation of fibroblasts to produce additional collagen (neocollagenesis)
- Radiesse
  - FDA approved for facial wrinkles as well as age-related volume loss of hands
  - Composed of calcium hydroxylapatite microspheres
  - **Calcium hydroxylapatite is a normal constituent of bone and thus can be seen on radiographic imaging**
- Silicone
  - A synthetic, viscous compound that is composed of long polymers of dimethylsiloxanes
  - **Silicone is not currently FDA approved for soft tissue augmentation**
  - **In addition to hypersensitivity reactions and product migration, granuloma formation can occur, even many years posttreatment**
- Filler complications: Often technique and/or product related; more common and less severe include pain, bruising, swelling, Tyndall effect, contour irregularities; less common and more severe include hypersensitivity reaction, nodule/granuloma/biofilm formation, vascular occlusion (that may result in vision impairment, blindness, stroke, and damage and/or necrosis of the skin and underlying facial structures)
- When an undesirable outcome occurs with hyaluronic acid filler product, correction is possible with the injection of commercially available hyaluronidase

Chemical Peels

- **The degree of clinical improvement is directly proportional to the depth of injury**
- Superficial peels cause necrosis of the epidermis; application results in mild stinging and level I frosting (erythema, streaky whitening)
  - Very light peels: Injury limited to stratum corneum
  - Light peels: Injure entire epidermis to basal layer
  - Jessner's solution (salicylic acid, 85% lactic acid, resorcinol, and ethanol); salicylic acid, 25-30% trichloroacetic acid (TCA), and 70% glycolic acid produce a superficial peel
- Medium-depth peels cause wounding to the level of the papillary dermis, variable involvement of upper reticular dermis; deep peels result in injury to the depth of the reticular dermis
  - TCA 35% and combination peels produce medium-depth ablation
  - TCA > 50% and phenol peels produce deep ablation
  - Baker-Gordon peel: 88% phenol, tap water, croton oil, and Septisol. **Croton oil most important for efficacy**
  - TCA CROSS: 90% TCA, for ice pick scars
- Patients should receive prophylactic antiviral therapy prior to medium-depth or deep resurfacing
- All peeling agents have the potential to cause pigmentary alterations, milia, and scarring
- Prolonged erythema is a side effect most commonly associated with phenol peeling

TABLE 4.1.13 COMMON PEELING AGENTS

Agent	Composition	Depth	Notes	Uses
Glycolic acid	50-70%	Superficial	Does not produce frosting. Must be neutralized with sodium bicarbonate	Acne, dyschromia, photoaging
Salicylic acid	20-30%	Superficial	Does not frost, though a white residue may be left behind. Has analgesic properties. Self-neutralizing	Acne, dyschromia, photoaging
Jessner's solution	Equal parts salicylic acid, resorcinol, and lactic acid in ethanol	Superficial	Produces patchy frosting. Self-neutralizing. May be used prior to TCA to produce a medium-depth peel	Acne, dyschromia, photoaging
Trichloroacetic acid (TCA)	10-100%	Superficial: 10-30% Medium: 35% following Jessner's solution, glycolic acid, or CO_2 slush Deep: >50% (rarely used)	Produces frosting with greater opacity at greater concentrations. Cannot be neutralized. Used at 70-100% concentration for TCA CROSS procedure	Dyschromia, photoaging, rhytides, actinic keratoses
Phenol	>80%	Deep	Carries the risk of cardiotoxicity. Must have continuous cardiac monitoring and pulse oximetry	Deep rhytides
Baker-Gordon formula	Phenol, water, Septisol, croton oil	Deep	Carries the risk of cardiotoxicity. Must have continuous cardiac monitoring and pulse oximetry	Deep rhytides

TIP

- Phenol is cardiotoxic, nephrotoxic, and hepatotoxic. Patients must have cardiac monitoring during phenol peeling to detect cardiac arrhythmias
- Chemical peeling of the neck is generally avoided because of the risk of hypertrophic scarring

Hair Restoration

- Transplantation is an outpatient procedure performed under local anesthesia
- Theory of donor dominance: Terminal hair from unaffected (not bald) area will continue to grow in affected (bald) area after transplantation
- **Primary limiting factor is amount of donor hair available**
- Follicular unit: Natural grouping of one to four follicles
  - < 40 follicular units/cm^3 = poor candidate
- Elliptical donor harvesting
  - Strip of scalp surgically excised, allowing for safe and rapid removal of large number of follicles, with minimal transection

- However, results in scarring (visible if hair cut short), and requires prolonged time to create grafts
- Lengthen rather than widen ellipse if greater number of follicles required

- Follicular unit extraction (FUE)
  - Single follicular units removed with manual cylindrical punch devices, needle, or more recently robotic systems
  - More time consuming to extract follicular units with variable rates of transection; however, less time required to create grafts, with little to no noticeable scarring (may see "white dots")
  - **As androgenetic alopecia is progressive, transplantation of hair into vertex scalp may result in an unnatural appearance**

Body Contouring: Liposuction and Noninvasive Techniques

- Liposuction
  - Can be used to treat localized adiposities at multiple anatomic sites, including the abdomen, thighs, flanks, and neck
  - Tumescent local anesthesia is performed with 0.05% lidocaine and epinephrine at a 1:1,000,000 ratio
  - Infusion occurs in 90-120 min at a rate of approximately 150 ml/min
  - Peak plasma levels of lidocaine occur at 12 hr postinfusion
  - CNS toxicity occurs when blood levels of lidocaine reach 5-6 μg/ml
  - Prolonged swelling, bruising, numbness common after liposuction
  - Complications:
    - **Paradoxical breast augmentation has been observed in patients after tumescent liposuction and is believed to be due to hormonal shifts**
    - Abdominal perforation (one of leading causes of death), respiratory failure, and pulmonary embolus are complications that are seen almost exclusively in liposuction patients who receive general anesthesia, intravenous sedation, and undergo prolonged procedures, rather than ambulatory tumescent local anesthesia
- Injectable lipolysis: Deoxycholic acid (Kybella)
  - FDA approved for treatment of submental fat; mechanism of action is disruption of cell membrane
- Multiple noninvasive body contouring technologies have received FDA clearance including:
  - Cryolipolysis: Cold-induced apoptosis and panniculitis
  - Laser: Thermal induced apoptosis
  - High-intensity focused ultrasound: Thermal destruction of adipocytes
  - Nonthermal focused ultrasound: Cavitation disruption of adipocytes
  - Radiofrequency: Thermal induced apoptosis
- Cellulite treatment options include:
  - 1,440-nm side-firing laser treats dermal banding, thermally induces apoptosis and results in neocollagenesis
  - Vacuum-assisted mechanical tissue release by a motorized microblade targets specific dimpling of the buttocks and posterior thighs

LIGHT, LASERS, AND ENERGY DEVICES

Background

- Ultraviolet radiation (UVR): UVC (200—290 nm), UVB (290—320 nm), and UVA (320-400; UVA further subdivided as UVA1 [340—400 nm] and UVA2 [320—340 nm])
- Longer wavelength, deeper penetration into dermis (UVA)
- >95% of the sun's UV radiation that reaches the earth's surface is UVA
- Exposure has wavelength-dependent acute, short-term, and chronic long-term effects
- Ability to induce sunburn decreases with increasing wavelength
- Tanning response of human skin to sun exposure is biphasic and also wavelength dependent
  - **Immediate pigment darkening: Oxidation and redistribution of existing melanin; UVA induced**
  - **Delayed tanning: Peaks 3 days after exposure; result of UVB exposure is increased number of melanocytes, melanin synthesis, arborization of melanocytes, and transfer of melanosomes to keratinocytes**
- Long-term effects of chronic sun exposure include photoaging and photocarcinogenesis

Photoimmunology

- Photoimmunologic effects, including both pro- and antiinflammatory effects
  - Suppressor T cells induce susceptibility to tumor
  - These cells arise in UV-irradiated hosts prior to tumor development

- Antigen-presenting cells (APCs) have depressed ability to prime UV-irradiated mice to subcutaneously injected hapten or protein and to applied contact-sensitizing agents
  - Prevents a normal delayed-type hypersensitivity (DTH) response
  - Reduces number of APCs
  - Mice exposed to short-term, high-dose UVR demonstrate decreased splenic APC function
- Both DTH and contact hypersensitivity show diminished responses
- There is an increased risk of malignancy in patients undergoing immunosuppressive therapies, with increased frequency of skin cancers (including melanoma)
- Immunologic effects of UV light
  - Clinical signs of proinflammatory/immune-stimulating effects
    - Sunburn
    - Dermatoheliosis
    - Phototoxic and photoallergic dermatoses
    - Photoaggravation of inflammatory skin diseases (e.g., psoriasis, atopic dermatitis, etc.)
    - Induction of autoimmune connective tissue diseases (e.g., cutaneous lupus erythematosus [LE], flares of systemic LE)
    - Efficacy of UV phototherapy for the treatment of skin infections (e.g., lupus vulgaris)
  - Clinical signs of antiinflammatory/immunosuppressive effects
    - Activation of recurrent orolabial herpes simplex
    - Increased risk of photocarcinogenesis in the setting of immunosuppression (e.g., solid organ transplant recipients)
    - Efficacy of UV phototherapy for the treatment of inflammatory skin diseases
  - Molecular signs of proinflammatory/immune-stimulating effects
    - Release of proinflammatory mediators by resident and nonresident skin cells (e.g., serotonin, prostaglandins, IL-1, IL-6, IL-8, TNF-α)
    - Induction of antimicrobial peptides (hypothesized to explain why UV-irradiated skin is not prone to bacterial infections)
  - Molecular signs of antiinflammatory/immunosuppressive effects
    - Depletion of Langerhans cells or modulation of their antigen-presenting function
    - Release of antiinflammatory mediators by resident and nonresident skin cells (e.g., IL-10, α-MSH)
    - Induction of regulatory T cells (antigen-specific)

Photocarcinogenesis

- UVR-induced mutations play pivotal role in photocarcinogenesis
- DNA damage
  - UVB is much more efficient than UVA in inducing DNA damage
  - UVB is most effective in producing cyclobutane pyrimidine dimers —most premutagenic DNA lesions
  - Dipyrimidine cyclobutane dimers most common (C-T mutation)
  - UVA induces oxidative guanine base modifications
- Midrange UVR (280-320 nm) more efficient in inducing neoplasia in mice
- Long-wave UVA, when added to UVB, may accelerate carcinogenesis
- Cells from patients with actinic keratoses (AKs) have less DNA repair capacity compared with control subjects

Photodynamic Therapy

- Photodynamic effect by generation of highly reactive singlet oxygen that results in cell necrosis, apoptosis, and/or antimicrobial action
- Three requirements:
  - Topical photosensitizer (5-aminolevulinic acid [ALA] or methyl-ALA [MAL])
  - Exposure to photoactive light source (e.g., daylight, intense pulsed light [IPL], blue light, red light, pulsed dye laser)
  - Tissue oxygen
- Photosensitizer metabolized in the skin to photoactive protoporphyrin IX
- Treatment of both oncologic conditions (such as actinic keratoses, superficial nonmelanoma skin cancers, mycosis fungoides [MF], extramammary Paget's) and nononcologic conditions (namely, photoaging, acne, psoriasis, cutaneous infections, vascular anomalies, hypertrophic scars, and keloids)
- Adverse effects may include photosensitivity, pain, inflammation, allergic reaction (to photosensitizing agent)

Cosmeceuticals/Topical Photorejuvenating Agents

- Nonprescription products designed to improve skin function, focus on rejuvenation/antiaging
- Tretinoin is the gold standard in topical photorejuvenating agents
  - It normalizes epidermal atypia, increases dermal collagen deposition, and increases new blood vessel formation
- Topical ascorbic acid (vitamin C) has both antioxidant and antiinflammatory properties

- Has been shown to increase the dermal production of collagen, reduce phototoxicity due to ultraviolet light, and lighten hyperpigmentation

- α-Hydroxy acids: Water soluble
  - Three categories: Monocarboxylic (glycolic, lactic, mandelic), dicarboxylic (malic, tartaric), tricarboxylic (citric)
  - Epidermal effects: Induce immediate disruption of skin barrier (ionic bonding disruption/cell disadhesion), resulting in thinning of stratum corneum and decreased melanogenesis
  - Dermal effects: Delayed, increased synthesis of GAGs, collagen; resulting in thickened dermis
  - **Requires neutralization**
- β-Hydroxy acids (salicylic acid): Reduction in cell adhesion; oil soluble and thus exerts effects on sebacoues units and has role in acne; also can act as keratinolytic, promoting exfoliation
  - β-Hydroxy acids eliminate outermost layer of stratum corneum compared with α-hydroxy acids, which disrupt cellular cohesion at lowest levels of the stratum corneum
  - Salicylic acid can be used alone or in combination (Jessner's)
  - **Self-neutralizing**

Sunscreens

- Sunscreens are divided into chemical blockers, which absorb UVR, and physical blockers (insoluble metal oxides), which reflect and scatter UVR
- Sun protection factor (SPF) = minimal erythema dose (MED) with applied sunscreen/MED without sunscreen
- **SPF does not measure UVA protection**
- Most commonly accepted in vitro method for assessing UVA protection is by critical wavelength (CW) determination
- Wavelength at which the **cumulative** absorption of solar-simulated radiation above 290 nm is 90%—sunscreen dissolved in solvent and absorption spectrum determined
- New FDA sunscreen-labeling guidelines
  - Only sunscreens that have been shown to block UVA and UVB can be labeled as "broad spectrum"
  - Sunscreens can have a label with a numbered SPF up to SPF 50. Higher SPF sunscreens will be labeled as "SPF 50+"
  - Only SPF 15+ broad-spectrum sunscreens can claim to reduce risk of skin cancer and slow photoaging
  - Elimination of the terms "sweat proof," "sunblock," and "water proof"
  - Water-resistant sunscreens can claim up to 40 or 80 min of resistance with sweating or swimming

TABLE 4.1.14 SUNSCREEN AGENT BLOCKING SPECTRUM

	UVB (290-320)	UVA2 (320-340)	UVA1 (340-400)	Visible Light (400-800)
PABA derivatives (PABA, octyl dimethyl PABA)	X			
Cinnamates (octinoxate, Parsol MCX)	X			
Salicylates (octisalate, homosalate, trolamine salicylate)	X			
Benzophenones (oxybenzone, dioxybenzone)	X	X		
Sulisobenzone		X	X	
Avobenzone		X	X	
Octocrylene	X			
Enzacamene	X			
Ecamsule (Mexoryl)		X	X	
Drometrizole trisiloxane (Mexoryl XL)	X	X	X	
Bisoctrizole (Tinosorb)	X	X	X	
Titanium dioxide	X	X	X	X
Zinc dioxide	X	X	X	X

PABA = *para*-aminobenzoic acid.

Lasers

- **LASER** is an acronym for light amplification by stimulated emission of radiation
- To exert a biologic effect, a specific wavelength of light must be absorbed by a target, referred to as a chromophore, resulting in creation of heat; the major chromophores in the skin are melanin, oxyhemoglobin, and water
- The theory of **selective photothermolysis** is based on the delivery of the appropriate wavelength/energy to heat and destroy the target chromophore (selective heating) without damaging surrounding tissue by loss of that heat via diffusion (nonselective heating). It requires:
  - The appropriate wavelength for the target
  - A pulse duration equal to or less than the target's thermal relaxation time
  - A fluence sufficient for target destruction while avoiding surrounding damage
- Thermal relaxation time (TRT): Time required for target chromophore to lose half of its heat by diffusion to surrounding tissue; proportional to the square of its size. Additionally affected by shape—for standardized size, planes will cool faster than spheres
- Pulse duration: Controls spatial confinement of laser energy
  - Nanosecond and picosecond pulses can damage small targets such as individual melanocytes and tattoo particles
  - Millisecond pulses damage multicellular structures: Vessels, hair, tissue layers
- Spot size: In general, larger spot size results in less scattering of energy and deeper penetration, while smaller spot size requires higher energy to compensate for increased scattered effect
- Photomechanical effect: Rapid heating results in thermal expansion and acoustic/shock waves that can disrupt and destroy cell membranes
  - Depth of penetration is proportional to wavelength until ~1,200 nm, above which water is absorbed and scatter is increased with less depth of penetration
- Resurfacing lasers target water and treat pigmentary and textural changes associated with photoaging, scarring, and laxity
  - Common wavelengths include infrared (1,540 nm, 1,550 nm, 1,927 nm, 2,940 nm, 10,600 nm)
  - Presently most ablative and nonablative resurfacing lasers utilize "fractional" photothermolysis, creating an array of microscopic thermal zones of injury (MTZs) that allows for more rapid reepithelialization and ultimately collagen remodeling
- Pigment lasers target endogenous (melanin) and exogenous (tattoo) chromophores, utilizing nanosecond and picosecond pulse duration lasers. These pulses are generated using a mechanism known as quality or Q-switching. Laser hair removal (LHR) also targets pigment with lasers in the millisecond pulse duration range
  - Common wavelengths include frequency-doubled Nd:YAG (532 nm), ruby (694 nm), alexandrite (755 nm), diode (800-810 nm), Nd:YAG (1,064 nm)
- Cutaneous vascular lasers share similar wavelengths with pigment lasers and therefore safety mechanisms such as contact cooling, or cryogen sprays, are utilized to protect epidermal pigment while targeting deeper dermal vasculature
  - Common wavelengths include potassium titanyl phosphate (KTP) (532 nm), pulsed dye (595 nm), alexandrite (755 nm), diode (800-940 nm), Nd:YAG (1,064 nm)
- Endovenous lasers are used in the treatment of varicose veins
- **Scarring, pigmentary alteration, and ocular damage are amongst the more serious risks of laser treatment.** The cornea is an aqueous structure and is particularly at risk for damage when using ablative lasers whose target chromophore is water, while the retina contains pigment and thus is susceptible to injury from lasers used to treat pigmented lesions (millisecond, nanosecond, and picosecond lasers)
- The intense pulsed light (IPL) source is not defined as a laser since it neither has coherent light nor does it emit light at a single wavelength. The IPL emits noncoherent light within the 515 nm-1,200 nm range of the electromagnetic spectrum. Clinically, utilized in treatment of vascular lesions, pigmented lesions, hair removal, and photorejuvenation

TABLE 4.1.15 LASERS AND OCULAR RISK

Laser	Ocular Risk
Pulsed dye (595 nm)	Retina
Er:YAG (2,940 nm)	Cornea
CO_2 (10,600 nm)	Cornea
Ruby (694 nm)	Retina

TABLE 4.1.16 OCULAR DAMAGE

Wavelength	Eye
Ultraviolet C (200-280 nm)	Photokeratitis
Ultraviolet B (280-315 nm)	Photokeratitis
Ultraviolet A1 (340-400 nm) and ultraviolet A2 (320-340 nm)	Photochemical cataract
Visible (400-780 nm)	Photochemical and thermal retinal injury
Infrared A (780-1,400 nm)	Cataract and retinal burn
Infrared B (1,400-3,000 nm)	Corneal burn, aqueous flare, cataract
Infrared C (3,000-1,000,000 nm)	Corneal burn

TABLE 4.1.17 LASERS AND STRUCTURE DAMAGED

Wavelength (nm)	Structure Damaged	Laser
<320	Cornea	Excimer
320-400	Lens	Excimer
400-700	Retina choroid	Pulsed dye, Nd:YAG, ruby
780-1,400	Lens, vitreous, retina	Diode, Nd:YAG
1,400	Cornea	CO_2, Er:YAG

Energy Devices: Radiofrequency, Ultrasound, Microwave

- In addition to lasers of UV, visible light, and infrared wavelengths, longer wavelengths are also used in cosmetic dermatology, in general to treat deeper targets such as deep dermis, sweat glands, and muscle. These treatments result in the creation of new collagen and resultant skin tightening, as well as sweat, hair, and odor reduction
- Radiofrequency devices
  - Monopolar: Grounding pad required; two poles often located far apart from each other, and require the energy to travel from the handpiece through the body to the grounding electrode; results in volumetric heating
  - Bipolar: The two poles are located close to each other, such as handpieces with closely arranged needles; devices differ based on their arrangement and insulation of needles
- Ultrasound (Ulthera): Delivery of microfocused ultrasound energy to dermis as well as subcutaneous tissue, where appropriate
  - FDA cleared for treatment of facial, submental, and neck laxity
- Microwave (miraDry): Delivery of heat to depth at which eccrine and apocrine glands as well has hair bulbs reside
  - FDA cleared for treatment of axillary hyperhidrosis, odor, and unwanted hair

4.2 Cutaneous Oncology

CUTANEOUS ONCOLOGY

Actinic Keratosis

- Epidemiology
  - Very common, premalignant lesion, with low potential to become squamous cell carcinoma (SCC)
  - Risk factors: Individual susceptibility (older age, male gender, fair skin phenotype, and light eye color), immunosuppression, lifetime sun exposure, and some genetic syndromes such as albinism and xeroderma pigmentosum
- Etiology
  - Ultraviolet B (UVB) radiation from sunlight is responsible for actinic keratosis (AK) development
  - UVB triggers formation of thymidine dimers in DNA and RNA, resulting in mutations in tumor suppressor gene *p53* within the keratinocytes, which results in impairment of apoptosis and clonal expansion of mutated keratinocytes and AKs
- Clinical presentation
  - Lesions commonly found on sun-exposed areas (head, neck, forearms, dorsal hands)
  - Typical AKs present as erythematous, flat, rough macules or papules that are better felt than seen
  - Clinical subtypes include: Hypertrophic AK (HAK), pigmented, cutaneous horn, and actinic cheilitis
    - HAK lesions are thicker, scaly, skin colored or erythematous plaques
    - The cutaneous horn is defined as a type of HAK that presents as a conical hypertrophic protuberance emanating from an erythematous base (Figure 4.2.1)
    - Actinic cheilitis develops from the confluence of several AKs on the lips (usually the lower lip). The patient typically presents with red, scaly, or chapped lips with erosions and fissures (Figure 4.2.2)

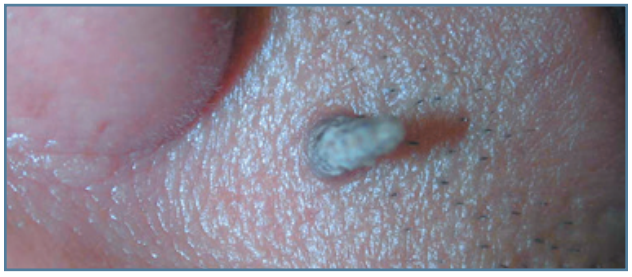

Figure 4.2.1 Cutaneous horn.

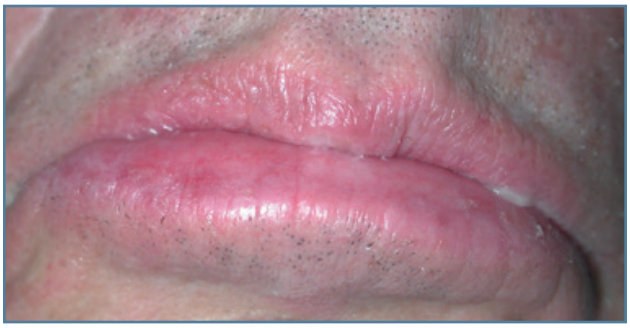

Figure 4.2.2 Hypopigmented, scaly plaque with fissures involving the lower lip of a male patient.

- Histopathology
  - Keratinocytes appear atypical, pleomorphic and disordered in arrangement
  - Foci of atypical keratinocytes are located in the basal layer, protruding as buds into the papillary dermis
  - The epidermis also shows irregular acanthosis with columns of parakeratosis and hyperkeratosis
  - Changes due to solar elastosis and inflammatory infiltrate can be found in the dermis (Figures 4.2.3 and 4.2.4)

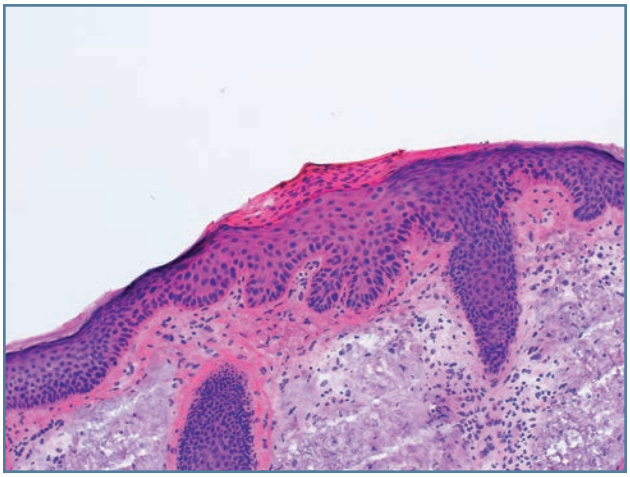

Figure 4.2.3 Actinic keratosis (AK), lower magnigication. Focal parakeratosis alternating with orthokeratosis. The neoplasm is confined to the epidermis. There is prominent solar elastosis in the subadjacent papillary dermis. The tumor spares the hair follicles. (Courtesy of Sailesh Konda, MD)

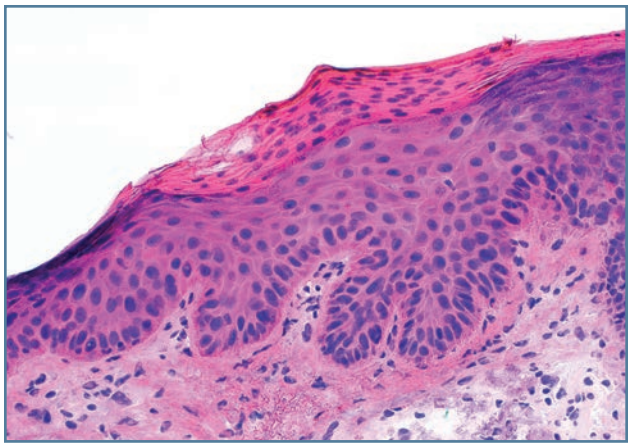

Figure 4.2.4 Actinic keratosis (AK), higher magnification. Marked parakeratosis and absence of the granular layer. Pleomorphism of the atypical keratinocytes within the basal layer of the epidermis. (Courtesy of Sailesh Konda, MD)

- Treatment
  - Several forms of therapy are available for the treatment of AKs, including lesion-targeted therapy, field-directed therapy, and oral therapy
  - Lesion-targeted therapy
    - Cryotherapy: The most common treatment for AKs with a cure rate of up to 88%
    - Curettage, with or without electrosurgery: Effective at the expense of potential scarring
    - Shave excision: Indicated when AK is suspicious for SCC or basal cell carcinoma (BCC) and histopathologic examination is needed
    - Photodynamic therapy (PDT) with aminolevulinic acid (ALA): Found to have similar effectiveness, but better cosmetic outcome, when compared with cryotherapy
  - Field-directed therapy
    - Tirbanubulin (ointment 1%): Sarcome/Tubulin Inhibitor with a 5-day application course to areas of 25cm2 that demonstrated complete clearance compared to placebo in 44% vs. 5% and 54% vs. 13% in two phase 3 randomized clinical trials.
    - Imiquimod (5%, 3.5%, 2%): Toll-like receptor-7 agonist, which stimulates the innate and cell-mediated immune pathways. Similar efficacy to 5-fluorouracil (5-FU) with better cosmetic outcome
    - 5-Fluorouracil (cream: 0.5%, 1%, 4%, 5%; solution: 2%, 5%): Blocks the methylation reaction of deoxyuridylic acid to thymidylic acid, thus interfering with the synthesis of DNA and RNA. At 4 weeks post-treatment, complete clearance rates of 0.5% and 5% 5-FU ranged from 16.7% to 57.8% and 43% to 100%, respectively
    - Four-day topical combination of 5-FU and 0.005% calcipotriene (thymic stromal lymphopoietin [TSLP] inducer) can lead to 87.8% mean reduction in number of AKs
    - Ingenol mebutate (0.015%, 0.05%): Hydrophobic diterpene ester extracted from the plant *Euphorbia peplus*. Induces swelling of mitochondria in dysplastic keratinocytes, leading to cell death by necrosis; can only apply to small area <25 cm^2. Short duration of treatment improves patient adherence
    - 3% diclofenac in 2.5% hyaluronic acid: Nonsteroidal antiinflammatory drug that inhibits cyclo-oxygenase 2 (COX-2) and reduces prostaglandin synthesis, which are thought to be increased in sun-exposed skin
    - PDT: The application of ALA leads to the formation of protoporphyrin IX (PpIX), which can be irradiated with certain wavelengths, leading to a photochemical reaction and ultimately reactive singlet oxygen formation
    - Mechanical resurfacing with both carbon dioxide (CO_2) and erbium:yttrium aluminum garnet (Er:YAG) lasers
    - Trichloroacetic acid (TCA) peel
    - In a randomized trial, 5% 5-FU cream was the most effective, at 12 months, of four field-directed treatments (5% 5-FU, 5% imiquimod cream, PDT, and 0.015% ingenol mebutate gel).
- Prevention
  - Sun avoidance
  - Low-fat diets have been reported as useful in decreasing the incidence of AKs
  - Retinoids in transplant patients may also reduce the formation of AKs
- Prognosis
  - A recent systematic review showed that progression rates of AK to SCC ranged from 0% to 0.075% per lesion-year

Bowen's Disease

- Epidemiology
  - Bowen's disease (BD) is a form of SCC in situ (SCCis) than may occur both in skin and mucous membranes
  - The exact incidence of BD is unknown. It affects elderly adults of both sexes, with a slight predominance in the female gender
- Etiology
  - Multiple etiologic factors have been associated with the development of BD including chronic sun exposure, arsenic exposure, ionizing radiation, immunosuppression, and the human papilloma virus (HPV)
- Clinical presentation
  - BD typically appears as a slowly enlarging, well-demarcated, often scaly, erythematous patch or plaque
  - It may be located on any sun-exposed or non-sun-exposed areas of the skin, including mucous membranes

- Most common locations include the head and neck, followed by the extremities and trunk (Figure 4.2.5)
- BD arising on the lower limbs is frequently found in women; whereas lesions located on the ears and scalp are more common in men
- BD on the nail bed presents as a periungual erythematous scale, onycholysis, or an erosion with crusting and nail discoloration
- Intertriginous BD appears as an acute oozing, erythematous dermatitis or as a pigmented plaque
- Mucosal BD may appear as a verrucous or polypoid plaque, an erythroplakic patch, or a velvety red plaque
- Erythroplasia of Queyrat is a term used to designate mucosal BD confined to the genitals. It is primarily seen in uncircumcised men and typically involves the inner surface of the foreskin, the glans penis, as well as the coronal sulcus. In women, it is most commonly found on the labia minora
- Arsenic-induced SCC in situ is difficult to distinguish clinically from the classic form of BD, but is more commonly multifocal and tends to favor non-sun-exposed areas on the trunk

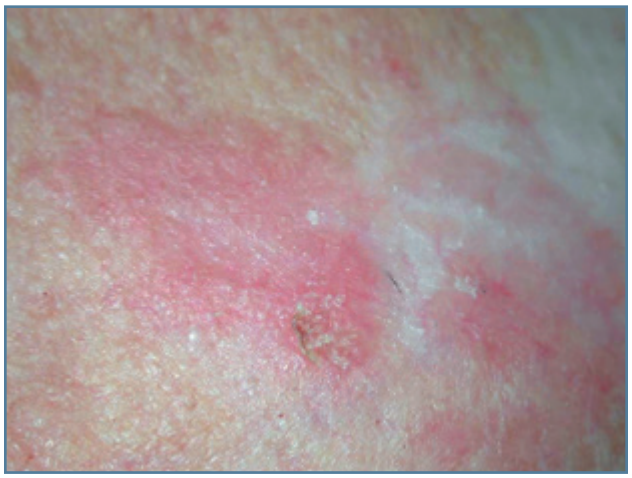

Figure 4.2.5 Pink, scaly, well-demarcated plaque located on the lower extremity of a white, female patient.

- Histopathology
  - Epidermal dysplasia and keratinocytic disorganization are seen through the entire thickness of the epidermis, from the stratum corneum down to the basal layer
  - However, the basement membrane remains intact. Often the basal layer is preserved (eyeliner sign)
  - Hyperkeratosis and parakeratosis are also present. Within the entire epidermis, pleomorphic keratinocytes show loss of polarity, atypia, and mitosis, producing a "wind-blown" appearance
  - Chronic inflammatory infiltrate composed of lymphocytes, plasma cells, and histiocytes is commonly found in the upper dermis (Figure 4.2.6)

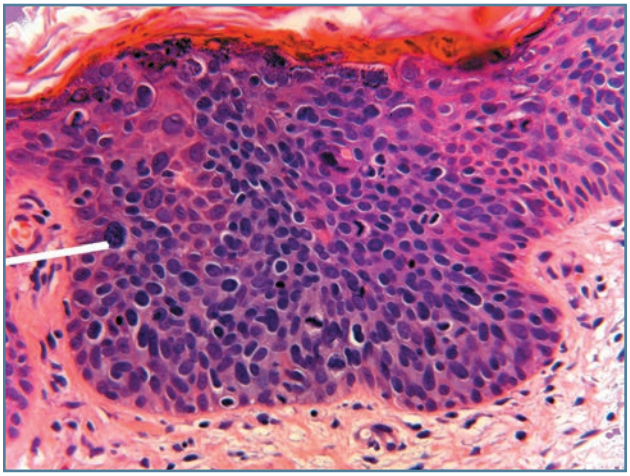

Figure 4.2.6 Neoplasm confined to the epidermis. Atypical keratinocytes are proliferating in all layers of the epidermis. Some dyskeratotic cells with pyknotic nuclei are observed in the upper layers of the epidermis. The white line is pointing at a multinucleated tumor cell.

- Diagnosis and differential
  - Differential diagnosis includes:
    - Superficial BCC
    - Chronic dermatitis
    - Psoriasis
    - Lichen planus
    - Actinic keratosis
  - Histologically, BD must be differentiated from Paget's disease, melanoma, bowenoid papulosis, and podophyllin-induced changes in a wart
- Treatment
  - Simple excision (recurrence rates of 5%)
  - Mohs micrographic surgery: In areas where there is an increased incidence of subclinical spreading, or when tissue sparing is a priority (e.g., face, genitals)
  - Curettage with or without electrosurgery can be used
  - Cryosurgery, 5-FU, and imiquimod have been reported with conventional excision
  - The superficial, large, and sometimes multifocal lesions of Bowen's disease may be considered an ideal indication for PDT
  - Radiotherapy can be used, but should not be considered first-line treatment
- Prognosis
  - An estimated ~5% of patients with BD develop invasive SCC (not necessarily in the BD lesion)

Squamous Cell Carcinoma (SCC)

- Epidemiology
  - SCC is the second most common skin cancer
  - Loss of function of NOTCH1 and NOTCH2 identified in 75% of cutaneous SCCs
  - It is more common in the male gender (a lifetime risk of 9-14% in men vs. 4-9% in women)
  - The incidence also increases with age (35 times higher in individuals older than 75 years of age when compared with ages 50-55)
  - The incidence of SCC doubles for each 8- to 10-degree decline in latitude; populations living closer to the equator have a greater risk
  - Risk factors:
    - Chronic sun exposure
    - Skin types I and II
    - Chemical carcinogens (arsenic, tobacco, coal, tar)
    - Immunosuppression (due to immunosuppressive treatment in transplant patients, or immunodeficiency syndromes such as HIV)
    - Chronic ulcers
    - Burn scars
    - Genetic syndromes (e.g., xeroderma pigmentosa)
- Etiology
  - AK is the precursor lesion of SCC. There is a sequence or continuum between AKs, SCC in situ (Bowen's disease), and invasive SCC. **However, most SCCs develop de novo and do not form from a previous AK**
  - Uncontrolled proliferation of abnormal keratinocytes may lead to the development of SCCis and ultimately invasive SCC
  - HPV infection has been linked with cutaneous SCC. Lesions on the genitals with risk of developing SCC have been associated with HPV types 16 and 18
- Clinical presentation
  - SCCs usually present as firm, skin-colored to pink, papules or plaques, commonly found on the head and neck region of elderly individuals (Figures 4.2.7, 4.2.8, and 4.2.9)
  - Other locations include the trunk, arms, dorsal hands and legs
  - Hyperkeratosis, ulceration, or crusting may be found on its surface. Symptoms such as itching, pain, and bleeding may be associated with the lesion

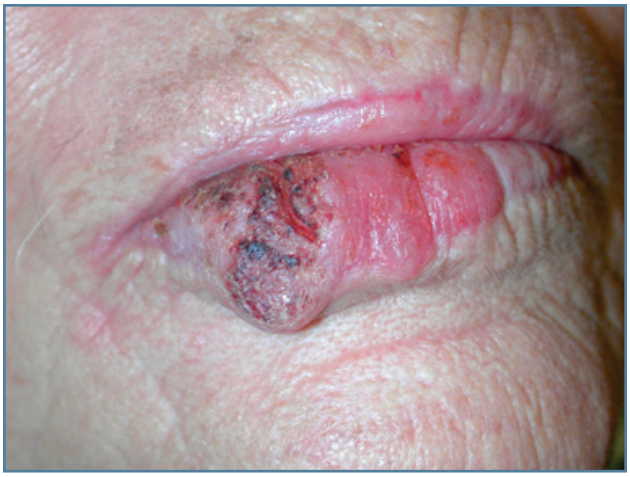

Figure 4.2.7 High-risk SCC on the lower lip.

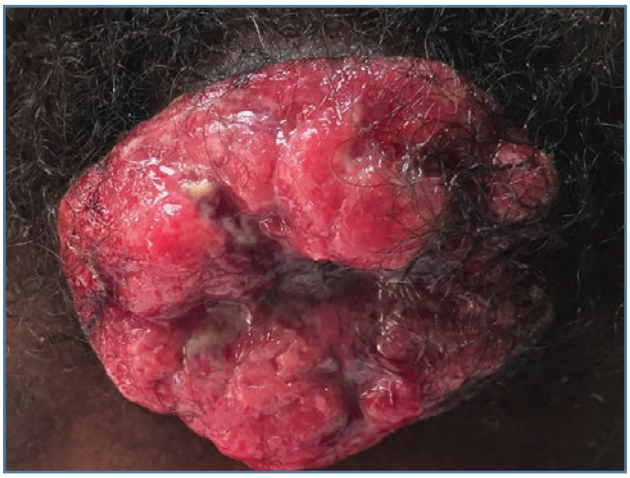

Figure 4.2.8 Large, fungating, poorly differentiated SCC on occipital scalp with invasion of muscle and bone. (Courtesy of Sailesh Konda, MD)

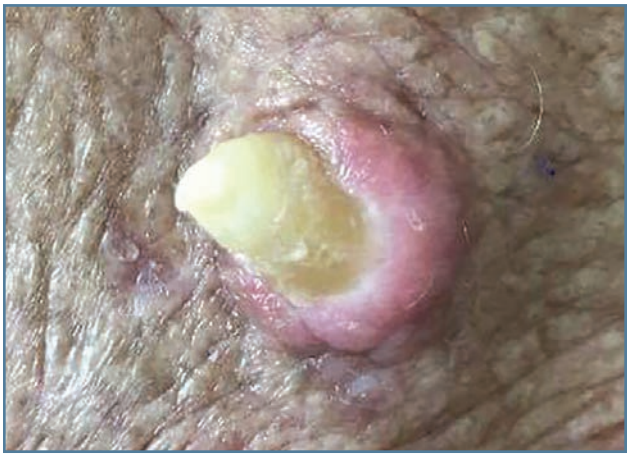

Figure 4.2.9 SCC with cutaneous horn. (Courtesy of Erin Ducharme, MD)

- Histopathology
  - Histopathologic evaluation of SCC reveals a proliferation of atypical keratinocytes that extends to (SCCis) or beyond (invasive SCC) the basement membrane into the dermis
  - The proliferation of cells can be seen as slender, long strands or as bulky masses. Individual cells have a glassy eosinophilic cytoplasm, with large nuclei. Mitotic figures (Figure 4.2.10) and horn pearls are also seen
  - Various degrees of differentiation may be seen and are usually described as well, moderately, or poorly differentiated
  - Increasing degrees of malignancy show less demarcation between the tumor masses and the stroma, greater atypia, less keratinization, and loss of intercellular bridges
  - Other histologic variants include acantholytic, adenosquamous, spindle-cell, verrucous, and desmoplastic SCC
- Staging: See Table 4.2.1

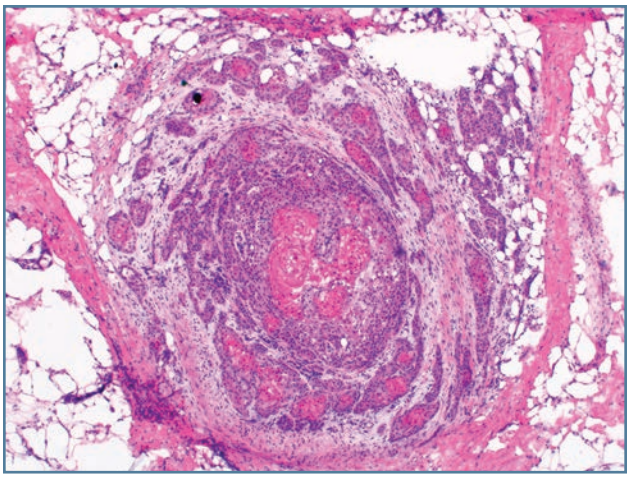

Figure 4.2.10 Invasive, well-differentiated SCC with keratin pearl formation. (Courtesy of Sailesh Konda, MD)

TABLE 4.2.1 SUMMARY OF THE AJCC-8 AND BWH (ALTERNATIVE) TUMOR STAGING SYSTEMS FOR CUTANEOUS SCC

Tumor Staging System	Definition
AJCC-8[a]	
T1	Tumor < 2 cm in greatest dimension
T2	Tumor ≥ 2 cm or larger but ≤ 4 cm in greatest dimension
T3	Tumor ≥ 4 cm in greatest dimension, or minor bone erosion, or perineural invasion, or deep invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement
BWH[b]	
T1	0 high-risk factors
T2a	1 high-risk factor
T2b	2 or 3 high-risk factors
T3	≥4 high-risk factors

Adapted from Karia et al (2014) and Montuno et al (2018).

AJCC= American Joint Committee on Cancer; BWH = Brigham and Women's Hospital; SCC = squamous cell carcinoma; T = tumor stage from TNM staging system.

[a]AJCC-8 perineural invasion defined as tumor cells within the nerve sheath of a nerve lying beneath the dermis, or measuring ≥0.1 mm in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression; deep invasion defined as involvement beyond the subcutaneous fat or >6 mm (measured from the granular layer of normal epidermis to the base of the tumor, so as to exclude the exophytic component of the tumor).

[b]BWH high-risk factors include tumor diameter ≥ 2 cm, poorly differentiated histology, perineural invasion ≥ 0.1 mm, or tumor invasion beyond fat (excluding bone invasion, which automatically upgrades tumor to BWH T3).

- Diagnosis and differential
  - AK
  - Cutaneous horn
  - Bowen's disease
  - Keratoacanthoma
  - Verruca
  - BCC
  - Amelanotic melanoma
  - Chondrodermatitis nodularis helicis
  - Pseudoepitheliomatous hyperplasia (PEH), if present, must be distinguished histologically from squamous cell carcinoma. PEH may be seen in hypertrophic lichen planus, prurigo nodularis, granular cell tumor, bromoderma, deep fungal infections (e.g., chromoblastomycosis, blastomycosis, paracoccidioidomycosis, sporotrichosis, etc.), leishmaniasis, granuloma inguinale, chronic pyodermas, chronic stasis ulcers, and ulcerations associated with thermal burns
- Treatment
  - Conventional excision for low-risk SCCs (less than 2 cm in diameter, well-differentiated pattern, located on the trunk or extremities). Recommended margins are 4 mm for low-risk lesions
  - Mohs micrographic surgery (overall cure rates are estimated to be as high as 98.1% for lesions less than 2 cm, but decrease to 74.8% for those larger than 2 cm. Well-differentiated SCCs have a 97% cure rate with Mohs, which drops to 67.4% for poorly differentiated lesions). Mohs is nonetheless indicated for primary aggressive SCCs of any size, in either immunocompetent or immunocompromised hosts, as well as in any location of the body. Mohs is not indicated for any primary AK with focal SCCis of any size or in any location, regardless of host immune status
  - Cryotherapy can be considered for small, superficial, low-risk lesions
  - Curettage and electrodesiccation
  - Radiation therapy used in combination with other modalities to treat aggressive, recurrent, or large, inoperable tumors or elderly patients who may not tolerate surgical procedures
  - Overall cure rates with non-Mohs modalities are 58.3% for tumors greater than 2 cm, 81% for well-differentiated SCCs, and 46.4% for poorly differentiated SCCs
  - Immunosuppressed solid organ transplant recipients: Consider switching to mammalian target of rapamycin inhibitors (sirolimus) instead of calcineurin inhibitors (cyclosporine, tacrolimus) and/or antimetabolites (azathioprine)
  - Chemotherapy (platinum based or taxol chemotherapy) or targeted epidermal growth factor receptor (EGFR) inhibitors (cetuximab and panitumumab) may be considered as a salvage or in addition to radiation therapy cases not amenable to surgery or radiation or as an adjuvant in the treatment of recurrent, high-risk, advanced, and/or metastatic SCC

TIP

IgG4 targeting programmed death 1 (PD-1): Cemiplimab, Pembrolizumab approved by FDA, and now NCCN preferred first line treatment for metastatic and nonresectable locally advanced cutaneous SCC. Side effects similar to melanoma trials for immune checkpoint inhibitors.

- Prognosis
  - The 10-year survival rate for individuals with regional and distant metastases is 20% and less than 10%, respectively
  - When metastases occur, regional lymph nodes are more commonly affected. Hematogenous spread usually involves lungs, liver, brain, skin, and bone
  - Management of the patients with high-risk cutaneous SCC and no clinical or radiological evidence of regional metastasis remains controversial
    - Some advocate the "watchful waiting" approach, while others prefer elective lymph node dissection
    - Recently, studies evaluating the usefulness of sentinel lymph node biopsy for the management of these patients have been reported

Keratoacanthoma

- Epidemiology
  - Keratoacanthomas (KAs) are rapid growing cutaneous tumors believed to arise from the hair follicles
  - There is much controversy as to whether or not KAs are benign lesions or well-differentiated variants of SCC capable of spontaneous degeneration
- Etiology
  - The origin of KAs has not been established
  - Due to its usual location on sun-exposed areas, ultraviolet exposure has been proposed as an important etiologic factor. Trauma, immunosuppression, and exposure to chemical carcinogens such as tar and pitch, as well as smoking, have also been linked to the development of KAs
  - A viral etiology, specifically the human papilloma virus, has also been proposed but its role in the origin of KAs remains unclear
  - Genetic factors probably play a major role in the familial type of KA. The presence of KAs in patients with Muir-Torre syndrome, and subungual KAs in incontinentia pigmenti patients, suggest the role of genetic defects

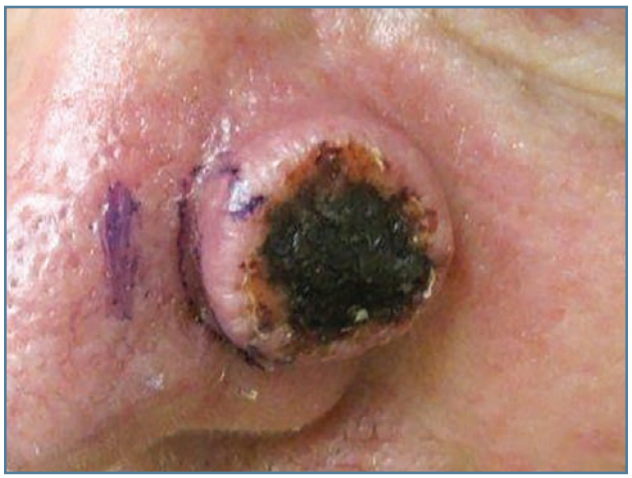

Figure 4.2.11 Dome-shaped nodules with crateriform centers typical of keratoacanthoma. (Courtesy of Cory Maughan, DO)

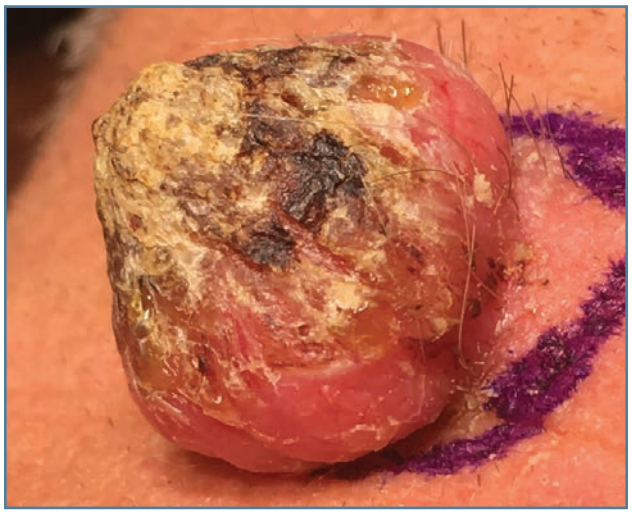

Figure 4.2.12 Exophytic hyperkeratotic nodule typical of a keratoacanthoma. (Courtesy of Stan Tolkachjov, MD)

- Clinical presentation
  - KAs usually appear as solitary, firm, dome-shaped crateriform nodules with a large keratotic core (Figures 4.2.11 and 4.2.12). Occasionally, KAs may be multiple
  - Patients are commonly fair-skinned, with history of sun exposure, and peak incidence between 50 and 69 years of age
  - The lesion can be located on any sun-exposed area, but the majority occur on the face, forearms, and hands. Typical of this tumor is its rapid growth, reaching a size of 1 to 2 cm within a few weeks and resolving slowly over a few months, often leaving an atrophic scar
  - KAs have three clinical stages: proliferative, mature, and resolving
    - The first stage (proliferative) is characterized by the sudden appearance of a firm, smooth, papule with fine telangiectasias. The papule may be skin colored or erythematous. As stated before, the tumor grows rapidly over 2 to 4 weeks until reaching a size of approximately 2 cm
    - During the mature phase, the nodule acquires a dome-shaped or bud-shaped appearance with a central, umbilicated, keratinous core. Its consistency is firm; however, fixation to underlying tissue is not present when palpating the nodule. KAs are largely asymptomatic; however, patients may or may not complain of tenderness
    - Tumor reabsorption occurs within 4 to 6 months (resolving stage), ultimately resulting in a slightly depressed, and hypopigmented scar. Usually, the process from origin to spontaneous resolution takes place within 4 to 6 months
    - KA progression to SCC with metastatic spread is rare but has been reported in immunosuppressed patients and those with Ferguson-Smith syndrome
  - There are several types of KAs including:
    - KA centrifugum marginatum is an unusual subtype of solitary KA that may reach a size of up to 20 cm in diameter. Enlargement and extension of the border with simultaneous central healing are characteristic of this type of KA
    - The giant KA is characterized by rapid growth reaching a diameter of 9 cm or more. This type of tumor can invade underlying structures including cartilage
    - The subungual KA originates in the nail bed and is locally destructive to the underlying bone. It presents as a painful, umbilicated, red, and swollen lesion, commonly located on the thumb and little finger. It is persistent, thus spontaneous involution is rarely seen
    - The Ferguson-Smith variant is characterized by the sudden appearance, during childhood or adolescence, of multiple eruptive KAs that slowly resolve and reappear later on. Face and extremities are the most common location. This condition is apparently inherited in an autosomal dominant pattern and seems to be a result of a single mutation that occurred in Scotland in the 1700s. The gene responsible for this syndrome is localized to chromosome 9q
    - Grzybowski type is typically diagnosed during adulthood, with the sudden appearance of hundreds to thousands of lesions in a disseminated fashion. Diameter of the lesions is usually 2-3 mm and can be found anywhere on the body including palms, soles, larynx, and oral mucosa. Similar incidence between men and woman. Clinically they may resemble milia cysts
    - Intraoral or mucosal membrane KAs: Extremely rare

Appears as a painless ulcer particularly difficult to differentiate from SCC, especially on the tongue, where the malignancy is a common site. Negative history of exposure to known risk factors may indicate KA
    - Multiple persistent
    - KA in special situations: Occupational (tar-induced), immunosuppressed patients (rapid progression to SCC), xeroderma pigmentosum, in Muir-Torre syndrome (autosomal dominant [AD], associated with a defective DNA mismatch repair gene, *MSH2* or *MLH1*)
- Histopathology
    - During the proliferative stage the tumor appears as a well-defined, keratin-filled invagination of the epidermis arising from contiguous hair follicles. Hyperkeratosis and acanthosis are also seen. Epidermal strands consisting of atypical squamous cells with mitotic figures extend into the dermis. A sparse dermal inflammatory infiltrate is usually found surrounding the tumor. **Perineural and vascular invasion may be present and should not be considered a sign of malignancy, in opposition to SCC, where it is a sign of metastatic disease**
    - Once the tumor progresses into the mature phase, the atypical squamous cells become less prominent. The fully developed crateriform nodule has a central depression filled with hyaline keratin. Irregular epidermal proliferations may be seen protruding into and around the base of the crater. Keratinization of the squamous cells is prominent, producing a glassy appearance
    - During involution, the lesion becomes flattened with a dense lichenoid infiltrate, fibrosis, and granulation tissue. The crater heals slowly, ultimately resulting in an irregularly shaped, atrophic scar
- Diagnosis and differential
    - The most important differential diagnosis for KA is SCC
        - Histological features such as the presence of a compact tumor, with a central crater filled with keratin, along with protruding epidermal proliferations surrounding the crater, pronounced keratinization, and neutrophilic microabscesses further confirm the diagnosis. **SCCs, even when well differentiated, show great pleomorphism and scarce keratin production, and ulceration is sometimes present**
    - Other differential diagnosis are:
        - Seboacanthoma (sebaceous adenoma + KA)
        - Exophytic pilomatricoma
        - Cutaneous metastatic disease
        - Verrucous carcinoma
        - Deep fungal infection
        - Giant molluscum contagiosum
    - **It is important to obtain a biopsy of the specimen down to the subcutaneous fat. This can be achieved either by complete excisional biopsy, full-thickness shave biopsy, or fusiform incision through the entire KA including its center and sides**
    - Even despite the fact that there are no adequately sensitive and specific criterion to distinguish KA from SCC, the five more significant are "epithelial lipping and sharp demarcation between tumor and stroma favoring KA and ulceration, numerous mitoses, and marked pleomorphism/anaplasia favoring SCC"
    - **Sometimes it is difficult to differentiate KA from SCC, both clinically and histologically. Therefore, management of the tumor as an invasive SCC should be done when clear distinction between the two tumors has not been achieved**
- Treatment
    - Even though KAs may resolve spontaneously, biopsy and treatment are usually undertaken to confirm the diagnosis and prevent further growth, discomfort, and scarring
    - Solitary KAs are usually treated by complete excision, which also provides an ideal specimen to confirm the diagnosis by histological evaluation
    - Mohs micrographic surgery is used in KAs when in critical anatomic areas and for large tumors. Recurrence after excision is seen in 4% to 8% and does not imply change in malignity
    - When a patient has multiple KAs, other treatment options should be considered (e.g., intralesional and topical therapy). These patients should have close follow-up, and tumors not responding to alternative treatments should be excised after 4 to 6 weeks. In early and small, either solitary or multiple KAs, cryosurgery with liquid nitrogen is indicated
    - Amputation of digits should be considered when there is bone involvement or failure of other therapies, especially in subungual lesions
    - Intralesional and topical therapies can also be considered. Intralesional 5-FU and methotrexate are widely used; methotrexate may be favored over 5-FU because fewer treatments are required. Intralesional bleomycin and interferon-α-2a are other options
    - Topical 5% imiquimod every other day in solitary facial KAs for 4 to 12 weeks is another treatment option
    - Systemic treatments are reserved for multiple lesions including the Ferguson-Smith variant, the Grzybowski type, and the centrifugum marginatum. Retinoids, methotrexate, 5-FU, and cyclophosphamide have been used. However, systemic retinoids are the most widely used due to their less toxic profile. Prophylactic retinoid regimen in the Ferguson-Smith variant is necessary to reduce outbreaks and minimize scarring

Basal Cell Carcinoma

- Epidemiology
  - Basal cell carcinoma (BCC) is the most common cancer that affects humans and occurs more commonly in men, with a male-to-female ratio of approximately 2:1. Over the past 30 years, the incidence has risen substantially, particularly in young women. While BCC rarely metastasizes or results in death, significant morbidity due to disability or disfigurement is not uncommon
  - Risk factors: UV radiation (UVR) exposure, fair skin phenotype, immunosuppression, family history of skin cancer, genetic syndromes (e.g., nevoid basal cell carcinoma syndrome, and xeroderma pigmentosa, among others), and radiation therapy
- Etiology
  - UVB damage to DNA produces C-T transition mutations, better known as "UVB signature" or "fingerprinting." The "UVB signature" is present in about 65% of them
  - The *p53* and *PTCH* (patch) genes are the major targets of UVB for the development of BCC
    - *p53* is a tumor suppressor gene that regulates the cell cycle and apoptosis, and has been found to be mutated in approximately 30-70% of human BCC
    - The *PTCH* gene (located on chromosome 9q22) is involved in the Hedgehog signal transduction pathway. Approximately 50% of all tumors have a mutated *PTCH* gene and 70% display loss of heterozygosity (LOH) in the *PTCH* locus. It is also responsible for the genetic defect in Gorlin syndrome. In approximately 50% of BCCs isolated from xeroderma pigmentosa both *p53* and *PTCH* genes are mutated
  - Other genes involved in the development of BCC include **smoothened-activating** mutations and *PTCH2* mutation
- Clinical presentation
  - Sun-exposed areas are the most frequent location of BCCs, with the nose being the most common site, but it can be found anywhere on the skin
  - There are several subtypes of BCC
    - The nodular subtype represents approximately half of all BCCs and initially presents as a small, translucent, pearly papule with telangiectasias on its surface. As the lesion progresses, the center may become ulcerated and the borders become indurated, rolled, and pearly (Figure 4.2.13). This classic lesion is better known as "rodent ulcer" (Figure 4.2.14)
    - The superficial BCC is commonly located on the trunk and limbs, and appears as a pink, scaly plaque with a slightly elevated pearly border (Figure 4.2.15). The superficial BCC subtype is the most prevalent variant in younger patients, with a mean age of onset of 57 years. Crusting and ulceration may sometimes be present
    - Pigmented BCCs may appear as the nodular or superficial variant, with central black, gray, blue, or brown pigmentation in the form of specks, dots, or globules (Figure 4.2.16)
    - The morpheaform BCC, also known as sclerosing BCC, presents as a skin-colored, pink or whitish, indurated plaque that resembles a scar (Figure 4.2.17). This variant has ill-defined borders and an aggressive growth pattern. It represents approximately 5% of all BCCs
    - The fibroepithelioma of Pinkus BCC appears as a pedunculated, pink, dome-shaped papule, frequently located on the back (lumbosacral area)

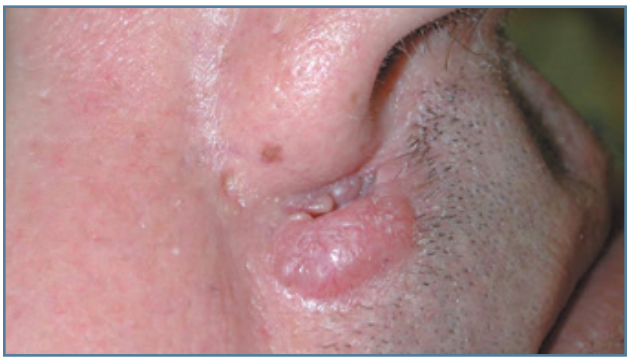

Figure 4.2.13 Nodular basal cell carcinoma (BCC). Notice the translucent appearance and pearly surface with telangiectasias.

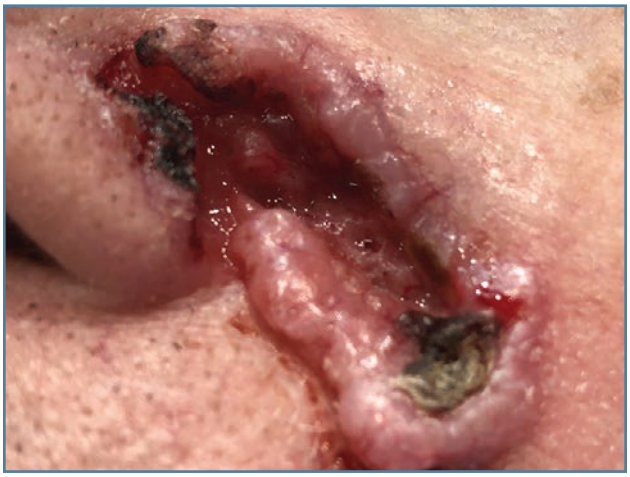

Figure 4.2.14 Nodular BCC. Classic appearance of "rodent ulcer." (Courtesy of Sailesh Konda, MD)

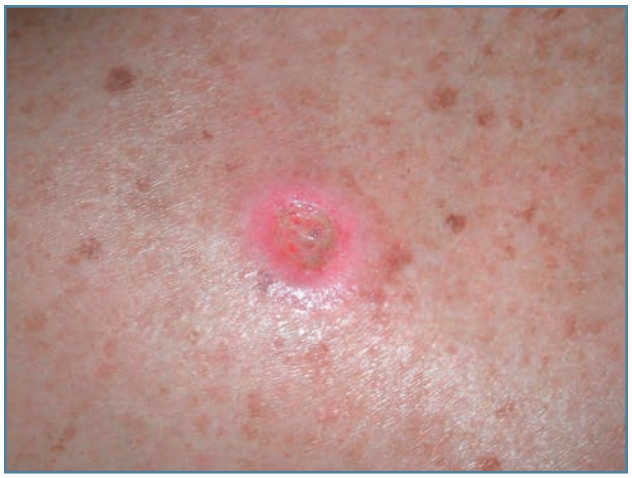

Figure 4.2.15 Superficial BCC. Pink plaque with pearly border and central ulceration on an upper extremity.

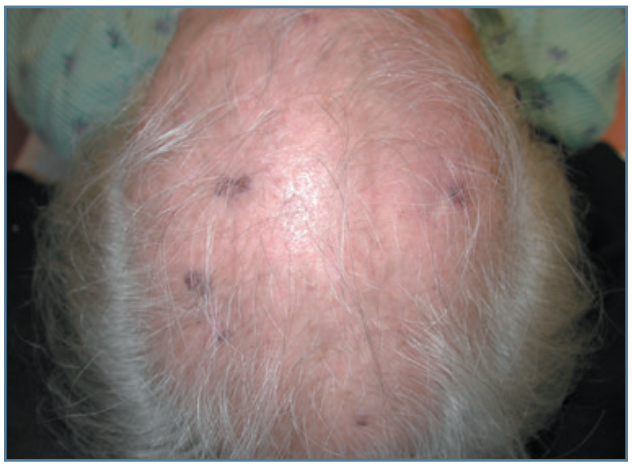

Figure 4.2.16 Multiple pigmented BCCs on the scalp of a white, elderly individual.

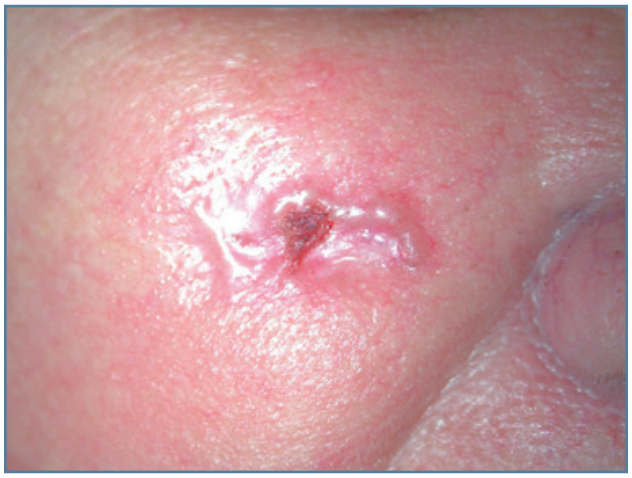

Figure 4.2.17 Morpheaform BCC. Atrophic plaque with raised, pearly borders and central crust.

TIP

Gorlin syndrome (i.e., nevoid basal cell carcinoma syndrome) is characterized by the appearance of multiple BCCs during childhood, palmar pits, odontogenic keratocysts of the jaw, and skeletal defects (e.g., macrocephaly, hypertelorism, frontoparietal bossing, spina bifida, or rib abnormality, among others). BCCs in Gorlin syndrome may present as any type of BCC but also can resemble nevi, milia, or skin tags. Tumors associated with this disease include medulloblastoma, meningioma, ovarian fibromas (bilateral), and cardiac fibromas. It is inherited in an autosomal dominant pattern, and is due to a mutation in the *PTCH* gene

- Histopathology
  - While several histologic patterns have been described, all BCCs share the characteristic histopathologic feature of large aggregates of basaloid keratinocytes, also known as tumor islands. Another feature that is helpful in distinguishing BCCs on histology is the presence of clefting caused by retraction of the stroma around the tumor islands
  - The nodular pattern is the most common, and a less aggressive pattern. It shows large, well-defined tumor masses with peripheral palisading
  - Superficial BCCs are less aggressive and characterized by the presence of tumor buds or proliferations originating in the epidermis and extending toward and into the dermis. Palisading is also evident
  - The micronodular variant shows small tumor masses surrounded by fibrous stroma. Palisading is not prominent
  - Infiltrative BCCs appear as tumor masses of variable size, with irregular, spiky outlines and scarce evidence of palisading or clefting
  - Morpheaform BCCs present with elongated strands of tumors cells within an abundant, sclerotic stroma
  - The Pinkus tumor shows long, branched, thin strands of tumor embedded in a fibromyxoid stroma, and connected to the overlying epidermis
  - **Two-thirds of BCCs show loss of heterozygosity ± truncating mutations in *PTCH* gene. The second most common genetic alteration found in BCCs is point mutations in *p53***
  - **Diffuse staining with Bcl-2 (vs periphery in trichoepitheliomas)**

- Dermoscopic features of pigmented BCC
  - Maple leaf–like structures
  - Large blue-gray ovoid nests
  - Spoke-wheel-like areas
  - Arborizing telangiectasias
- Metatypical variant = basosquamous carcinoma: Merging of basaloid tumor areas with squamoid areas with keratinization (Figure 4.2.18)

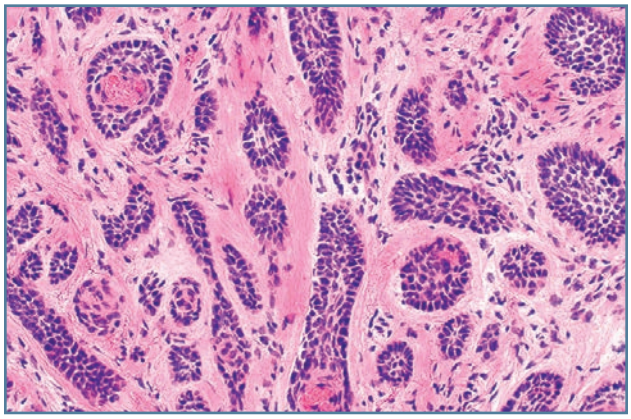

Figure 4.2.18 BCC with squamous differentiation. (Courtesy of Sailesh Konda, MD)

- Diagnosis and differential
  - Some suggest that for morpheaform-appearing BCC a punch biopsy of the central, indurated area of the lesion should be done to establish the diagnosis. Whereas, for all other types of BCC, a shave biopsy is usually enough to confirm the diagnosis
  - Differential diagnosis for noduloulcerative BCC includes:
    - Ulcerative SCC
    - Amelanotic melanoma
    - Sebaceous hyperplasia
    - Dermal nevus
    - Fibrous papule
  - Differential diagnosis for superficial BCC include:
    - Bowen's disease
    - AK
    - Psoriasis
    - Eczema
  - Differential diagnosis for pigmented BCC:
    - Malignant melanoma
    - Melanocytic nevi
  - Differential diagnosis for morpheaform BCC:
    - Scar
    - Isolated plaque of morphea
- Treatment
  - In a large systematic review of 89 articles evaluating 16,066 lesions, the authors concluded that a 3-mm surgical margin can be safely used for nonmorpheaform basal cell carcinoma to attain 95% cure rates for lesions 2 cm or smaller
  - Other methods: Cryosurgery, radiotherapy, and topical 5-FU or imiquimod for superficial BCCs are less often used techniques
  - PDT and lasers have recently gained popularity for the therapeutic management of low-risk, small, superficial BCC
  - IgG4 targeting programmed death 1 (PD-1): Cemiplimab recently approved by FDA for metastatic and nonresectable locally advanced BCC. Side effects similar to melanoma trials for immune checkpoint inhibitors
  - Cemiplimab is the first approved (2021) anti-PD-1 antibody for treatment of locally advanced or metastatic BCC

TIP

Hedgehog pathway inhibitors: Abnormal activation of the Hedgehog signaling pathway is a key driver in BCC pathophysiology. Vismodegib and sonidegib are smoothened (SMO) inhibitors for the treatment of adults with basal cell nevus syndrome or those with metastatic or locally advanced BCC that has recurred following surgery or who are not candidates for surgery or radiation. Side effects are frequent and can limit their use. They include muscle spasms (72%), alopecia (64%), dysgeusia (55%), and weight loss (45%)

Prognosis

- BCCs are characterized by their slow, indolent growth and progressive invasion of adjacent tissues. However, their metastatic potential is very low with rates ranging from 0.0028 to 0.1%
- Those BCCs that do metastasize tend to be large, ulcerated, neglected lesions, with an aggressive growth pattern. Rare metastasis have occurred in the lymph nodes and lungs

Dysplastic Nevi

- Epidemiology
  - Dysplastic nevus, also known as Clark's nevus or atypical nevus, is a controversial term that can be

used pathologically to describe a nevus with architectural and/or cytological atypia. It is also used clinically to describe a nevus with features such as asymmetry, irregular borders, or multiple colors

- Etiology
  - Dysplastic nevi can be familial or sporadic. Familial occurrence has been termed dysplastic nevus syndrome or familial atypical multiple mole melanoma (FAMMM) syndrome. **FAMMM has autosomal dominant inheritance with mutations in the *CDKN2A* gene (p14^{ARF} and p16^{INK4})**
- Clinical presentation
  - Dysplastic nevi appear in a wide age range of patients. They have a predilection for the trunk but can occur anywhere on the cutaneous or mucous surface. They are characterized by asymmetry; irregular, ill-defined borders; irregular pigment pattern; and can be any size. No single defining feature is present in all lesions
- Histopathology
  - Dysplastic nevi are characterized into mild, moderate, or severe atypia based on their cytological and architectural features
  - Cytological atypia can include:
    - Enlarged nucleus
    - Prominent nucleolus
    - Dirty gray cytoplasm
  - Architectural atypia can include:
    - Irregularly sized or placed nests
    - Bridging of junctional nests (called lentiginous pattern)
    - Papillary dermal fibrosis in a lamellar or concentric pattern
    - Asymmetry
    - Lack of circumscription
    - Shouldering phenomenon (the junctional component of the nevus extends more than 3 rete ridges past the dermal component)
- Diagnosis and differential
  - Dermoscopy can be helpful to pick up suggestive clinical features such as lack of organization, pigment variation, and asymmetry
  - Differential diagnosis includes:
    - Melanoma
    - Commonly acquired nevi
    - Congenital nevi
    - Pigmented keratinocytic lesions
- Treatment
  - Treatment is controversial. A recent consensus statement (Kim et al, 2015) reviewed the management of dysplastic nevi. Recommendations included the following:
    - Mildly and moderately dysplastic nevi with clear margins do not need to be reexcised
    - Mildly dysplastic nevi biopsied with positive histologic margins without clinical residual pigmentation may be observed
    - Observation may be a reasonable option for management of moderately dysplastic nevi with positive histologic margins without clinically apparent residual pigmentation
    - Reexcision of severely dysplastic nevi with positive margins to achieve a 2- to 5-mm clinical margin is generally recommended
- Prognosis
  - **Risk of melanoma or malignant degeneration from an individual dysplastic nevus is controversial but most likely very low. The risk of melanoma is tied more to the number of dysplastic nevi**

Malignant Melanoma

- Epidemiology
  - Cutaneous malignant melanoma (MM) is a potentially fatal tumor that originates from malignant melanocytes. The incidence of MM has risen over the past decade. It was estimated that the lifetime risk for the development of melanoma in a person born in the year 2000 is 1 in 75
  - The incidence between males and females in the United States is equal. Compared with nonmelanoma skin cancer (NMSC), MM affects a younger population (peak incidence, 20-45 years old)
  - The most common locations are the back, chest, and upper extremities for men. However, in women, the most common locations are the back, lower legs, and upper extremities
- Etiology
  - The etiology of MM has not been clearly determined. UV radiation causing DNA mutations has been associated with the development of MM. It has been reported that the risk is higher than twofold with a history of five or more episodes of sunburn during adolescence
  - Around 10% of melanoma cases are considered familial. *CDKN2A* mutations are the most frequent genetic events underlying familial melanoma susceptibility and have been reported in 8% to 57% of familial melanoma cases. Cyclin-dependent kinase 4 *(CDK4)* is another high-risk melanoma susceptibility gene. **In melanoma genetic counseling, genet-**

ic testing is mainly focused on *CDKN2A* and *CDK4* genes. In addition to familial susceptibility, somatic mutations in key genes pose as considerable risk factors for melanoma. ***BRAF* is the gene most frequently mutated (50-70%) in melanoma, while *NRAS* is mutated in 15-30% of cases, and *KIT* is mutated in less than 17%. It is reported that *KIT* mutations are more common in mucosal and acral melanomas, while *GNAQ* and *GNA11* mutations are associated with uveal melanomas.** Other genetic defects involve *BAP1, POT1, ACD, TERF2IP,* and *TERT*

- Clinical presentation
  - There are four types of melanoma: Superficial spreading, nodular, acral lentiginous, and lentigo maligna melanoma
  - Superficial spreading melanoma (SSM) accounts for approximately 70% of all melanomas in the white population
    - It may be located anywhere, but the back and lower legs are the most common sites for men and women, respectively
    - It is usually diagnosed in individuals during their fourth or fifth decade of life
    - It may evolve from melanocytic nevi
    - It usually arises as a dark pigmented macule or slightly raised plaque. Mixed colors may be seen, such as dark brown or black, with shades of pink, blue, or gray. The lesion is found to be well demarcated and asymmetrical, with indented borders
  - Nodular melanoma (NM) is the second most common type of melanoma in persons of fair complexion (15%) (Figure 4.2.19)
    - This type of melanoma may be located anywhere on the body of individuals with ages ranging from 40 to 50 years
    - The lesion is characterized by the sudden appearance and growth of a dark brown, black, or blue nodule, with well-defined and regular borders
  - Acral lentiginous melanoma (ALM) is the predominant type of melanoma in dark-skinned individuals (Figure 4.2.20)
    - It is usually located on the soles, palms, and subungual region of older patients (fifth to sixth decade of life)
    - It presents as a flat, brown to black lesion with irregular borders
- Lentigo maligna melanoma (LMM) is the least common (approximately 5%) and arises from the precursor lesion, lentigo maligna (melanoma in situ)
  - It usually affects older individuals (sixth to seventh decade of life) and involves sun-exposed regions, with cheeks, nose, and temples being the favored sites
  - LMM appears as a flat lesion with nodular areas, and different shades of brown and black colors. The borders are sharply demarcated and very irregular

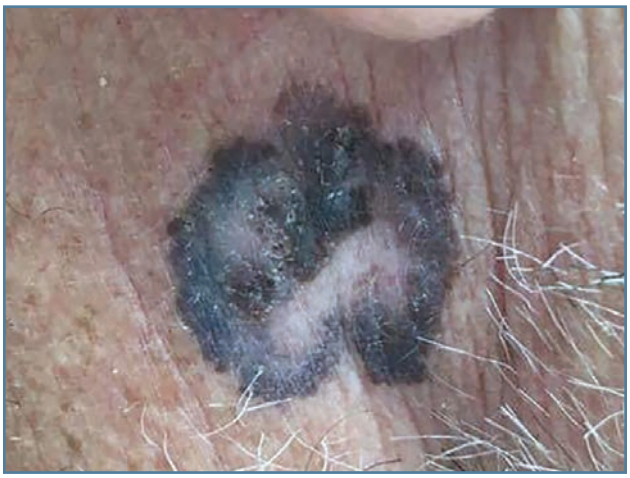

Figure 4.2.19 Nodular melanoma with areas of regression on jawline of white individual. (Courtesy of Erin Ducharme, MD)

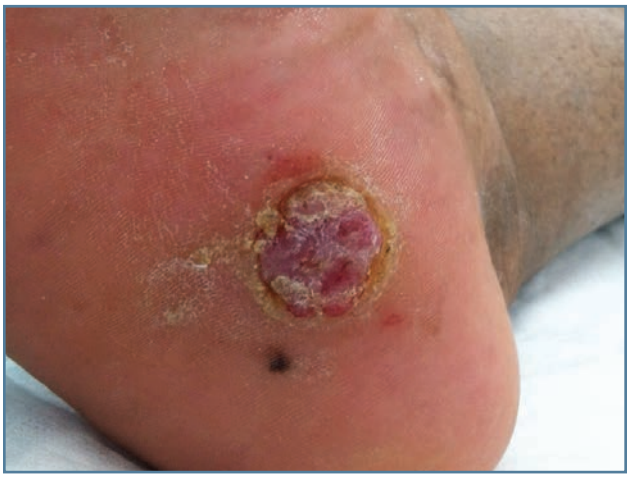

Figure 4.2.20 Acral lentiginous melanoma on foot of dark-skinned individual. (Courtesy of Stan Tolkachjov, MD)

- Histopathology
  - Histologic findings such as asymmetry, poor circumscription, and the presence of single melanocytes at and above the dermal-epidermal junction on sun-damaged skin are diagnostic for melanoma (Figure 4.2.21)

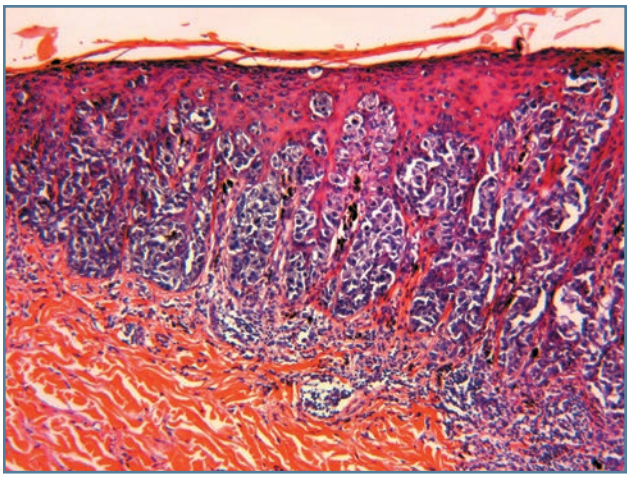

Figure 4.2.21 Pagetoid melanoma. Neoplastic proliferation of melanocytes forming irregular nests in the basal layer. Single atypical melanocytes are spreading within all the layers of the epidermis. The cells have large atypical nuclei and abundant eosinophilic cytoplasm and a surrounding halo resembling cells of Paget disease.

- Atypical melanocytes may also be distributed in the adnexal structures
- MM has two growth phases, horizontal and vertical
  - During the horizontal growth period, atypical melanocytes are mainly located within the epidermis and may be singly seen infiltrating the papillary dermis
  - This phase is followed by a vertical growth period, in which large nests of malignant melanocytes invade the dermis and obtain the potential of metastasizing. Nodular melanomas exhibit mainly a vertical growth phase and become thick lesions in a short amount of time

- Diagnosis and differential
  - Identification of melanoma is initially done through visual examination of suspicious lesions. The ABCDE rule should be used, where A stands for asymmetry, B is for irregular borders, C is for diversity of colors, D is for diameter larger than 6 mm, and E is for evolving
  - Dermoscopy or epiluminescence microscopy is another noninvasive technique used for the evaluation of pigmented lesions and diagnosis of MM
    - Several dermoscopic diagnostic algorithms have been proposed including the ABCD rule of dermoscopy, the Menzies method, the seven-point checklist, and more recently the three-point checklist
  - In general, the following dermoscopic features are suggestive of MM:
    - Asymmetry
    - Multicomponent pattern
    - Parallel-ridge pattern (for acral melanocytic lesions)
    - Atypical pigment network (characterized by black, brown, or gray network, irregularly distributed within the lesion, that usually ends abruptly in the periphery)
    - Uneven arrangement of streaks (radial streaming) throughout the lesion
    - Blue-whitish veil
    - Localized irregular and diffuse pigmentation
    - Irregularly distributed or isolated globules (dark or slate blue)
    - Regression structures seen as white (scar-like) or blue-gray areas
  - Once clinical examination and dermoscopic features lead to the initial diagnosis of MM, a biopsy must be performed for histologic confirmation. Excisional biopsies are favored and provide adequate tissue specimen for histologic diagnosis and staging of the lesion
  - Incisional biopsies may be considered when the suspicion for melanoma is low, the lesion is large, located in a cosmetic sensitive area, or when excision is unfeasible

- Staging: See Table 4.2.2

TABLE 4.2.2 AJCC MELANOMA TUMOR (PATHOLOGIC) STAGE SYSTEM

T Category									Sentinel Lymph Node Positive	Node Category
T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b		
No evidence of primary tumor	< 0.8 mm without ulceration	< 0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration	> 1.0-2.0 mm without ulceration	> 1.0-2.0 mm with ulceration	> 2.0-4.0 mm without ulceration	> 2.0-4.0 mm with ulceration	> 4.0 mm without ulceration	> 4.0 mm with ulceration		
	IA	IA	IB	IIA	IIA	IIB	IIB	IIC	No	**NO**
	IIIA	IIIA	IIIA	IIIB	IIIB	IIIC	IIIC	IIIC	Yes	**N1a**

T0 = no evidence of primary tumor (e.g. unknown primary or completely regressed melanoma); Tis = melanoma in situ; Tx = thickness cannot be assessed (Tis and Tx are not included in the table but are part of the staging system).

Exception: Pathological N category is not required for T1 melanomas; use clinical N information. If SLNB was performed, the results can and should be used for pathological evaluation.

- **Major Changes in the AJCC-8 Tumor Staging System for Cutaneous Melanoma (2018)**
  - T1 now subcategorized by tumor thickness threshold at 0.8 mm
  - Tumor mitotic rate is removed as staging criterion for T1 tumors
  - Tumor thickness measurements now recorded to nearest 0.1 mm, not nearest 0.01 mm
  - Presence or absence of nonnodal regional metastases (i.e., microsatellites, satellites, or in-transmit metastases) is categorized in the N-category criterion based on the number of tumor-involved regional lymph nodes
  - Stage III groupings redefined and increased from three to four subgroups; addition of stage IIID subgroup; stage III disease associated with heterogeneous outcomes; 5-year melanoma-specific survival rates range from 93% for stage IIIA disease to 32% for stage IIID disease
  - Site of distant metastasis remains primary component of M category: nonvisceral, M1a; lung, M1b; non-CNS visceral, M1c; and new M1d for CNS metastasis
  - Elevated lactate dehydrogenase (LDH) no longer M1c criterion; however, LDH remains an important predictor of survival in stage IV and is recorded for any M1 anatomic site of disease
- Sentinel lymph node biopsy (SLNB)
  - According to the American Society of Clinical Oncology—Society of Surgical Oncology (ASCO-SSO) guidelines, SLNB is recommended for patients with primary melanomas ≥ 1.0 mm. Both the ASCO-SSO and the National Comprehensive Cancer Network (NCCN) guidelines state SLNB may be considered for patients with T1b (<0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration) melanomas
  - If indicated, SLNB should be performed during the same operation immediately prior to excision of the primary tumor to minimize disruption of lymphatics
- Treatment
  - The treatment of choice for MM is surgery, and the goal is complete removal of the lesion histologically confirmed with negative margins. Although Mohs micrographic surgery can be used for primary or locally recurrent melanoma in situ in both healthy and immunocompromised hosts, formalin-fixed permanent section histology remains superior to frozen sections for histologic evaluation of surgical margin of melanocytic lesions

TABLE 4.2.3 MELANOMA SURGICAL MARGINS

Tumor Thickness	Surgical Margin
In situ	0.5-1 cm
≤1.0 mm	1 cm
>1.0-2.0 mm	1-2 cm
>2.0 mm	2 cm

  - Mohs micrographic surgery has been suggested for the treatment of MM. However, the exact situations where it should be used is not currently clear.
  - Topical imiquimod should be considered only if surgery is impractical or contraindicated, and only for melanoma in situ, lentigo maligna type, as the cure rates associated with these treatments are lower
  - Adjuvant therapy with interferon-α has been used for patients with a high risk of recurrence (primary melanoma with tumor thickness ≥ 4.0 mm or level V invasion, primary melanoma with in-transit metastases, primary melanoma with regional lymph node metastases that are clinically apparent or detected at elective lymph node dissection, regional lymph node recurrence, involved nodes excised but no known primary melanoma). It has been shown to improve disease-free and overall survival
  - Treatment options for distant metastases include:
    - Surgical excision of isolated metastases (skin, subcutaneous tissue, lung, brain)
    - Radiation therapy
    - Immunotherapies: Interferon-α-2b, interleukin-2 (IL-2)
    - Melanoma therapeutic vaccines
    - Oncolytic virus: Talimogene laherparepvec (Imlygic) is a genetically modified herpes simplex virus (HSV)-1 that produces granulocyte-macrophage colony-stimulating factor (GM-CSF). It is injected directly into the lesions, causing cell lysis and releasing tumor-derived antigens and GM-CSF, promoting an anti-tumor immune response
    - Tyrosine kinase inhibitors: Imatinib, dasatinib
    - Newer monoclonal antibodies
      - Ipilimumab: IgG1 directed against cytotoxic T lymphocyte—associated antigen 4 (CTLA-4); assess patients for signs and symptoms of immune-mediated adverse reactions, e.g., enterocolitis, hepatitis, dermatitis, Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), neuropathy, and endocrinopathy
      - Pembrolizumab, nivolumab: IgG4 targeting programmed death 1 (PD-1); assess for immune-mediated adverse reactions, e.g.,

pneumonitis, colitis, hepatitis, nephritis, endocrinopathy, and dermatitis (SJS/TEN)

- Relatlimab: first-in-class human IgG4 LAG-3—blocking antibody that binds to LAG-3 and restores the effector function of exhausted T cells. It is used in combination with nivolumab to treat metastatic melanoma with similar immune-mediated adverse reactions as anti-CTLA-4 and anti-PD1 therapies e.g.,pneumonitis, colitis, hepatitis, nephritis, endocrinopathy, and dermatitis (SJS/TEN)

- Oncogene-targeted drugs
  - BRAF inhibitors (vemurafenib, dabrafenib): *BRAF* mutations have been found in at least 50% of melanomas. BRAF inhibitor—induced keratoacanthoma-like lesions are common. Their incidence is reduced when combined with a MEK inhibitor
  - MEK inhibitor (trametinib, cobimetinib): MEK inhibitors have been used in combination with BRAF inhibitors and have extended progression-free survival from 5 months with BRAF or MEK inhibitor monotherapy to 9-10 months with BRAF + MEK combination therapy

- Prognosis
  - Increasing age and male gender have a negative effect on survival
  - Patients with primary lesions located on the extremities have a better prognosis than those with tumors located on the head, neck, or trunk
  - Increasing tumor thickness, invasion, and ulceration are considered poor prognostic factors
  - In stage III melanoma, the fewer the number of nodes involved the better the prognosis
    - There is significantly lower survival for those patients with palpable metastatic nodes (macrometastasis) when compared with those with micrometastatic nodes (nonpalpable)
  - For stage IV melanoma, patients with nonvisceral metastases (skin, subcutis, distant lymph nodes) have a better prognosis compared with those with visceral metastases
  - Ancillary diagnostic molecular techniques may be used for equivocal melanocytic neoplasms. Routine molecular testing is not recommended at this time until better criteria are defined

Merkel Cell Carcinoma (MCC)

- Epidemiology
  - Also known as cutaneous neuroendocrine carcinoma, this tumor is an unusual malignant neoplasm that arises from neuroendocrine cells with features of epithelial differentiation
  - Caucasians older than 50 years of age are typically affected, and a slight female preponderance has been noted. There have been reports of MCC in children and young adults
- Etiology
  - The origin of this neoplasm is unknown
  - UV light exposure, advanced age, and immune suppression have been postulated as risk factors
  - **A newly identified virus, the Merkel cell polyomavirus, is present in approximately 80% of these tumors and appears to be associated with the development of Merkel cell carcinoma**
- Clinical presentation
  - The tumor usually appears as a solitary, 1- to 2-cm, dome-shaped nodule, most frequently located on the head and neck region and extremities (Figure 4.2.22)
  - The nodule is commonly found to be dark red or violaceous with a shiny surface that often has telangiectasias. The overlying skin may be intact or ulcerated

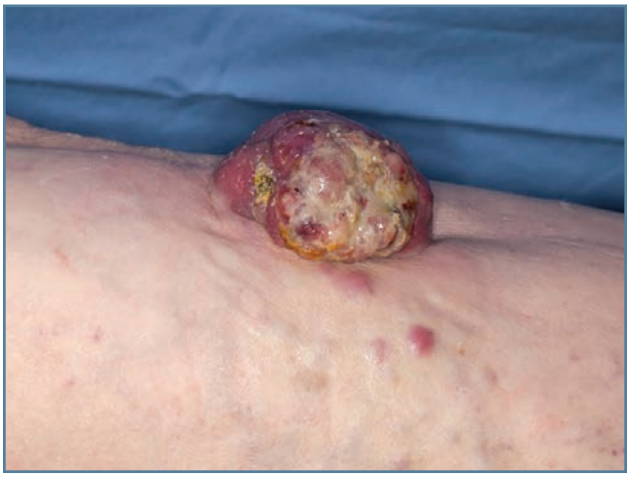

Figure 4.2.22 Merkel cell carcinoma (MCC) on upper extremity of white individual. (Courtesy of Stan Tolkachjov, MD)

- Histopathology
  - Light microscopy: There are three histologic patterns of MCC: trabecular, intermediate-cell type, and small-cell type
    - The trabecular variant consists of interconnecting trabeculae separated by strands of connective tissue. Also, pseudorosettes may be found
    - The majority of MCCs belong to the intermediate-cell type, characterized by large, solid nests of cells of intermediate size, with a trabecular pattern in the periphery
    - The least frequent variant is the small-cell type, which consists of diffusely infiltrating sheets of small neoplastic cells that may be mixed with intermediate cells. The tumors involve the dermis and spread into the subcutaneous fat, usually sparing the overlying epidermis (Figure 4.2.23)
    - The neoplastic cells are round and uniform in size, with a round to oval nucleus, small nucleoli, and evenly dispersed chromatin. A "ball-in-mitt" pattern is said to be typical, with one or two crescentic tumor cells wrapped around one central round tumor cell. Numerous mitotic figures and necrotic areas, in addition to neural and vascular invasion, are often seen

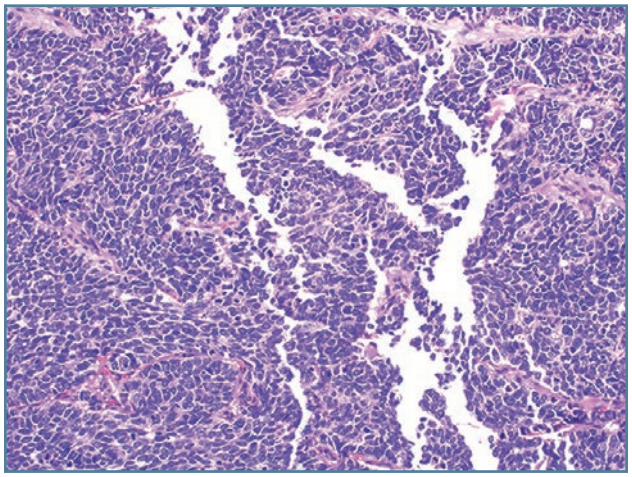

Figure 4.2.23 Basophilic aggregates of small-round cells. The tumor cells have prominent round, vesicular nuclei and scant, ill-defined cytoplasm. Occasional mitoses are present. The neoplastic cell islands connect to each other via anastomosing cords. (Courtesy of Sailesh Konda, MD)

  - Electron microscopy: The main ultrastructural features of MCC include dense core granules concentrated in cytoplasmic processes and perinuclear aggregates of intermediate filaments (cytokeratins, neurofilaments) that parallel or have a whorled arrangement near the nucleus
  - Immunohistochemistry: MCC exhibits both epithelial and neuroendocrine markers
  - The most commonly used markers for MCC are monoclonal antibodies to:
    - Cytokeratins 8, 18, and 20
    - **Neuron-specific enolase (the most consistent marker)**
    - Chromogranin A/B
    - Synaptophysin
    - Leukocyte common antigen, vimentin, desmin, glial fibrillary acidic protein, and S-100 are consistently absent in MCC
- Diagnosis and differential
  - **Thyroid transcription factor 1 (TTF-1) and cytokeratin-7 are negative in MCCs, but positive in metastatic small-cell carcinomas (SCCs)**
  - Both clinical and histopathological (light microscopy, electron microscopy, and immunohistochemistry) evaluation are required for the diagnosis of MCC
  - **A correct diagnosis of MCC may be confirmed by positive juxtanuclear labeling of tumor cells with anti-cytokeratins, cytoplasmic reactivity to neuron-specific enolase, and focal presence of neurofilament proteins in perinuclear location**
  - Differential diagnosis includes:
    - SCC
    - BCC
    - Pyogenic granuloma
    - Keratoacanthoma
    - Amelanotic and melanotic melanoma
    - Adnexal tumors
    - Lymphoma
    - Metastatic oat cell carcinoma
    - Undifferentiated anaplastic carcinomas
    - Neuroblastomas
- Sentinel lymph node biopsy
  - Intraoperative mapping and SLNB are indicated for the treatment and prognosis of MCC. The presence of metastatic disease in the sentinel node may be used as rationale for complete node dissection and additional adjuvant therapy

- Treatment
  - Surgical treatment: Wide local excision with 2- to 3-cm margins has long been advocated as the treatment of choice. However, Mohs micrographic surgery has successfully been used for the treatment of MCC, yielding the lowest local recurrence rates
  - Radiation and chemotherapy: MCCs are sensitive to radiation and chemotherapy
    - Controversy exists regarding the usefulness of radiation for the treatment of MCC
    - Radiation monotherapy may be used as an alternative treatment modality for patients who are poor surgical candidates. Outcomes may be inferior compared with complete surgical excision
    - Adjuvant radiation may improve overall survival in patients with localized disease
  - For patients with systemic disease, multiple cytotoxic agents have been employed including cyclophosphamide, methotrexate, 5-FU, cisplatin, etoposide, and doxorubicin, among others
  - Checkpoint inhibitor avelumab (anti-PD-L1 antibody) has been approved (2017) for the treatment of metastatic MCC
  - Avelumab (anti-PD-L1 antibody) was approved (2017) for the treatment of metastatic MCC. Additionally, pembrolizumab (anti-PD-1 antibody) was approved (2018) for recurrent locally advanced or metastatic MCC
- Prognosis
  - As stated before, MCC displays aggressive behavior and has a high incidence of local recurrence, regional and systemic spread. The overall survival rates have been estimated to be 88% for 1 year, 72% for 2 years, and 55% for 3 years
  - The incidence of regional lymph node metastases has been reported to be between 50 and 60%
  - Distant or hematogenous metastases occur in 30-40% of patients, and usually involve the liver, bone, brain, or lung

Sebaceous Carcinoma

- Epidemiology
  - Sebaceous carcinoma is a rare adenocarcinoma of sebaceous differentiation
- Etiology
  - Sebaceous carcinomas can arise de novo or in association with Muir-Torre syndrome
- Clinical presentation
  - **Sebaceous carcinoma most commonly presents on the head and neck, with a predilection for the periorbital area**
    - **The most common location of sebaceous carcinoma is the upper eyelid**
  - Less commonly, they are also seen on the trunk. It typically presents as a nonspecific flesh-colored, yellow-pink to red nodule and can be shiny or pearly
- Histopathology
  - Sebaceous carcinomas arise from the epidermis and extend or infiltrate into the dermis with arrangements of nests, lobules, and strands. They show asymmetry, atypical mitoses, and are poorly defined
  - **Staining for epithelial membrane antigen (EMA) and adipophilin, using an indirect immunoperoxidase method, can be done to confirm sebaceous origin**
  - Ocular sebaceous carcinoma is often noted to have prominent pagetoid scatter within the epidermis
  - Sebaceous carcinomas with a keratoacanthoma-like pattern can occur with Muir-Torre syndrome
- Diagnosis and differential
  - Differential diagnosis includes:
    - BCC
    - SCC
    - Sebaceoma
    - Sebaceous adenoma
    - Ocular sebaceous carcinoma is often misdiagnosed as chalazion or blepharitis
- Treatment
  - Mohs micrographic surgery provides higher cure rates compared with conventional excision
  - Extensive ocular involvement, especially of the conjunctiva, may necessitate ocular enucleation
- Prognosis
  - Sebaceous carcinomas can metastasize to regional lymph nodes. Metastatic disease has been reported in 9-50% of the cases
  - Five-year mortality rate is 80%

Dermatofibrosarcoma Protuberans

- Epidemiology
  - Dermatofibrosarcoma protuberans (DFSP) is a spindle cell tumor more common in individuals 30-50 years old, with a higher incidence in males (3:2 male-to-female ratio)
  - It accounts for approximately 0.1% of all skin neoplasms

- Etiology
  - The histogenesis of DFSP has been proposed to be fibroblastic, histiocytic, or neuroectodermal
  - Chromosomal abnormalities are present in the vast majority of cases
    - A chromosomal reciprocal translocation t(17;22)(q22;q13), and supernumerary ring chromosome, have been reported as cytogenetic characteristics of DFSP
      - **In translocation t(17;22), an exon of the platelet-derived growth factor-B gene (*PDGFB*) in chromosome 22 is fused with the collagen type I α1 gene (*COL1A1*) in chromosome 17**
      - The final *COL1A1-PDGFB* fusion oncogene produces mature and fully functional PDGFB protein

TIP

The identification of this deregulated expression of PDGFB is the basis for the use of inhibitors of PDGFB receptors (PDGFRB), such as imatinib, as an alternative therapy in this disease

    - More than 90% of DFSPs present a translocation in different regions of chromosomes 17 and 22. Other translocations, such as t(2;17) and t(9;22), have also been proposed
- Clinical presentation
  - DFSP is characterized by a slow, infiltrative growth pattern
  - DFSP has considerable morbidity because of its aggressive local invasiveness. It is typically located on the trunk, followed by extremities
  - Initially it arises as an asymptomatic, reddish or skin-colored indurated plaque. Some telangiectasia may be present in the surrounding skin (Figure 4.2.24)
  - It may slowly enlarge, and become raised, firm, and multinodular until late in its course (Figure 4.2.25)
  - It is usually fixed to overlying skin but remains freely movable from deep tissue. At this stage, it may ulcerate, bleed, or become painful.
  - Palpation of lymph nodes is necessary to detect rare cases of lymphatic (1%) or hematogenous dissemination (4%), predominantly to the lungs

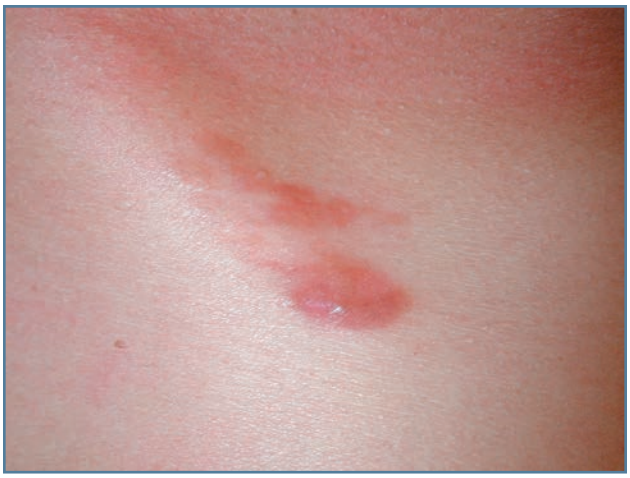

Figure 4.2.24 Dermatofibrosarcoma protuberans (DFSP) located on the right clavicle area of a female patient.

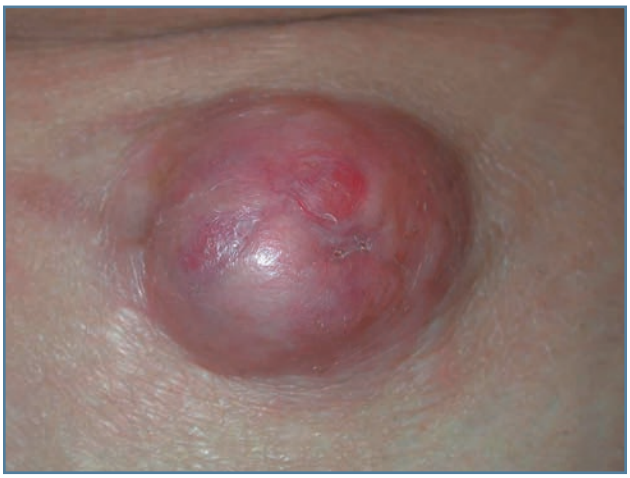

Figure 4.2.25 Large multinodular DFSP located on the left hip of a female patient.

- Histopathology
  - DFSP is histologically characterized by the presence of monomorphic spindle cells arranged in a "storiform" or "cartwheel" pattern. Some cells may show slight atypia
  - At later stages, the cells infiltrate the subcutaneous adipose tissue, resulting in a honeycomb pattern of entrapped adipocytes (Figures 4.2.26 and 4.2.27)

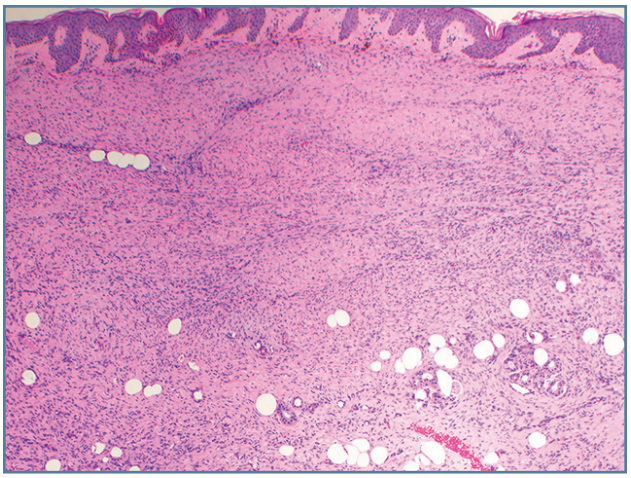

Figure 4.2.26 Dermatofibrosarcoma protuberans (DFSP). (Courtesy of Sailesh Konda, MD)

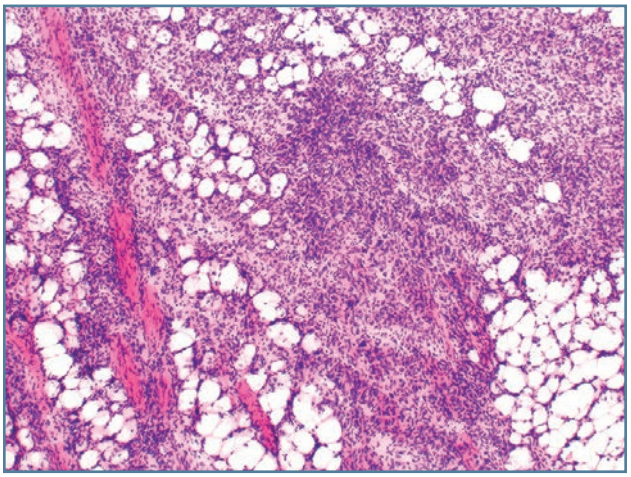

Figure 4.2.27 Dermatofibrosarcoma protuberans (DFSP) higher magnification. Neoplasm composed of ill-defined, dense, spindle cells within the reticular dermis extending toward the subcutaneous fat. The tumor cells are monomorphic and may be arranged in a whorl-like pattern. The neoplastic cells are invading the subcutaneous fat lobules in a lace-like fashion. (Courtesy of Sailesh Konda, MD)

- Diagnosis and differential
  - **Immunohistochemistry of the specimen shows CD34 positive and factor XIIIa negative, allowing its differentiation from dermatofibroma**
  - Magnetic resonance imaging (MRI) is useful to determine deep tumor invasion, especially in recurrent lesions
  - Other differential diagnoses include:
    - Scar
    - Keloid
    - Morphea plaque
    - Fibrous histiocytoma
    - Morpheaform BCC
- Treatment
  - DFSP is characterized by an overall high recurrence rate after wide local excision. The tumor shows a subclinical growth pattern through finger-like projections. Accurate removal with the least recurrence requires careful and extensive evaluation of all the margins. Therefore, Mohs micrographic surgery has become a favorite treatment alternative for DFSP
  - In one review (Snow et al, 2004), patients treated by Mohs micrographic surgery demonstrated a low rate of local recurrence, approaching 1%. In contrast, the pooled data on wide local excision in the treatment of DFSP showed a risk of recurrence of 7.3%
  - In recurrent cases, extensive infiltration or discontinuous tumor growth is usually seen. Treatment of recurrent DFSPs by second Mohs surgery yielded a 98.5% cure rate
  - Adjuvant radiotherapy (RT) reduces local recurrence in patients who have close or positive margins and patients with unresectable macroscopic disease
  - Imatinib mesylate is a tyrosine kinase inhibitor currently FDA-approved for adults with unresectable, recurrent, and/or metastatic DFSP with the translocation t(17;22)(q22;q13)
- Prognosis
  - Older age, male sex, and large tumor size have been identified as negative predictors of survival
  - Head or neck location, high mitotic index, increased cellularity, and fibrosarcomatous changes may also worsen survival
  - Negative surgical margins are considered the most significant prognostic factor
  - Metastatic disease is rare and typically occurs after inadequate resection and multiple local recurrences
  - The overall risk of metastatic disease is approximately 5%
    - Regional lymph node involvement is a poor prognostic indicator, with most patients dying within 2 years
    - The lungs are the most common site of distant metastasis

Microcystic Adnexal Carcinoma

- Epidemiology
  - Microcystic adnexal carcinoma (MAC), also known as sclerosing sweat duct carcinoma, is an uncommon, locally aggressive adnexal tumor
  - Patients diagnosed with MAC are usually 40-60 years old
  - Sex distribution seems to be equal
- Etiology
  - The origin of this tumor is unknown
  - Eccrine, follicular, apocrine, or sebaceous differentiation has been reported
  - Risk factors include immunosuppression and a prior history of radiation
- Clinical presentation
  - The most common tumor locations include the perioral, lip, nasolabial, and periorbital areas
  - Clinically MAC appears as a solitary, skin-colored, indurated plaque or nodule
  - It is usually asymptomatic, but symptoms such as paresthesia, numbness, and burning sensation may be present when perineural invasion has occurred (Figure 4.2.28)

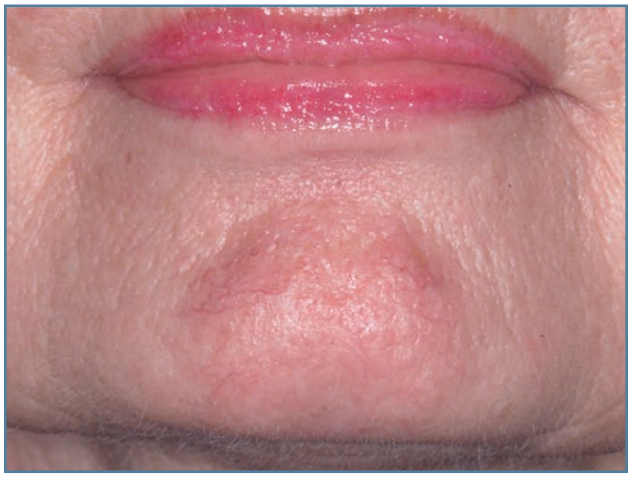

Figure 4.2.28 Microcystic adnexal carcinoma (MAC) arising in perioral area. (Courtesy of Stan Tolkachjov, MD)

- Histopathology
  - Histologically, MAC presents with poorly demarcated tumor cells invading the dermal and subcutaneous tissue
  - Islands of basaloid keratinocytes, horn cysts, and duct structures are also seen within a desmoplastic stroma. Cytologic atypia and mitotic figures are rarely observed (Figures 4.2.29 and 4.2.30)

TIP

BerEP4, a monoclonal antibody that marks epithelial tissues and not mesothelial tissue, may help differentiate MAC from morpheaform basal cell carcinoma. Presence of mitotic figures and lack of keratocysts, keratin granulomas, and calcifications may also help to differentiate MAC from desmoplastic trichoepithelioma. Depth of invasion helps distinguish it from syringoma

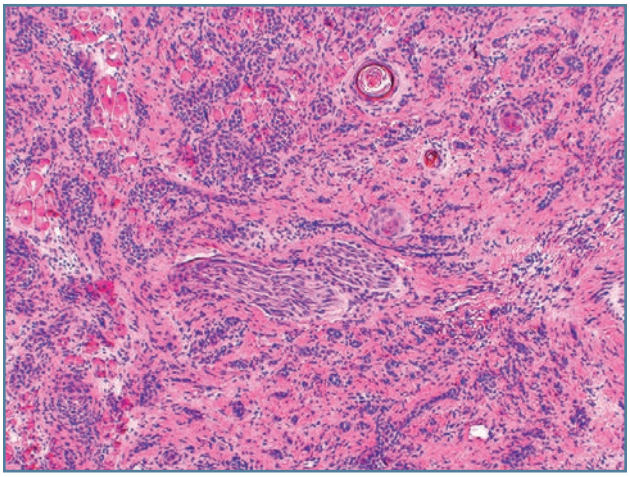

Figure 4.2.29 Microcystic adnexal carcinoma (MAC). Keratocysts and variably sized basaloid tumor nests and ducts surrounding nerves within a fibrotic desmoplastic stroma. (Courtesy of Sailesh Konda, MD)

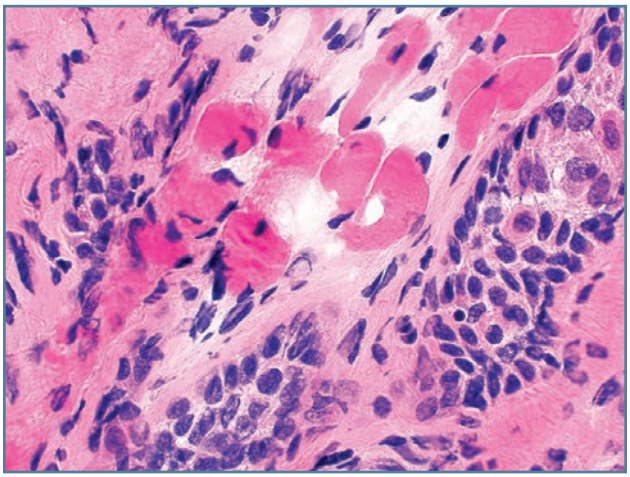

Figure 4.2.30 Microcystic adnexal carcinoma (MAC). Higher magnification reveals neoplastic cells with prominent oval nuclei. (Courtesy of Sailesh Konda, MD)

- Diagnosis and differential
  - Clinical and histological evaluation is required to diagnose MAC
  - A deep biopsy is required for complete architectural examination
  - Histological differential diagnosis includes:
    - Desmoplastic trichoepithelioma
    - Syringoma
    - Morpheaform BCC
  - **MAC shows deep subcutaneous and perineural invasion, as well as carcinoembryonic antigen (CEA) positive staining, all features that may help differentiate it from desmoplastic trichoepitheliomas**
- Treatment
  - Due to the high recurrence rate after conventional excision (approximately 47%), and its infiltrative and aggressive growth pattern, Mohs micrographic surgery has become the preferred treatment option for MAC
  - MAC is relatively radioresistant, but radiation may play a role in tumor formation or progression to more aggressive histology and behavior
- Prognosis
  - Overall prognosis is good with a modest tendency for recurrence and rare reports of histologically confirmed lymphatic metastasis
  - A retrospective chart review found a 12% recurrence rate at a mean follow-up of 39 months

Atypical Fibroxanthoma/Undifferentiated Pleomorphic Sarcoma (UPS)

- Epidemiology
  - Atypical fibroxanthomas (AFXs) and undifferentiated pleomorphic sarcomas (UPSs) are rare fibrohistiocytic neoplasms with variable aggressiveness
  - Patients diagnosed with AFX/UPS are usually male and elderly. Of note, UPS was previously known as malignant fibrous histiocytoma
- Etiology
  - AFX has a greater association with sun exposure compared with UPS
  - UPS may arise in areas of radiodermatitis or chronic ulceration. Some cases may represent dedifferentiation of SCCs that fail to express keratin
- Clinical presentation: See Table 4.2.4
- Histopathology
  - **AFX and UPS are distinguished primarily by their depth**
  - They are characterized by a dermal proliferation of pleomorphic spindle cells with numerous, often atypical, mitoses and multinucleated giant cells
  - Tumor cells may stain for CD68, CD163, CD10, S100A6, procollagen I, and focal smooth muscle actin (SMA); however, none of these markers are tumor-specific
- Diagnosis and differential
  - Differential diagnosis includes:
    - BCC
    - SCC
    - Amelanotic melanoma
    - Merkel cell carcinoma
    - Cutaneous metastasis

TABLE 4.2.4 COMPARISON OF AFX AND UPS

	Atypical Fibroxanthoma	Undifferentiated Pleomorphic Sarcoma
Presentation	Pink to red papule/nodule, often ulcerated	Painless, rapidly growing SQ mass/nodule ± surface changes
Typical size	<2 cm	As large as 5-10 cm
Most common age at presentation	7th decade	6th-7th decades
Gender distribution	M > F	M > F
Most common anatomic location	Head and neck	Extremities, especially lower extremities
Associated with sun exposure?	Yes	No
Recurrence rates (%)	0-16	6-71
Rate of metastasis (%)	0-4	17-40

AFX = atypical fibroxanthomas; SQ = subcutaneous; UPS = undifferentiated pleomorphic sarcomas.

- Treatment
  - Mohs micrographic surgery results in fewer recurrences compared with conventional excision
- Prognosis
  - In general, UPS tends to have a poorer prognosis with higher recurrence and metastasis rates compared with AFX, given its deeper involvement
  - Myxoid variants of UPS are less likely to metastasize
  - Tumors in sites of radiodermatitis may also have a poorer prognosis

Extramammary Paget's Disease

- Epidemiology
  - Extramammary Paget's disease (EMPD) is a rare tumor of neoplastic Paget cells usually diagnosed in patients 50-80 years old
  - EMPD typically affects women > men and has a predilection for Caucasian races. Japan has a male predominance
- Etiology
  - Primary EMPD may arise from Toker cells as an intraepithelial adenocarcinoma
  - Secondary EMPD presents as a cutaneous extension of an underlying adnexal adenocarcinoma or distant visceral malignancy
  - The majority of patients do not have an underlying carcinoma
  - Perianal EMPD has a higher frequency of associated malignancies than vulvar EMPD
- Clinical presentation
  - EMPD targets cutaneous sites rich in apocrine glands. The most commonly affected site is the vulva. EMPD may also commonly affect perineal, perianal, scrotal, and penile skin (Figure 4.2.31)

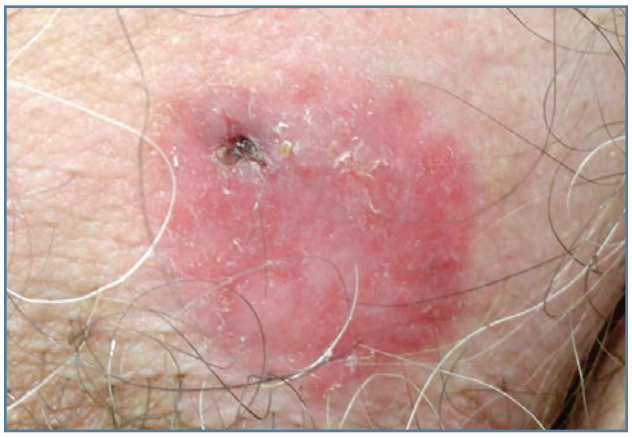

Figure 4.2.31 Extramammary Paget's disease (EMPD) presenting as erythematous, well-demarcated, scaly plaque on suprapubic area. (Courtesy of Sailesh Konda, MD)

  - Patients present with slowly expanding, well-demarcated, nonresolving, erythematous, eczematous plaques. The most common symptom is pruritus
- Histopathology
  - Histologically, EMPD presents with diffusely infiltrating, irregular, neoplastic Paget cells within the epidermis. These cells are large and vacuolated with pale bluish cytoplasm and large vesicular nuclei, which may be compressed. Mucin is often present
  - **Paget cells stain for immunohistochemical markers of apocrine and eccrine derivation: low molecular weight cytokeratins, gross cystic disease fluid protein 15 (GCDFP-15), periodic acid—Schiff (PAS), and CEA**
- Diagnosis and differential
  - Differential diagnosis includes:
    - Pruritus ani
    - Fungal infection
    - Contact dermatitis
    - Lichen simplex chronicus
    - Psoriasis
    - Candidiasis
    - Erosive lichen planus
    - Lichen sclerosus, and intertrigo
- Treatment
  - Recurrence rates after Mohs micrographic surgery (16%) are significantly lower compared with conventional excision (33-60%). **Cytokeratin-7 (CK7) immunostaining may assist with visualization of Paget cells intraoperatively**
  - Solitary or combination topical chemotherapy, radiation, and PDT have also been used to treat EMPD
  - Trastuzumab and paclitaxel can be considered for treatment of ERBB2-positive EMPD
  - Patient should be thoroughly evaluated for any underlying carcinomas, with a focus on the urethra, bladder, vagina, cervix, endometrium, prostate, colon, and rectum
  - Location may be related to the underlying malignancy
    - Penile, scrotal, groin EMPD = bladder, prostate carcinomas
    - Vulvar EMPD = cervical, uterine, ovarian, bladder, breast carcinomas
    - Perianal EMPD = colorectal adenocarcinomas
- Prognosis
  - EMPD may recur as discussed above. Any underlying malignancies, if present, may affect ultimate prognosis

Angiosarcoma

- Epidemiology
  - Idiopathic angiosarcomas are commonly diagnosed in men
  - The most common form of angiosarcoma is cutaneous angiosarcoma not associated with lymphedema
  - It generally occurs in patients over 40 years of age, with the highest incidence seen in patients older than 70
- Etiology
  - Angiosarcoma is a very rare, aggressive, and rapidly proliferating tumor of endothelial origin
  - Radiotherapy is an independent risk factor for angiosarcoma development
  - Vinyl chloride, thorium dioxide arsenic, radium, and anabolic steroids have been linked to angiosarcoma
- Clinical presentation
  - The lesion initially arises as a painless, purple macule-patch or plaque on the scalp or face
  - Evolution of the lesion occurs in a centrifugal pattern and may become quite large. Associated facial swelling or edema may also be noted
  - Later on, it becomes an elevated, bluish or purple nodule that may ulcerate
  - Tumors may be single or multiple. Common symptoms include bleeding, edema, and ultimately pain
  - Cervical lymph node and hematogenous metastasis commonly occur
    - The lungs, spleen, and liver are the most common organs where distant metastasis occurs
  - The overwhelming majority of angiosarcomas that arise in the presence of chronic lymphedema are associated with a previous history of mastectomy and lymph node dissection
    - This variant is referred to as Stewart-Treves syndrome
    - The most common location of the primary tumor in Stewart-Treves syndrome is the inner surface of the proximal upper extremity
- Histopathology
  - Angiosarcomas are commonly seen infiltrating the dermis, but may also invade the fascia and subcutis
  - Multiple anastomosing vascular spaces are found. The cells lining the vessels are large, pleomorphic, and hyperchromatic with atypia (Figure 4.2.32)
  - Hemorrhage may also be seen
  - **Immunohistochemistry markers such as CD31, CD34, and factor VIII are positive in angiosarcomas. These neoplasms are vimentin negative and cytokeratin positive**

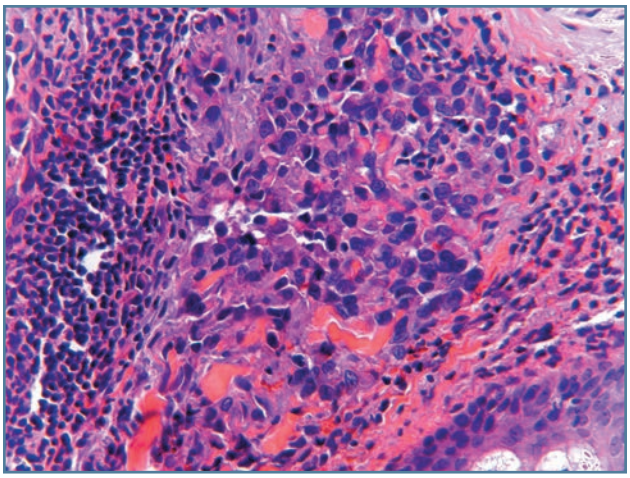

Figure 4.2.32 Angiosarcoma. Ill-defined neoplastic proliferation of plump-cuboidal mostly pleomorphic endothelial cells intermingled with slit-like spaces with many erythrocytes.

- Diagnosis and differential
  - Clinical and histological evaluation is required to diagnose angiosarcoma
  - Differential diagnosis includes:
    - Dabska-like and retiform hemangioendothelioma
    - Epithelioid hemangioendothelioma
    - Tufted angioma
    - Intravascular papillary endothelial hyperplasia
    - Kaposi's sarcoma
- Treatment
  - Wide surgical excision remains the treatment of choice
    - However, this tumor's propensity for subcutaneous spreading make the achievement of true free margins very difficult, and the possibility of recurrence and/or metastatic spread remains very high
  - Radiation therapy may be employed after surgical excision but often is purely palliative
- Prognosis
  - Recurrence rate is high
  - Unfortunately, prognosis is poor with a reported 15% survival rate at 5 years
  - Approximately 50% of cases have local or distant metastases at the time of diagnosis

Kaposi's Sarcoma (KS)

- Epidemiology
  - Four types:
    - Classic: Jewish Ashkenazi or Mediterranean/Eastern European descent; men > women
    - African endemic: Men > women; lymphadenopathic variant affects primarily children
    - Iatrogenic immunosuppression: Cyclosporine associated with higher incidence and rapid onset; can resolve after stopping immunosuppressive therapy; men > women
    - AIDS-related epidemic: 40% of men who have AIDS acquired via homosexual contact can develop KS
- Etiology
  - KS likely has a multifactorial etiology related to the patient's immune status
  - **Human herpesvirus (HHV)-8 is implicated agent in all clinical variants**
- Clinical presentation
  - Classic: Reddish and violaceous macules and plaques coalescing into plaques on lower extremities
  - African endemic: Nodular, infiltrating, lymphadenopathic types on lower extremities
  - Iatrogenic immunosuppression: Clinically similar to classic KS; may resolve immunosuppressive therapy; clinical does not correlate with degree of immunosuppression
  - AIDS-related epidemic: Variable presentation ranging from single lesion to disseminated cutaneous disease (Figures 4.2.33 and 4.2.34)

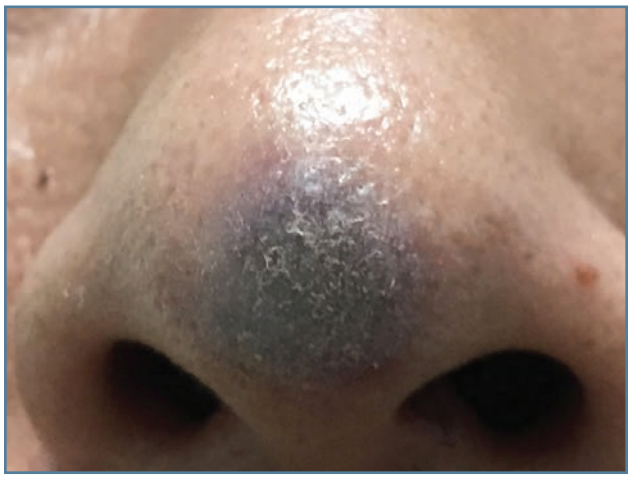

Figure 4.2.33 Kaposi's sarcoma of the Nasal Tip. (Courtesy of Sailesh Konda, MD)

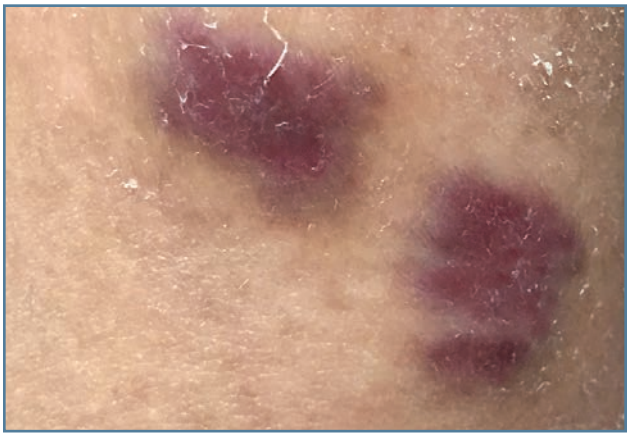

Figure 4.2.34 Patch and plaque Kaposi's sarcoma. (Courtesy of Sailesh Konda, MD)

- Histopathology
  - Histopathology varies according to stage of KS
    - Patch: Superficial dermal proliferation with jagged vessels separating collagen bundles; few lymphocytes, plasma cells, and spindle cells expressing endothelial markers
    - Plaque: Extends to include deeper dermis and subcutis; increased spindle cells
    - Nodular: Increased spindle cells replace dermal collagen and form intersecting fascicles separated by slit-like spaces of erythrocytes
- Diagnosis and differential
  - Differential diagnosis includes:
    - Kaposiform hemangioendothelioma
    - Spindle cell hemangioma
    - Angiosarcoma
    - Acroangiodermatitis of chronic venous insufficiency
    - Stewart-Bluefarb syndrome
    - Fibrosarcoma
    - Leiomyosarcoma
- Treatment
  - Radiation therapy, local excision, cryotherapy, alitretinoin gel, locally injected chemotherapy (vinblastine/vincristine), interferon-α, PDT, and laser ablation
  - KS with extensive multifocal disease, rapidly progressive lesions, pulmonary/visceral involvement, and lymphedema may warrant systemic chemotherapy
  - Rapamycin (mammalian target of rapamycin [mTOR] inhibitor), especially in organ transplant patients
- Prognosis
  - Classic: Slow progression
  - African endemic: Aggressive, death within several years
  - Iatrogenic immunosuppression: May resolve after stopping immunosuppressants
  - AIDS-related epidemic: Most patients die of intercurrent infection

TABLE 4.2.5 FDA APPROVED TARGETED MOLECULAR THERAPIES FOR CUATNEOUS MALIGNANCIES

Malignancy	Medication	Target/Mechanism
Dermatofibrosarcoma protuberans	Imatinib mesylate	PDGFB inhibitor
Melanoma	Ipilimumab Dabrafenib Vemurafenib Cobimetinib Trametinib Pembrolizumab Nivolumab	Anti-CTLA-4 antibody BRAF inhibitor BRAF inhibitor MEK inhibitor MEK inhibitor Anti-PD-1 antibody Anti-PD-1 antibody
Basal cell carcinoma	Vismodegib Sonidegib Cemiplimab	Smoothened protein Smoothened protein Anti-PD-1 antibody
Squamous cell carcinoma	Cetuximab Panitumumab Cemiplimab	EGFR inhibitor EGFR inhibitor Anti-PD-1 antibody
Merkel cell carcinoma	Avelumab	Anti-PD-L1 antibody

Adapted and updated from Council (2017).

SURGICAL TECHNIQUES AND THERAPY

Biopsy Techniques

- Punch biopsy
- Shave biopsy
- Saucerization biopsy
- Incisional biopsy
- Excisional biopsy: Extends to subcutaneous fat

Excisional Therapy

- Elliptical/fusiform excisions
- Length of ellipse typically 3-4 times the width
- Apical angles are typically 30 degrees
- Billing for excision → lesion size + largest margins
- Scalpel blade should be maintained 90 degrees to skin surface

TABLE 4.2.6 EXAMPLES OF BIOPSY TECHNIQUES FOR SELECT CUTANEOUS TUMORS

Suspected Disease	Recommended Biopsy Technique
BCC/SCC	Shave or punch biopsy of adequate depth to show invasive pattern and detect perineural invasion, if present
Suspected dysplastic nevus	Saucerization biopsy, shave biopsy
Suspected melanoma	Excisional biopsy when possible, saucerization biopsy, shave biopsy
Merkel cell carcinoma	Deep shave or punch biopsy
Sebaceous carcinoma	Deep shave or punch biopsy
Dermatofibrosarcoma protuberans	Deep incisional biopsy
Microcystic adnexal carcinoma	Deep shave or punch biopsy
Atypical fibroxanthoma/Undifferentiated pleomorphic sarcoma	Deep shave or punch biopsy
Extramammary Paget's disease	Shave or punch biopsy below depth of dermal-epidermal junction

Micrographic (Mohs) Surgery

- Key concepts
  - Designed to answer "Is it all out?"
  - Method of excision that provides complete microscopic evaluation and control of tumor margins
  - Offers cure rates superior to those of other surgical or destructive treatment options
  - Designed to treat skin cancers that have contiguous growth patterns and can be traced to their termination
  - The Mohs surgery technique removes, processes, and horizontally sections fresh tissue in real time, which allows for 100% of the peripheral and deep margins of the excised lesion to be examined
    - Standard surgical excision (SSE) and vertical (or breadloaf) sections only examine 0.1% of the margin

TIP

In order to use Mohs surgery, tumors must grow as a contiguous lesion. If a tumor exhibits discontiguous growth, discrete foci may be missed and thereby lead to a false-negative pathology interpretation

  - Immunostains can be utilized during Mohs surgery in certain cases. This includes:
    - **Cytokeratin stains: Useful in poorly differentiated SCC/BCC (AE1/AE2) or microcystic adnexal carcinoma (AE1/AE3)**
    - **Cytokeratin 7: A structural component of the cytoskeleton that stains poorly differentiated tumors of the epithelium and especially useful in extramammary Paget's disease (EMPD)**
    - **Cytokeratin 20: Nuclear dot pattern staining in Merkel cell carcinoma**
    - **CD34: Stains positive in spindle cells of DFSP**
    - **Melan-A: A melanosome-associated glycoprotein also known as MART-1 (melanoma antigen recognized by T cells) that stains in situ and invasive melanomas. It does not reliably stain desmoplastic or spindle cell melanomas**

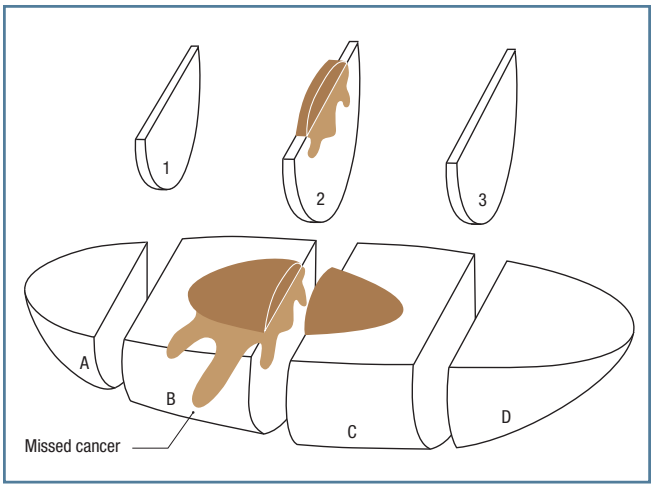

Figure 4.2.35 Traditional breadloafing of tumor specimen.

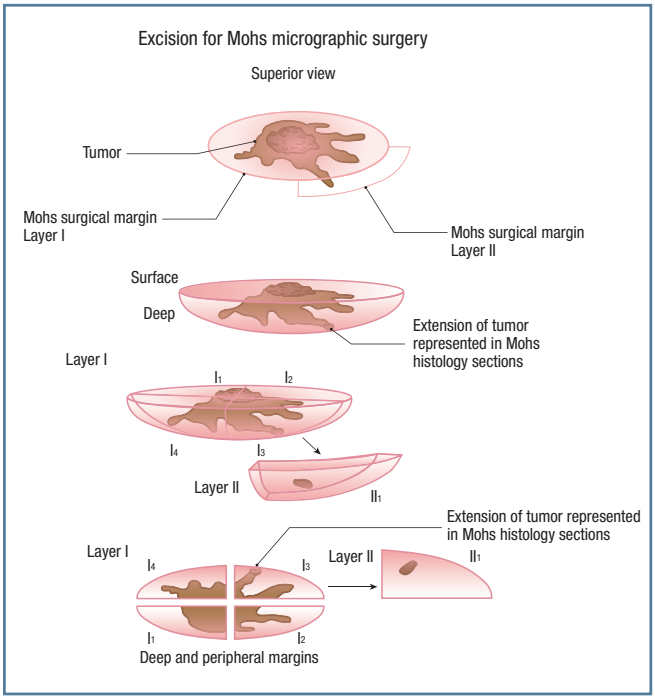

Figure 4.2.36 Mohs micrographic surgical technique.

- Mohs appropriate use criteria
  - In 2012, the AAD/ACMS/ASDSA/ASMS published appropriate use criteria (AUC) for Mohs surgery. The indications for Mohs surgery include:
    - Recurrent tumors
    - Tumors with positive margin after simple excision
    - Tumors occurring at a critical location (area H), which includes:
      - Orbital/periorbital
      - Oral/perioral

- Auricular/periauricular
- Nasal/perinasal
- Hands and feet
- Genitalia
- Anterior shins

- Tumors with aggressive or unusual histology, including:
  - Sclerosing/morpheaform BCC
  - Metatypical BCC
  - Any tumor with perineural invasion
  - Deeply invasive SCC
  - Poorly differentiated SCC
  - Desmoplastic SCC
  - Malignant melanoma
  - Lentigo maligna or in situ melanoma
  - Dermatofibrosarcoma protuberans (DFSP)
  - Sebaceous carcinoma
  - Merkel cell carcinoma
  - Microcystic adnexal carcinoma
  - Verrucous carcinoma
  - Angiosarcoma
- NMSC arising in patient with history of:
  - Immunosuppression: HIV, organ transplant, hematologic malignancies with immunosuppressants
  - Radiation
  - Genetic syndromes: Gorlin, xeroderma pigmentosum, other syndromes associated with high risk of skin cancer

- **AUC scores are calculated based on tumor/patient characteristics. AUC scores of 7-9 are indicated, 4-6 are uncertain—in extenuating circumstances may consider, and 1-3 are inappropriate**
- The advantages of Mohs surgery include:
  - **Highest cure rates**
    - 99% for primary tumors (vs. ~92% for SSE)
    - 95% for recurrent tumors (vs. ~80% for SSE)
  - **Precision margin control → entire periphery evaluated microscopically**
    - Standard excision takes a guess at margins and excises additional tissue (3-5 mm in each direction)
  - Tissue conservation
    - Smallest margin possible to remove all of skin cancer
    - Smallest surgical defect possible, thus preserving maximal normal skin
  - Cost effective
    - Approximately same cost as SSE for primary tumors
    - Lower rates for recurrent tumors, which are more expensive to treat
  - Efficient and safer delivery
    - Outpatient office setting, not operating room
    - Local, not general, anesthesia

Global Periods and Modifiers

- Reimbursement for surgical procedures includes a bundled payment for all related services and supplies necessary to perform the procedure, including routine postoperative care. Global periods start with some surgical procedures and last for a set period of time. During a global period, normal postoperative care related to the procedure is not eligible for a separate reimbursement

TABLE 4.2.7 GLOBAL PERIODS

Procedure	Global Period (Days)[a]
Skin biopsy	0
Simple repair	0
Nail avulsion	0
Mohs surgery	0
Application of skin substitute graft	0
Destruction	10
Excision	10
Intermediate repair	10
Complex repair	10
Adjacent tissue transfer (e.g., advancement, rotation, transposition flaps)	90
Pedicle formation	90
Pedicle takedown/sectioning	90
Split-thickness skin graft	90
Full-thickness skin graft	90
Dermabrasion	90

[a]If two procedures performed same day, the procedure with the higher global period takes precedence.

TABLE 4.2.8 SURGERY MODIFIERS AND X MODIFIERS

Modifier	Description/Clinical Scenario
79	Unrelated procedure by same physician during postoperative period of another procedure; also used for postoperative complications that result in another surgical procedure during postoperative period (e.g., wound dehiscence, hematoma evacuation)
58	Staged excision (e.g., additional staged excision for melanoma with positive margins)
51	Multiple surgery reductions (e.g., excision and repair performed on BCC or pilar cyst)
59 or Xs[a]	Surgical services performed on two separate lesions/sites (e.g., excision × 2 and repair × 2 performed on chest BCC and right forearm SCC)
X-Modifier	**Description/Clinical Scenario**
XE	Separate encounter; second, distinct procedure performed during a second encounter on the same date of service
XS	Separate structure; second, distinct procedure performed on a separate organ/structure
XP	Separate practitioner; second, distinct procedure performed by a different practitioner
XU	Unusual nonoverlapping service; second, distinct procedure, which does not overlap with usual components of primary procedure

[a]In 2015, Medicare established (2015) four new modifiers to use instead of modifier 59: XE, XS, XP, and XU. The X modifiers are more specific versions of modifier 59 and should be used when the specificity is appropriate.

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Chapter 5

DERMATOPATHOLOGY

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5.1 Introduction

TISSUE MEDIA

- Formalin: Fixative for routine processing
- Michel's medium: Nonfixative, stabilizes proteins for direct immunofluorescence
- Saline: Nonfixative, can be used for fresh tissue for flow cytometry, molecular studies, and electron microscopy

DIRECT IMMUNOFLUORESCENCE

Biopsy Guidelines

- **Most blistering diseases: Perilesional skin (within 1 cm of blister)**
- **Dermatitis herpetiformis: Perilesional skin at least 0.5 cm away from blister**
- **Porphyria/pseudoporphyria: Involved skin (the edge of a new blister)**
- **Cutaneous lupus erythematosus: Active border of lesion**
- **"Lupus band" for systemic lupus erythematosus: Non-sun-exposed, nonlesional skin**
- **Vasculitis: Active border of new lesion (<48 h old)**

Process

- Tissue submitted in Michel's medium or saline-soaked gauze
- Studies performed on frozen sections, using fluorescein isothiocyanate (FITC)-conjugated antisera to immunoglobulins (IgA, IgG, IgM), fibrinogen, and complement
- Antibodies bind to antigens in patient's skin and can be detected by fluorescence microscopy

Patterns

- Intercellular IgG, C3 (complement component): Superficial pemphigus (pemphigus foliaceus, pemphigus vulgaris)
- Intercellular IgA: IgA pemphigus
- Diffuse linear basement membrane zone (BMZ) IgG, C3: C3 predominates in pemphigoid (bullous pemphigoid, cicatricial pemphigoid, pemphigoid gestationis); IgG predominates in epidermolysis bullosa acquisita; both or mixed pattern in bullous lupus
- Diffuse linear BMZ IgA: Linear IgA bullous disease
- Granular IgA at tips of dermal papillae: Dermatitis herpetiformis
- Granular immunoglobulins and complement at BMZ: Lupus band
- Granular immunoglobulins and complement in vessel walls: Vasculitis (IgA in IgA vasculitis)
- Diffuse linear immunoglobulins and complement in vessel walls: Porphyria, pseudoporphyria

NORMAL HISTOLOGY

TABLE 5.1.1 NORMAL HISTOLOGY

Structure	Features	Pearls
Hair follicle	• Infundibulum: From orifice to insertion of sebaceous duct, looks like normal epidermis = granular layer present with basophilic keratohyaline granules • Isthmus: From insertion of sebaceous duct to arrector pili, trichilemmal keratinization = no granular layer, cuboidal pale pink cells • Inferior segment: From arrector pili to base of follicle, keratinization with eosinophilic trichohyaline granules • Dendritic melanocytes present within upper half of hair bulb • Features on horizontal sections: ▸ Terminal anagen: Bulb in fat, large-diameter hair shaft, inner root sheath keratinizes above level of isthmus ▸ Vellus/miniaturized: Diameter of hair shaft smaller than width of inner root sheath ▸ Catagen: Brightly eosinophilic center with dyskeratosis ▸ Telogen: Stellate basophilic center	• Layers of the lower portion from outside in: Fibrous root sheath, glassy/vitreous layer, outer root sheath, inner root sheath (Henle, Huxley, cuticle), hair cuticle, hair medulla • Fibrous streamers (stelae) present beneath miniaturized hairs, catagen/telogen hairs, or sign of follicular dropout/destruction • Hair counts done at level of the isthmus on horizontal sections (sebaceous glands present)

TABLE 5.1.1 NORMAL HISTOLOGY CONTINUED

Structure	Features	Pearls

Sebaceous gland	• Holocrine glands associated with hair follicles
	• Secretions = disintegrated cells
	• Two cell types:
	  ▸ Single layer of peripheral basaloid germinative cells
	  ▸ Mature sebocytes with vacuolated cytoplasm and centrally located scalloped nucleus
	• Stains: EMA, CK5/6, androgen receptor, adipophilin
		• Prominent on facial skin
		• Not found on palms and soles
		• Other sites:
		  ▸ Meibomian/Zeis on eyelid
		  ▸ Fordyce on vermilion
		  ▸ Tyson on penis
		  ▸ Montgomery on nipple

Eccrine gland	• Secretory portion: Convoluted tube in the dermis with glandular structures around central lumen to form coils
	  ▸ Clear cells and dark cells with surrounding myoepithelial cells
	  ▸ Merocrine secretion = granular contents released from vesicles
	• Excretory portion (duct): Convoluted near secretory coils + straight dermal component + spiral acrosyringium opening to skin surface
	  ▸ Narrow tubes surrounded by two layers of cuboidal cells
	• Stains: S100, CEA, CAM 5.2
		• All over the body, but concentrated on palms, soles, forehead, axillae
		• Not present on vermilion, glans penis, inner prepuce, labia minora, nail beds

Apocrine gland	• Always connected to pilosebaceous unit
	• Secretory portion: Coiled, quite long, located in subcutis or deep dermis
	  ▸ Single layer of cuboidal, columnar, or flat cells with surrounding myoepithelial cells
	  ▸ Decapitation secretion = "pig snout" with cap of eosinophilic material at apex of cells
	• Excretory portion (duct): Resembles eccrine duct with two layers of cuboidal cells
	• Stain with keratin AE1 (ducts), CAM 5.2, EMA, GCDFP-15
		• Located in axillae, anogenital areas, mammary region, eyelids (Moll's), and external ear canal (ceruminous)
		• Ectopic apocrine glands seen in nevus sebaceous of Jadassohn

Nail	• Proximal nail fold: Normal acral epidermis with granular layer, thick stratum corneum
	• Cuticle: Thick compact stratum corneum on dorsal surface of plate
	• Matrix: Acanthotic epithelium with no granular layer, rare melanocytes in basal layer, abrupt keratinization with broad eosinophilic "keratogenous" zone overlying epithelium
	• Bed: Flat epithelium, no melanocytes
	• Hyponychium: Distal portion of nail bed, similar appearance to normal epidermis with granular layer, thick compact stratum corneum like cuticle
	• Plate: Thick compact keratin
		• Keratin expression
		  ▸ Nail fold: 1, 10, 16, 6
		  ▸ Bed: 6, 16, 17
		  ▸ Matrix: 1, 7, 8, 10, 14, 17

CAM = cytokeratin-specific antibody, monoclonal; CEA = carcinoembryonic antigen; CK5/6 = cytokeratin 5/6; EMA = epithelial membrane antigen; GCDFP-15 = gross cystic disease fluid protein 15.

REGIONAL DIFFERENCES IN MICROANATOMY

TABLE 5.1.2 REGIONAL DIFFERENCES IN MICROANATOMY

Site	Features
Acral (palms, soles)	• Compact hyperorthokeratosis • Stratum lucidum = thin clear layer between stratum corneum and granular layer • Numerous eccrine glands with acrosyringia (spiral excretory portions of duct through epidermis to open onto skin surface) • No pilosebaceous units
Scalp	• Terminal anagen hair follicles extending into the subcutis
Face	• Numerous pilosebaceous units • Numerous sebaceous glands on nose and cheeks in particular

TABLE 5.1.2 REGIONAL DIFFERENCES IN MICROANATOMY CONTINUED

Site	Features
Eyelid	• Thin epidermis • Vellus hairs + modified apocrine glands (Moll's) • Skeletal muscle at base sometimes seen
Scrotum	• Gently papillated epidermis • Smooth muscle bundles
Areola	• Smooth muscle bundles • Modified apocrine glands
Trunk	• Thick dermis

NORMAL SKIN DIFFERENTIAL DIAGNOSIS

TABLE 5.1.3 NORMAL SKIN DIFFERENTIAL DIAGNOSIS

Entity	Features	Pearls
Dermatophytosis (in particular, tinea versicolor)	• Hyphae ± spores in stratum corneum • PAS confirms diagnosis • May also have spongiosis and/or parakeratosis	• Candidiasis: Hyphae oriented vertically within stratum corneum, subcorneal pustules common • Tinea: Often with spongiosis and parakeratosis
Ichthyosis	• Absent or reduced granular layer • May have thickened stratum corneum	
Macular amyloidosis	• Subtle pink globules of amyloid within papillary dermis ▸ Depending on staining, may look pink-orange or slightly purple ▸ Clefting within globules • Basal layer hyperpigmentation common	• Stains for amyloid: crystal violet, Congo red, thioflavin T
Urticaria	• Subtle proliferation of neutrophils and eosinophils around blood vessels and between collagen bundles	• Predominant cell type is either neutrophil or eosinophil
Vitiligo	• Complete absence of melanocytes within epidermis • MART-1/Melan-A or Sox-10 can be used to confirm • Absence of melanin confirmed with Fontana-Masson	• In inflammatory stage, may see lymphocytic inflammation • Completely regressed melanocytic neoplasm may look similar, but typically has numerous melanophages in dermis
Dermal elastolysis, anetoderma	• Need elastic stain to highlight decreased/absent elastic fibers	• Need high degree of clinical suspicion
Telangiectasia macularis eruptiva perstans	• Slightly increased mast cells surrounding dilated blood vessels in dermis • Tryptase or c-kit stain to confirm mast cells	• Need high degree of clinical suspicion • Helpful to have adjacent normal skin to compare mast cell density

MART-1 = melanoma antigen recognized by T cells-1; PAS = periodic acid–Schiff.

5.2 Stains

SPECIAL STAINS

TABLE 5.2.1 SPECIAL STAINS

Name	Target	Color
Amyloid		
Congo red	Amyloid	Reddish orange in histology sections; apple green birefringence with polarized light
Crystal violet	Amyloid	Purple
Thioflavin T	Amyloid	Yellow (fluorescence microscope needed)
Orcein-Giemsa	Amyloid	Light blue
Bacteria		
Giemsa	*Leishmania* *Histoplasma* *Rickettsia*	Purple Purple Red
Gram (Brown-Brenn, Brown-Hopps, McCallum-Goodpasture)	Gram (+) Gram (−)	Blue-purple Red
Fite-Faraco	*Mycobacterium leprae, Nocardia*	Red
Steiner	Spirochetes	Black
Warthin-Starry	Spirochetes	Black
Ziehl-Neelsen	Acid-fast bacteria	Red
Calcium		
Aldehyde fuchsin	Calcium	Brown
Alizarin red	Calcium	Red
Pentahydroxy flavanol	Calcium	Fluoresces
Von Kossa	Calcium phosphate	Black
Collagen/Muscle		
Masson trichrome	Collagen Muscle/nerve/keratin	Blue-green Red
PTAH (phosphotungstic acid hematoxylin)	Collagen Striated muscle Glial fibers Fibrin	Orange-red Blue-black Blue Blue
Movat's pentachrome	Collagen Muscle Fibrin Glycosaminoglycans	Yellow Red Red Light blue
DNA/RNA		
Feulgen	DNA	Magenta
Methyl green—pyronin	DNA and RNA	DNA (green-blue); RNA (red)

TABLE 5.2.1 SPECIAL STAINS CONTINUED

Name	Target	Color
Elastic Tissue		
Gomori's aldehyde-fuchsin	Elastic fibers	Purple
Movat's pentachrome	Elastic fibers	Black
Orcein-Giemsa	Elastic fibers	Black
Verhoeff–Van Gieson	Elastic fibers	Black
Fat (Fresh/Frozen Tissue)		
Oil red O	Lipid	Red
Osmium tetroxide	Lipid	Black
Scarlet red	Lipid	Reddish brown
Sudan black	Lipid, lipofuscin	Black
Fungi		
GMS (Grocott-Gomori methenamine–silver nitrate)	Fungi	Black
PAS (periodic acid–Schiff)	Fungi, basement membrane, glycogen, some mucins	Pink
Hemosiderin		
Perls' Prussian blue	Hemosiderin/iron	Blue
Melanin		
Fontana-Masson	Melanin	Black
Orcein-Giemsa	Melanin	Dark green to black
Mast Cells		
Giemsa	Mast cell granules	Purple
Leder	Mast cell granules	Red
Toluidine blue	Mast cell granules	Purple
Tryptase	Mast cell granules	Red
Mucin/Mucopolysaccharides (MPS)		
Alcian blue	Acid MPS (pH 2.5) Sulfated MPS (pH 0.5)	Blue Blue
Colloidal iron	Acid MPS	Blue
Mucicarmine	Epithelial mucin	Pink
PAS	Neutral MPS	Pink
Toluidine blue	Acid MPS	Blue-purple
Nerve		
Bodian	Nerve fibers	Black
Protein gene product 9.5	Nerve fibers	Brown-black
Neurofilament	Nerve fibers	Brown-black
Ochronosis		
Cresyl violet or methylene blue	Ochronotic pigment	Black
Reticulin		
Foote's or Snook's stain	Reticulin fibers (liver, bone marrow, lymphatics)	Black

IMMUNOHISTOCHEMISTRY

TABLE 5.2.2 IMMUNOHISTOCHEMISTRY

Name	Stain	Useful For
Epithelial Markers		
Cytokeratin (AE1/AE3, 34BE12, MNF116, 5/6, etc.)	Epidermis and adnexal epithelium	Squamous cell carcinoma (SCC)
CAM 5.2	Low molecular weight cytokeratins	Paget's disease of the breast
CK7	Many normal epithelia other than the skin	Nongastric adenocarcinoma, Paget's disease of the breast
CK20	Merkel cells, gastrointestinal epithelium	Merkel cell carcinoma (perinuclear dot pattern), metastatic colon, adenocarcinoma
p63	Basal and spinous layers of epidermis, sebaceous glands, myoepithelial cells of sweat glands	Differentiating a primary cutaneous adnexal neoplasm from metastatic carcinoma
CDX2	Gastrointestinal epithelium	Metastatic adenocarcinoma
EMA	Sebaceous, eccrine, and apocrine glands	Sebaceous carcinoma, SCC (but negative in BCC), epithelioid sarcoma
CEA	Eccrine and apocrine glands	Adnexal neoplasms, Paget's disease of the breast, extramammary Paget's
BerEp4	Epithelial cells not undergoing squamous differentiation	Basal cell carcinoma
RCC	Glycoprotein in renal proximal tubular brush border	Metastatic renal cell carcinoma
TTF-1	Thyroid follicular and parafollicular cells	Metastatic small-cell lung carcinoma (negative in Merkel cell carcinoma)
Adipophilin	Lipid droplets of sebaceous tumors	Sebaceous carcinoma
Melanocytic Markers		
S100	Neural crest—derived cells, such as melanocytes, nerve cells, fat, chondrocytes, etc. Also stains Langerhans cells	Desmoplastic melanoma, Langerhans cell histiocytosis, Rosai-Dorfman disease, granular cell tumor, neurofibroma
S100A6	Similar as above	Spitz nevi (diffusely), cellular neurothekeoma, AFX
Melan-A/MART-1	Melanocytes	Nevi, melanoma
HMB-45	Melanocytes	Melanoma (diffuse), blue nevi (diffuse), other nevi (lost in deeper portion)
MITF	Melanocytes	Melanoma, cellular neurothekeoma
Sox10	Melanocytes and Schwann cells	Sensitive marker of melanoma
Neuroendocrine Markers		
Synaptophysin	Neuroendocrine cells	Merkel cell carcinoma
Chromogranin	Neuroendocrine cells	Merkel cell carcinoma
Neuron-specific enolase	Neuroendocrine cells	Merkel cell carcinoma

TABLE 5.2.2 IMMUNOHISTOCHEMISTRY CONTINUED

Name	Stain	Useful For
Mesenchymal Markers		
Vimentin	Stains mesenchymal cells and many other cell lines except for keratinocytes	General marker for sarcoma
Desmin	Skeletal and smooth muscle (does not stain vascular smooth muscle)	Piloleiomyoma, leiomyosarcoma
Smooth muscle actin (SMA)	Smooth muscle, including vascular smooth muscle	Piloleiomyoma, glomus tumor, glomangioma
CD34	Vascular endothelium and hematopoietic progenitor cells	Dermatofibrosarcoma protuberans
CD31	Vascular endothelial cells	Angiosarcoma
GLUT1	Vascular endothelial cells and perineurial cells	Infantile hemangioma (negative in vascular malformations), perineurioma
Factor XIIIa	Dermal dendritic cells	Dermatofibroma
D2-40	Lymphatic endothelium	Lymphangioma, highlights lymphovascular invasion
Some Hematopoietic Markers		
CD19, CD20, CD79a	B Cell marker	B Cell lymphomas
CD3	Pan T Cell marker	T Cell lymphomas
CD4	Helper T cells Histiocytes (Langerhans cells)	T Cell lymphomas
CD8	Cytotoxic T cells	T Cell lymphomas
CD5	T cells	Lost in mycosis fungoides, marker of CLL, mantle cell lymphoma
CD7	T cells	Lost in mycosis fungoides
CD23		Positive marker in CLL, negative in mantle cell lymphoma
CD30	Lymphocyte activation antigen	Anaplastic large-cell lymphoma, lymphomatoid papulosis, mycosis fungoides with transformation
CD56	NK cells	Blastic plasmacytoid dendritic cell neoplasm
CD68 and CD163	Monocytes/macrophages	Histiocytic marker
Myeloperoxidase	Neutrophilic myeloid cells	AML
CD138	Plasma cell marker	Multiple myeloma
CD117 (c-kit)	Mast cells	Urticaria pigmentosa
CD1a	Langerhans cells	Langerhans cell histiocytosis
Bcl2	Small B lymphocytes in mantle zone and T cells	Mantle cell lymphoma
Bcl6	Germinal center marker	Follicle center cell lymphoma
CD10	Germinal center marker	Follicle center cell lymphoma
MUM-1		Diffuse large B Cell lymphoma, leg type

TABLE 5.2.2 IMMUNOHISTOCHEMISTRY CONTINUED

Name	Stain	Useful For
Proliferation Markers		
Ki-67 (Mib-1)	Not cell type specific	Nuclear proliferation marker
Infectious Immunohistochemical Markers		
Spirochete	Epithelium infected with *Treponema pallidum*	Syphilis
HSV	Virally infected cells	Herpes simplex virus
VZV	Virally infected cells	Varicella-zoster virus
HHV-8	Virally infected cells	Kaposi's sarcoma

AFX = atypical fibroxanthoma; AML = acute myeloid leukemia; BCC = basal cell carcinoma; CAM = cytokeratin-specific antibody, monoclonal; CEA = carcinoembryonic antigen; CK = cytokeratin; EMA = epithelial membrane antigen; GLUT1 = glucose transporter type 1; HHV = human herpesvirus; HMB = human melanoma black; MART-1 = melanoma antigen recognized by T cells-1; MITF = microphthalmia-associated transcription factor; MUM-1 = multiple myeloma oncogene-1; NK = natural killer; RCC = renal cell carcinoma antigen; TTF = thyroid transcription factor-1.

5.3 Tissue Reaction Patterns

SPONGIOTIC PATTERN

TABLE 5.3.1 SPONGIOTIC PATTERN

Name	Special Features	Differential Diagnosis/Pearls
Acute spongiotic dermatitis *Figure 5.3.1*	• Spongiosis (intercellular edema) and basket-weave stratum corneum (acute) • Intraepidermal vesicles filled with mononuclear cells • May see lymphocyte exocytosis • Perivascular lymphocytes ± interstitial eosinophils	• Allergic contact dermatitis, dyshidrotic eczema if acral
Subacute spongiotic dermatitis *Figure 5.3.2*	• Epidermal acanthosis with spongiosis • Parakeratosis • May see lymphocyte exocytosis • Perivascular lymphocytes ± interstitial eosinophils	• Allergic contact dermatitis, nummular dermatitis, id reaction • Dermatophyte infection (hyphae in stratum corneum) • Seborrheic dermatitis has parakeratosis at the openings of follicular ostia ("lipping")
Eosinophilic spongiosis *Figure 5.3.3*	• Epidermis may show features of acute or subacute spongiotic dermatitis • Eosinophils are seen percolating between epidermal keratinocytes	• HAAPPIE DDx: **H**erpes gestationis, **a**rthropod assault, **a**llergic contact dermatitis, **p**emphigus, **p**emphigoid, **i**ncontinentia pigmenti, **e**rythema toxicum neonatorum
Chronic dermatitis (lichen simplex chronicus) *Figure 5.3.4*	• Acanthosis and hypergranulosis • Stratum corneum resembles acral skin but hair follicles are evident • May not see any spongiosis • Vertical streaking of the collagen in the papillary dermis	• Prurigo nodularis appears more papular than plaque-like

TABLE 5.3.1 SPONGIOTIC PATTERN CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Pityriasis rosea *Figure 5.3.5*	• Subacute spongiotic dermatitis (spongiosis may be basilar and not always full thickness) • Mounds of scale with parakeratosis • Erythrocyte extravasation in the papillary dermis • Lymphocyte exocytosis	• Erythema annulare centrifugum may look identical
Stasis dermatitis *Figure 5.3.6*	• Subacute spongiotic dermatitis • Nodular proliferation of vessels in the papillary dermis • Interstitial hemosiderin	• Stasis changes: Dermal changes without epidermal spongiosis

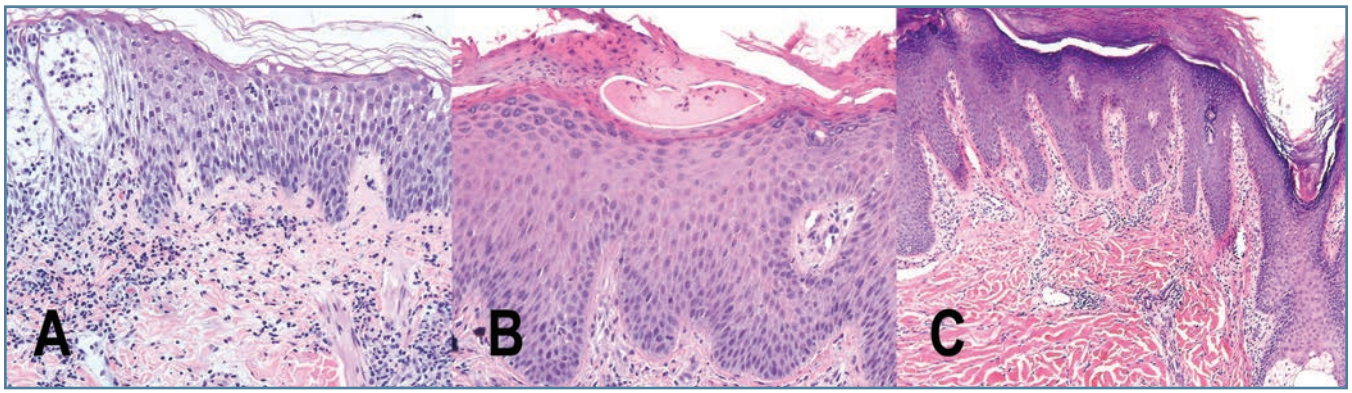

Figure 5.3.7 Spongiotic dermatitis.
In acute spongiotic dermatitis A) there is basket weave stratum corneum, intercellular edema and vesiculation in the epidermis. Eosinophils are present in the inflammatory infiltrate and may be seen percolating in the epidermis. B) Subacute spongiotic dermatitis will often show acanthosis, parakeratosis and hyperkeratosis besides intercellular edema. C) Lichen simplex chronicus has minimal spongiosis, prominent epidermal acanthosis, hypergranulosis, and is reminiscent of acral skin. One notable difference is the presence of adnexal structures (hair follicles).

PSORIASIFORM PATTERN

TABLE 5.3.2 PSORIASIFORM PATTERN

Name	Special Features	Differential Diagnosis/Pearls
Plaque psoriasis *Figure 5.3.8*	• Parakeratosis with sandwiched neutrophils and no serum (dry) (Munro's microabscess) • Loss of granular layer • Acanthotic epidermis with even hyperplasia of the rete ridges (in mature lesions) • Thin suprapapillary plates atop dilated capillary vessels in the tips of dermal papilla (may bleed if scale is picked off—Auspitz sign) • Intraepidermal collections of neutrophils (spongiform pustules of Kogoj)	• Chronic spongiotic dermatitis: Usually has some serum in the cornified layer (wet), preserved granular layer
Pustular psoriasis *Figure 5.3.9*	• As above • Large collections of subcorneal and/or intraepidermal neutrophils	• Dermatophyte infection: PAS stain

TABLE 5.3.2 PSORIASIFORM PATTERN CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Guttate psoriasis *Figure 5.3.10*	• Slightly acanthotic epidermis • Slightly dilated capillary vessels in the papillary dermis • Stratum corneum with mounds of parakeratosis with neutrophils in multiple foci	• Pityriasis rosea: Less neutrophils in cornified layer
Mycosis fungoides *Figure 5.3.11*	• May see psoriasiform hyperplasia • Epidermotropism (atypical lymphocytes percolating in the epidermis) • Atypical lymphocytes lining up at the dermoepidermal junction • Pautrier microabscesses (intraepidermal collections of atypical lymphocytes) • Papillary dermal fibrosis	• Chronic eczematous dermatitis: More spongiosis • Please see Section 5.18 for more information
Syphilis *Figure 5.3.12*	• Psoriasiform acanthosis • Parakeratosis, often with neutrophils • Vacuolar interface dermatitis • Perivascular and interstitial lymphocytes and plasma cells • Endothelial swelling of small blood vessels	• Psoriasis: No plasma cells, less lichenoid inflammation • Pityriasis lichenoides: No plasma cells, no neutrophils
Pityriasis rubra pilaris *Figure 5.3.13*	• Psoriasiform acanthosis • Stratum corneum: Parakeratosis alternating with orthokeratosis in a checkerboard pattern • Usually preserved granular layer • Follicular plugging	• Psoriasis: Loss of granular layer, neutrophils in parakeratotic cornified layer
Nutritional-deficiency dermatitis *Figure 5.3.14*	• Psoriasiform acanthosis • Pallor of the top half of the epidermis and ballooning of the keratinocytes	• Identical findings may be seen in pellagra, acrodermatitis enteropathica (zinc deficiency), and glucagonoma (aka necrolytic migratory erythema) • **Don't confuse** necrolytic migratory erythema with necrolytic acral erythema (hepatitis C); the latter has a psoriasiform dermatitis pattern just like acrokeratosis neoplastica **WITHOUT** epidermal pallor and ballooning of the keratinocytes

PAS = periodic acid—Schiff.

INTERFACE PATTERN

TABLE 5.3.3 INTERFACE PATTERN

Name	Special Features	Differential Diagnosis/Pearls
Lichenoid (More Lymphocytes)		
Lichen planus *Figure 5.3.15*	• Compact orthokeratosis • Sawtooth rete ridge pattern • Wedge-shaped hypergranulosis • Lichenoid inflammation (lymphocytic band) • Destruction of the basal layer with evident eosinophilic Civatte bodies • Melanophages in the papillary dermis	• If eosinophils and parakeratosis are present the DDx includes: Lichen planus—like keratosis (solitary lesion), lichenoid drug eruptions (rash)

TABLE 5.3.3 INTERFACE PATTERN CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Lichen striatus *Figure 5.3.16*	• Lichenoid dermatitis in the upper dermis, often with significant number of histiocytes • Lichenoid aggregates around eccrine coils	• Lichen planus: More lymphocytic • Syphilis: Tends to have neutrophils and plasma cells • Lichen nitidus: Epidermal collarette *Figure 5.3.17*
Resolving lichen planus *Figure 5.3.18*	• May see effaced rete pattern • Civatte bodies may or may not be present • Pigment incontinence (melanophages in the upper dermis) • Dermal fibrosis	• Other resolving lichenoid dermatitides, ashy dermatosis, postinflammatory hyperpigmentation (no Civatte bodies) • Lichenoid regression of pigmented lesion
Vacuolar (Fewer Lymphocytes)		
Lupus erythematosus *Figure 5.3.19*	• Interface vacuolar dermatitis • Compact hyperkeratosis (follicular plugging) is prominent in discoid lupus erythematosus • Basement membrane zone thickening (may need a PAS stain to better visualize this) • Pigment incontinence (melanophages in the papillary dermis) • Superficial and deep perivascular and periadnexal lymphocytic infiltrate • Specimen is devoid of eosinophils • Mucin is present between collagen bundles • **Direct immunofluorescence (DIF): "Full house" immunoreactants can be deposited (IgG, IgA, IgM, and C3)**	• Dermatomyositis may be identical to cutaneous lupus erythematosus, epidermis may be atrophic, but no thickened basement membrane and hyperkeratosis
Pityriasis lichenoides et varioliformis acuta (PLEVA), aka Mucha-Habermann disease *Figure 5.3.20*	• Vacuolar interface dermatitis • Lymphocytic exocytosis • Compact stratum corneum with parakeratosis, inflammatory cells, and serum (dirty scale) • Necrotic keratinocytes in all levels of epidermis • Erythrocyte extravasation • Perivascular lymphocytic infiltrate	• Sufficiently characteristic if all features are present • $CD8^+$ cytotoxic T cells in the infiltrate • May be clonal • DDx: Syphilis
Pityriasis lichenoides chronica *Figure 5.3.21*	• Vacuolar interface dermatitis • Less pronounced epidermal changes and less robust inflammatory infiltrate in the dermis • Transepidermal elimination of erythrocytes • Melanophages may be present	• $CD4^+$ T cells predominate
Erythema multiforme *Figure 5.3.22*	• Basket-weave stratum corneum (the process is acute) • Scattered individual or clusters of necrotic keratinocytes • Vacuolar interface dermatitis • Perivascular lymphocytes	• Stevens-Johnson syndrome/toxic epidermal necrolysis shows basket-weave stratum corneum, full-thickness epidermal necrosis, and is pauciinflammatory • DDx: Fixed drug eruption (more eosinophils)
Fixed drug eruption *Figure 5.3.23*	• Vacuolar interface dermatitis • Acute stratum corneum (basket weave) • Perivascular lymphocytes and some eosinophils • Melanophages and sometimes papillary dermal fibrosis	• DDx: Erythema multiforme (fewer eosinophils, fewer melanophages)
Graft-versus-host disease (GVHD) *Figure 5.3.24*	• Vacuolar interface • Necrotic keratinocytes • May see epithelial atypia and disorder	• Inflammation tends to be more brisk in GVHD after solid organ transplant and more sparse after bone marrow transplant

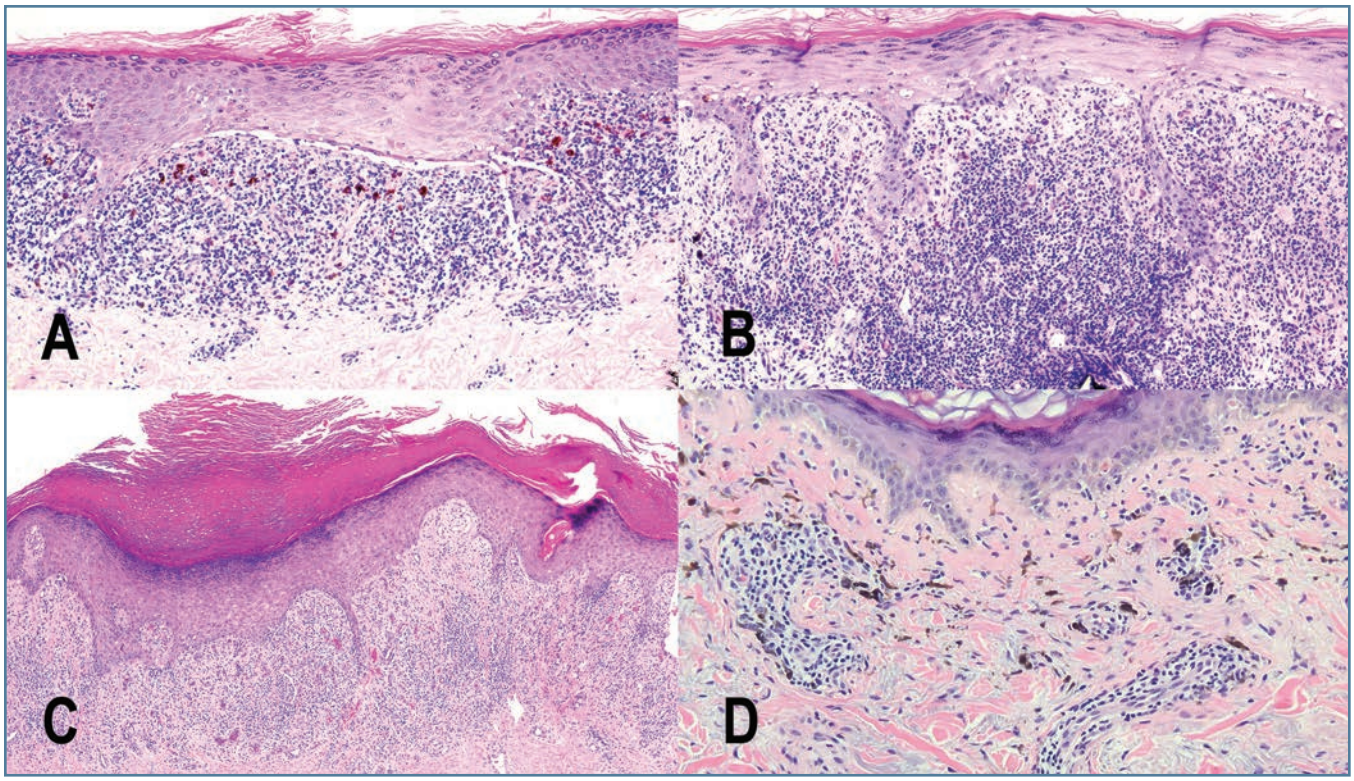

Figure 5.3.25 Lichenoid dermatitis differential.

A) Lichen planus has a lichenoid band of inflammation with civatte bodies, hypergranulosis, saw-tooth rete ridges and pigment incontinence. Note absence of parakeratosis and eosinophils. B) Lichen planus-like keratosis and lichenoid drug eruptions have parakeratosis and eosinophils are often present; differentiate with clinical information. C) Hypertrophic LP exhibits acanthosis and hyperkeratosis, commonly involves lower extremities, and the lichenoid infiltrate often contains eosinophils. D) Resolving lichen planus has prominent melanophages in the dermis with fibrosis and occasional civatte bodies. The differential includes ashy dermatosis and post-inflammatory hyperpigmentation from other lichenoid processes.

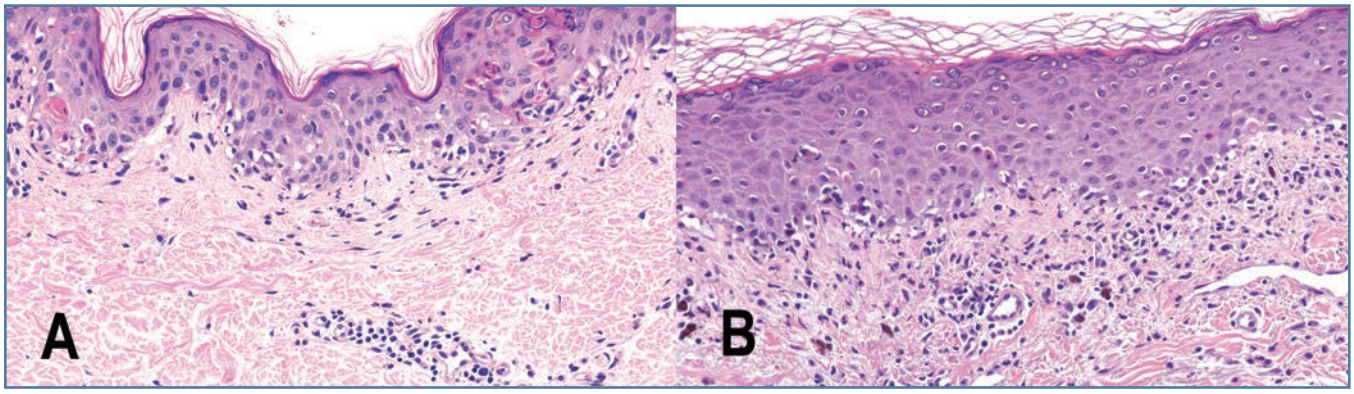

Figure 5.3.26 Acute interface dermatitis.

A) Erythema multiforme (EM) and B) Fixed drug eruption (FDE) both show acute stratum corneum (basket weave), interface dermatitis, dyskeratotic keratinocytes, and perivascular lymphocytic inflammation. In EM, one can see clusters of necrotic keratinocytes, while in FDE, the perivascular inflammation is more likely to have eosinophils as well as melanophages from prior episodes.

MISCELLANEOUS

TABLE 5.3.4 MISCELLANEOUS PATTERNS

Name	Special Features	Differential Diagnosis/Pearls
Granular parakeratosis *Figure 5.3.27*	• Psoriasiform acanthosis • Preserved granular layer • Thickened stratum corneum with compact parakeratosis and granules	
Inflammatory linear verrucous epidermal nevus *Figure 5.3.28*	• Alternating areas of orthokeratosis with retained/prominent granular layer, and areas of parakeratosis with lost granular layer	• Psoriasis: Doesn't have tufted alternating pattern

5.4 Granulomatous Infiltrates

PALISADED

TABLE 5.4.1 PALISADED GRANULOMATOUS INFILTRATES

Name	Special Features	Clinical Scenario/Pearls
Granuloma annulare (GA) *Figure 5.4.1*	• Palisaded histiocytes surrounding mucin and altered collagen • Associated with perivascular lymphocytic inflammation • May have interstitial eosinophils	• May be perforating, dermal, or subcutaneous • Necrobiosis lipoidica: Less mucin and a more horizontal layered appearance
Lupus miliaris disseminatus faciei *Figure 5.4.2*	• Palisaded histiocytes on facial skin • Inside the palisade, the dermis has been replaced by caseous necrosis	• AFB stains are NEGATIVE • Considered a variant of rosacea • Looks like a little rheumatoid nodule on the face
Necrobiosis lipoidica *Figure 5.4.3*	• Horizontal layering of histiocytes • Degenerated collagen between layers • Plasma cells commonly seen • No mucin • Appears rectangular	• DDx: GA that has less horizontal layering of histiocytes and has mucin
Necrobiotic xanthogranuloma *Figure 5.4.4*	• Dense histiocytic infiltrate throughout the dermis, large multinucleated giant cells, plasma cells, cholesterol clefts • Lipidized histiocytes and Touton giant cells may be seen • Neutrophils may be present within the areas of necrosis	• **Associated with paraproteinemia (IgGκ)**
Rheumatoid nodule *Figure 5.4.5*	• Well-formed palisading granuloma with homogeneous eosinophilic center (fibrin) • Located in the deep dermis and subcutis • No mucin	• Subcutaneous granuloma annulare is similar but typically will have some mucin

AFB = acid-fast bacillus.

INTERSTITIAL

TABLE 5.4.2 INTERSTITIAL GRANULOMATOUS INFILTRATES

Name	Special Features	Clinical Scenario/Pearls
Granuloma annulare (GA) *Figure 5.4.6*	• Single histiocytes splayed between collagen bundles • Mucin and perivascular lymphocytic inflammation • Eosinophils usually present	• **"Busy" Dermis DDX (Busy Dermis Can Kill Grandma's Sweet Niece):** ▸ **B**lue Nevus ▸ **D**ermatofibroma or Dermal Spitz ▸ **C**utaneous Mets (breast) ▸ **K**aposi's sarcoma (patch stage) ▸ **G**ranuloma Annulare ▸ **S**cleromyxedema ▸ **N**eurofibroma
Actinic granuloma *Figure 5.4.7*	• Also known as annular elastolytic giant cell granuloma • On sun-damaged skin • Interstitial histiocytes and giant cells that engulf elastic fibers	• Some consider it a variant of granuloma annulare on sun-damaged skin
Palisaded neutrophilic and granulomatous dermatitis (interstitial granulomatous dermatitis with arthritis) *Figure 5.4.8*	• Neutrophils, interstitial or palisaded—looks like GA but with increased neutrophils, ± eosinophils and more diffuse • Early lesions can have vasculitis, late lesions can have fibrosis	• "Busy" dermis DDx
Interstitial granulomatous drug reaction	• Eosinophils, ± interface change	

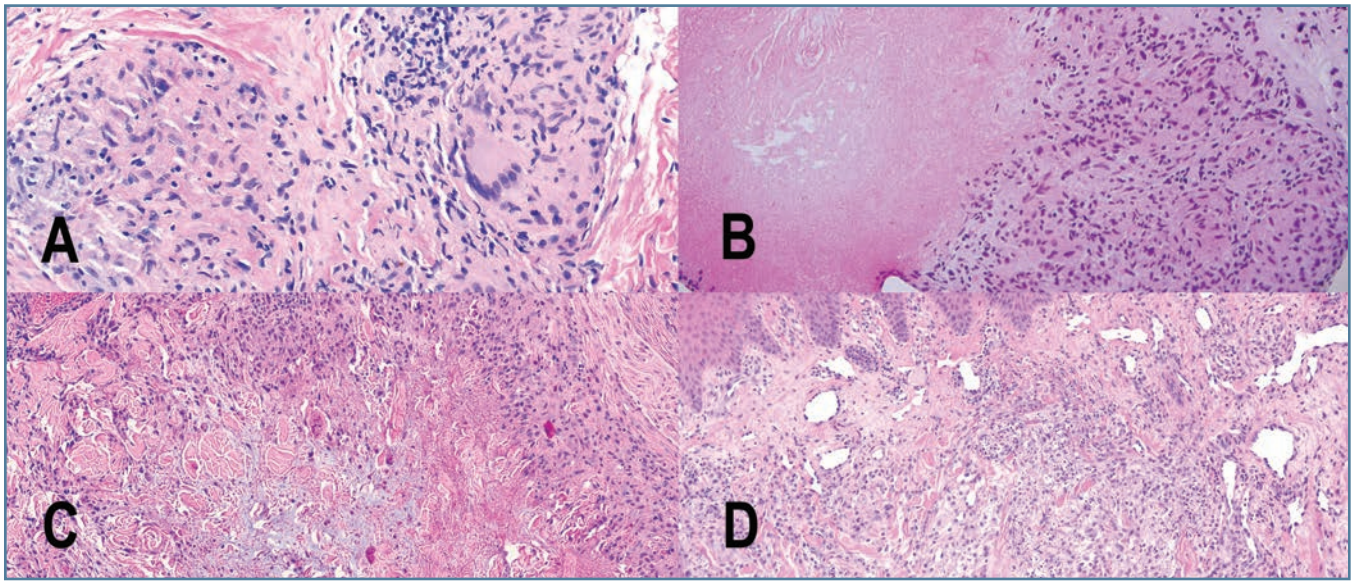

Figure 5.4.9 Granulomatous dermatitis differential.
A) Nodular "naked" granulomas with minimal lymphocytic inflammation are characteristic of sarcoidosis. B) Lupus miliaris disseminatus faciei is a palisaded granuloma with central necrosis that resembles a mini rheumatoid nodule on the face. C) Granuloma annulare exhibits palisading and interstitial histiocytes around degenerating collagen with mucin. D) Palisaded neutrophilic granulomatous dermatitis can look similar to GA with palisading and interstitial histiocytes, however, there are prominent neutrophils and the process is usually more diffuse, with less mucin.

SARCOIDAL/NODULAR/TUBERCULOID

TABLE 5.4.3 SARCOIDAL/NODULAR/TUBERCULOID GRANULOMATOUS INFILTRATES

Name	Special Features	Clinical Scenario/Pearls
Sarcoid *Figure 5.4.10*	• Epithelioid histiocytes form discrete nodules in the dermis • **"Naked" granulomas (lack of surrounding lymphocytic inflammation); however, if one looks closely there are some scattered lymphocytes indeed!** • No necrosis • Asteroid bodies: Star-like eosinophilic inclusions inside giant cells • Schaumann bodies: Cytoplasmic purplish calcifications inside giant cells	• Sarcoidal foreign body giant cell reaction does not exclude sarcoidosis since cutaneous sarcoidosis often appears at sites of trauma
Foreign body granuloma *Figure 5.4.11*	• Foreign material in sarcoidal-appearing granuloma	• Examine under polarized light
Tuberculosis/tuberculids	• Less well-formed nodular granuloma with central caseation • Granulomas are surrounded by lymphoplasmacytic inflammation	• Organisms can be seen with an AFB special stain
Crohn's *Figure 5.4.12*	• Noncaseating granulomas • May be difficult to distinguish from sarcoid, but tends to be more diffuse	• Clinical information will help
Lupus miliaris disseminatus faciei	• See above	• Noninfectious
Leprosy	• See Section 5.8	
Late syphilis (Tertiary)	• See Section 5.8	
Leishmaniasis	• See Section 5.8	
Rosacea and perioral dermatitis *Figure 5.4.13*	• Late lesions have nodular granulomas in the dermis or around ruptured follicles on facial skin • Perivascular lymphocytic inflammation and telangiectases are also seen	• *Demodex* (multiple) often seen inside hair follicles

SUPPURATIVE AND GRANULOMATOUS INFLAMMATION

- See Section 5.8 Infections

5.5 Bullous Disorders

INTRAEPIDERMAL

TABLE 5.5.1 INTRAEPIDERMAL SPLIT DISORDERS

Name	Special Features	Differential Diagnosis/Pearls
Pemphigus foliaceus *Figure 5.5.1*	• Acantholysis in the subcorneal/granular layer • Intercellular IgG and C3 binding on direct immunofluorescence in the superficial layer of the epidermis • Autoantibody to desmoglein 1 • **IIF: Guinea pig esophagus substrate is best**	• **Staphylococcal scalded skin syndrome**—can look identical • **Bullous impetigo**—more neutrophils • Both not antibody mediated; DIF is negative
Hailey-Hailey disease (familial benign chronic pemphigus) *Figure 5.5.2*	• Full-thickness acantholysis resembling a "dilapidated brick wall" • Does not extend down adnexal structures, unlike pemphigus vulgaris • Not antibody mediated • DIF is negative • *ATP2C1* gene mutation • Autosomal dominant • Flexural involvement	• **Pemphigus vulgaris:** Suprabasilar split, extends down adnexal structures, positive DIF findings
Pemphigus vulgaris *Figure 5.5.3*	• Suprabasal acantholysis, leaving behind keratinocytes attached at the basement membrane resembling a **"row of tombstones"** • Acantholysis extends down adnexa • Intercellular IgG and C3 binding on direct immunofluorescence to the lower half of the epidermis • Autoantibody to desmogleins 1 and 3 • **IIF: Monkey esophagus substrate is best**	• **Paraneoplastic pemphigus:** Suprabasal acantholysis, necrotic keratinocytes, and vacuolar interface changes at the DEJ • Intercellular and linear DEJ deposits against desmogleins 1 and 3, plectin, desmoplakin, envoplakin, periplakin, unknown 170-kDa antigen • IIF: Rat bladder epithelium substrate
Pemphigus vegetans *Figure 5.5.4A-B*	• Epidermal hyperplasia with characteristic eosinophilic abscesses in the lower portions of the epidermis • Acantholysis may be minimal • DIF similar to pemphigus vulgaris	

DEJ = dermoepidermal junction; DIF = direct immunofluorescence; IIF = indirect immunofluorescence.

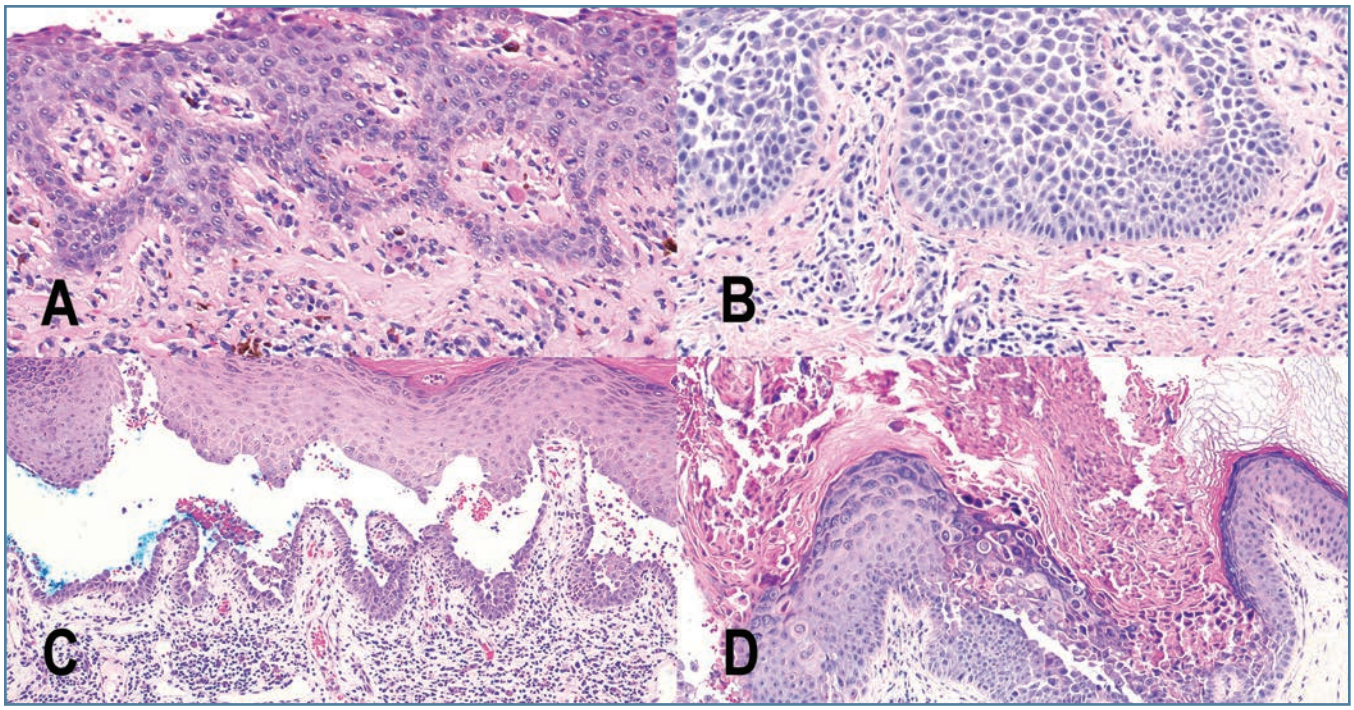

Figure 5.5.5 Intraepidermal blistering disorders.

A) Pemphigus foliaceus demonstrates acantholysis at the surface of the epidermis, mostly in the granular layer. B) Hailey-Hailey on the other hand has acantholysis through the whole thickness of the epidermis and looks like a "dilapidated brick wall" C) Pemphigus vulgaris splits above the basal layer and involves hair follicles. D) Darier's disease — Acantholysis with dyskeratosis (corps ronds and grains).

SUBEPIDERMAL AND PAUCI-INFLAMMATORY

TABLE 5.5.2 SUBEPIDERMAL AND PAUCI-INFLAMMATORY DISORDERS

Name	Special Features	Differential Diagnosis/Pearls
Porphyria cutanea tarda *Figure 5.5.6*	• Subepidermal blister with minimal to no inflammatory infiltrate on acral skin • Caterpillar bodies—eosinophilic elongated wavy structures (degenerated type IV collagen) • Dermis with solar elastosis and festooning of the dermal papillae • DIF shows IgM and C3 in dermal vessel walls	• Pseudoporphyria can look exactly alike
Epidermolysis bullosa acquisita (EBA) *Figure 5.5.7*	• Subepidermal blister with or without neutrophilic inflammation (usually pauciinflammatory) • Antibody to type VII collagen • DIF—linear IgG and/or C3	• Pauciinflammatory bullous pemphigoid: Salt-split skin will differentiate EBA (binding on the floor of the blister) from bullous pemphigoid (binding on the roof of the blister)
Toxic epidermal necrolysis/Stevens-Johnson syndrome *Figure 5.5.8*	• Subepidermal blister with full-thickness necrosis of the epidermis • Residual evidence of interface change • Minimal dermal inflammatory infiltrate • DIF is negative	• Erythema multiforme—clustered necrotic keratinocytes and vacuolar interface inflammation; will not have full-thickness epidermal necrosis

SUBEPIDERMAL AND INFLAMMATORY

TABLE 5.5.3 SUBEPIDERMAL AND INFLAMMATORY DISORDERS

Name	Special Features	Differential Diagnosis/Pearls
Bullous pemphigoid (BP) *Figure 5.5.9*	• Subepidermal blister with eosinophils • Clue to urticarial stage of BP is eosinophilic spongiosis and eosinophils lining up at the DEJ • **Infiltrate is usually only superficial** • DIF: Linear IgG and C3 at the DEJ • Antibodies to BPAg1 and BPAg2	• Herpes gestationis—BP in pregnancy. DIF shows linear C3 at the DEJ
Cicatricial pemphigoid *Figure 5.5.10*	• Subepidermal blister • Variable inflammation, usually fewer eosinophils than in BP • Scarring in the papillary dermis • DIF: Linear deposition of IgG and C3 at the DEJ • Antibodies to BPAg1, BPAg2, integrin $\alpha_6/ß_4$, laminin-5, laminin-6, type VII collagen • Antibodies to laminin-5 associated with malignancy	
Dermatitis herpetiformis *Figure 5.5.11*	• Narrow subepidermal split(s) with neutrophilic abscesses in the dermal papillae • DIF shows granular IgA deposition within dermal papillae • Autoantigen: Transglutaminase-3	• DDx: Linear IgA on histologic grounds, need DIF to differentiate
Linear IgA bullous dermatosis *Figure 5.5.12*	• Subepidermal blister with mixed inflammatory infiltrate where neutrophils predominate • DIF shows linear IgA deposition at the dermoepidermal junction	• DDx: Dermatitis herpetiformis
Bullous lupus erythematosus *Figure 5.5.13*	• Subepidermal bulla with neutrophils • Full house linear deposits at the DEJ including IgG, IgM, IgA, and C3 • Binding at the floor of salt-split skin (antibodies to collagen VII)	• DDx: Epidermolysis bullosa acquisita—DIF findings can be identical; clinical features and response to treatment may be necessary to distinguish

SUBCORNEAL PUSTULAR DERMATOSES

TABLE 5.5.4 SUBCORNEAL PUSTULAR DERMATOSES

Name	Special Features	Differential Diagnosis/Pearls
Acute generalized exanthematous pustulosis (AGEP) *Figure 5.5.14*	• Subcorneal pustule with lymphocytes and eosinophils. No acantholytic cells. DIF negative	• Pustular psoriasis, neonatal pustular melanosis, Candida
Sneddon-Wilkinson disease (subcorneal pustular dermatosis) *Figure 5.5.15*	• Larger subcorneal pustule. No acantholytic cells. DIF negative	
Bullous impetigo *Figure 5.5.16*	• Subcorneal pustule with neutrophils and bacteria	
IgA pemphigus	• Subcorneal split with neutrophils. Antibodies to desmocollin 1; DIF shows intercellular IgA binding	

ACANTHOLYSIS WITH CORPS RONDS AND GRAINS

TABLE 5.5.5 ACANTHOLYSIS WITH CORPS RONDS AND GRAINS

Name	Special Features	Differential Diagnosis/Pearls
Darier's (keratosis follicularis) *Figure 5.5.17*	• Intraepidermal acantholysis with corps ronds and grains (dyskeratosis) • Corps ronds—rounded basophilic cells, large nuclei, perinuclear halo • Grains (resemble rice grains)—flattened nuclei, eosinophilic cytoplasm • Negative DIF	• Grover's (transient acantholytic dermatosis), warty dyskeratoma

5.6 Vasculitis/Vasculopathy

SMALL-VESSEL VASCULITIS

TABLE 5.6.1 SMALL-VESSEL VASCULITIS

Name	Special Features	Clinical Scenario/Pearls
Leukocytoclastic "allergic" vasculitis (LCV) *Figure 5.6.1*	• **Histologic findings of leukocytoclastic vasculitis:** Perivascular mixed infiltrate with leukocytoclasis of neutrophils, fibrin deposition within the vessel wall, endothelial cell swelling and erythrocyte extravasation	• Purpuric dermal hypersensitivity reaction will not have fibrin in vessel walls
Mixed cryoglobulin disease	• Same as above	• Often associated with Hepatitis C infection
Serum sickness	• Same as above	• Serum sickness-like reaction seen in young children after ingestion of medications, particularly cefaclor
Henoch-Schonlein purpura	• Same as above	• Deposition of IgA in vessels on direct immunofluorescence

MEDIUM-VESSEL VASCULITIS

TABLE 5.6.2 MEDIUM-VESSEL VASCULITIS

Name	Special Features	Clinical Scenario/Pearls
Septic vasculitis	• **Histologic findings of leukocytoclastic vasculitis:** Involving small and large vessels • **Vascular thrombi with neutrophils in and around vessels** • Often see necrosis of epidermis and superficial dermis	• Meningococcemia, gonococcemia, *Pseudomonas* septicemia, streptococcal septicemia, and endocarditis
Rheumatoid vasculitis	• **Histologic findings of leukocytoclastic vasculitis:** Involving small and large vessels	• In patients with rheumatoid arthritis
Microscopic polyangiitis	• **Histologic findings of leukocytoclastic vasculitis:** Involving small and large vessels	• p-ANCA/anti-myeloperoxidase

TABLE 5.6.2 MEDIUM-VESSEL VASCULITIS CONTINUED

Name	Special Features	Clinical Scenario/Pearls
Wegner's granulomatosis **NEW NAME:** Granulomatosis with polyangiitis	• **Histologic findings of leukocytoclastic vasculitis:** Involving small and large vessels • **PLUS:** May see palisaded granulomatous inflammation and giant cells surrounding central collection of **neutrophils**, as well as granulomatous vasculitis	• c-ANCA/anti-proteinase 3
Churg-Strauss syndrome **NEW NAME:** Eosinophilic granulomatosis with polyangiitis	• **Histologic findings of leukocytoclastic vasculitis:** Involving small and large vessels • **PLUS:** May see palisaded granulomatous inflammation and giant cells surrounding central collection of eosinophils, as well as **eosinophilic** vasculitis • **May see flame figures**	• p-ANCA/anti-myeloperoxidase

c-ANCA = cytoplasmic anti-neutrophil cytoplasmic antibody; p-ANCA = perinuclear anti-neutrophil cytoplasmic antibody.

LARGE-VESSEL VASCULITIS

TABLE 5.6.3 LARGE-VESSEL VASCULITIS

Name	Special Features	Clinical Scenario/Pearls
Polyarteritis nodosa *Figure 5.6.2*	• Acute phase: Neutrophilic vasculitis with leukocytoclasis, fibrin deposition, and red blood cell extravasation • Chronic phase: Granulomatous vasculitis • Fat necrosis may be present sometimes • Inflammation remains localized around involved vessel • Involves a large artery at the dermal—subcutaneous fat junction	• DDx: Erythema induratum, which has lobular panniculitis that extends beyond involved vessel
Thrombophlebitis *Figure 5.6.3*	• Vasculitis involving large veins in subcutaneous tissue • Acute phase: With neutrophils • Chronic phase: Granulomatous • Often thrombus in vessel	• Not limited to upper and lower extremities • Mondor's disease: Involvement of the superficial veins of the breast and adjacent thoracoabdominal wall
Giant cell arteritis	• Muscular artery with subendothelial granulomatous inflammation (histiocytes and giant cells), which may lead to transluminal inflammation with time	• **Temporal arteritis can have a focal/beaded pattern, so beware of skip areas on biopsy**

VASCULOPATHY

TABLE 5.6.4 VASCULOPATHY

Name	Special Features	Clinical Scenario/Pearls
Type I cryoglobulinemia *Figure 5.6.4*	• Occlusion of multiple vessels in the upper half of the dermis with a dark pink amorphous substance • Minimal perivascular inflammation • Extravasation of red blood cells	• These cryoglobulin plugs are PAS positive
Cholesterol embolization	• Occlusion of one or multiple arterioles with cholesterol clefts	• Typically after catheterization
Livedoid vasculopathy *Figure 5.6.5*	• Nodular angiodysplasia with hyalinized vessel walls • Multifocal fibrin thrombi	• Also known as atrophie blanche

PAS = periodic acid—Schiff.

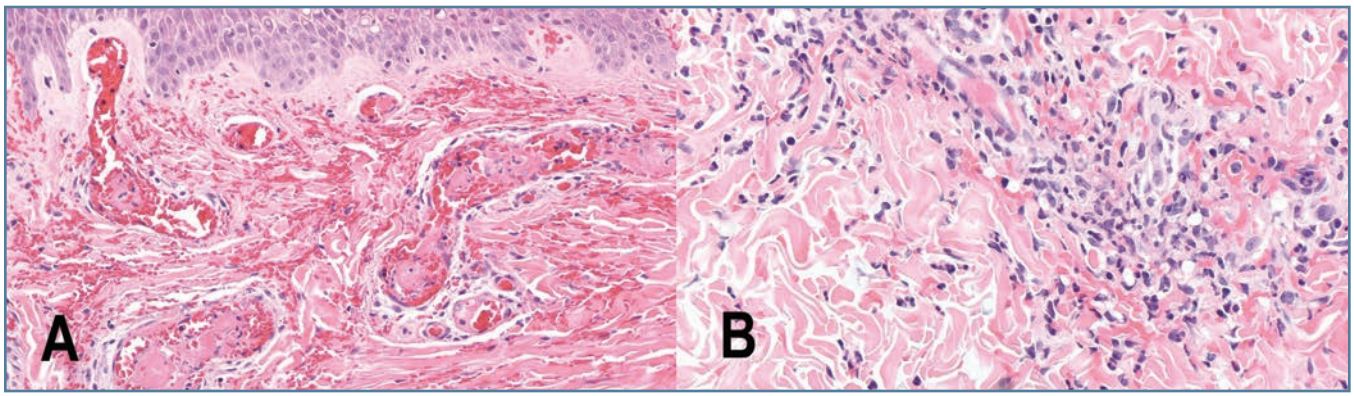

Figure 5.6.6 Vasculopathy vs vasculitis.
In a thrombotic vasculopathy A) such as type 1 cryoglobulinemia, there is prominent fibrin within the vessels with minimal surrounding inflammation. In leukocytoclastic vasculitis B) there is a prominent inflammatory cell infiltrate composed of lymphocytes, neutrophils with leukocytoclasis, and eosinophils. As a result of the inflammation, there is damage to the vessel wall and resultant fibrin deposition in the vessel lumen.

MISCELLANEOUS

TABLE 5.6.5 MISCELLANEOUS VASCULITIS

Name	Special Features	Clinical Scenario/Pearls
Granuloma faciale *Figure 5.6.7*	• Dense dermal infiltrate with "everybody at the party" (eosinophils, lymphocytes, neutrophils, and plasma cells) ± LCV • Grenz zone present • Contrary to the name, there is NO granulomatous inflammation	• Looks like early EED, but more eosinophils and fewer neutrophils
Erythema elevatum diutinum (EED) *Figure 5.6.8*	• Leukocytoclastic vasculitis and eosinophils in early lesions • Late lesions: Multifocal onion-skin fibrosis surrounding the previously affected blood vessels, scattered neutrophils	• Late lesions look like sclerotic fibroma with neutrophils
Incidental vasculitis	• Focal leukocytoclastic vasculitis at the base of a chronic ulcer	• Not a true vasculitis • Can see with trauma and tick bites

LYMPHOCYTIC INFILTRATES

TABLE 5.6.6 LYMPHOCYTIC INFILTRATES

Name	Special Features	Clinical Scenario/Pearls
Degos disease *Figure 5.6.9A-B*	• Perivascular lymphocytic inflammation • Damage to the vessel wall • Other features: Central epidermal depression, epidermal atrophy and wedge-shaped scar below • Dermal mucin	• Vasculopathy usually more acute with tissue necrosis rather than scar
Perniosis *Figure 5.6.10*	• Superficial and deep perivascular lymphocytic inflammation • ± Damage to the vessel wall • Papillary dermal edema • Acral	• Chilblain lupus: Interface change favors lupus

TABLE 5.6.6 LYMPHOCYTIC INFILTRATES CONTINUED

Name	Special Features	Clinical Scenario/Pearls
Polymorphous light eruption *Figure 5.6.11*	• Papillary dermal edema • Superficial and deep perivascular lymphocytic infiltrate	• Perniosis (acral skin)
Pigmented purpuric dermatosis *Figure 5.6.12*	• Perivascular lymphocytic infiltrate with erythrocyte extravasation and hemosiderin deposition • Spongiosis or interface changes can be present	Variants: • Schamberg's disease (cayenne pepper pigmentation on the lower extremities) • Purpura annularis telangiectodes of Majocchi (annular) • Gougerot and Blum (lichenoid) • Lichen aureus (golden patches)
Gyrate erythema *Figure 5.6.13*	• Dense "coat sleeve-like" perivascular lymphocytic infiltrate • Vessels are intact • Deep gyrate erythemas lack epidermal changes • May see spongiosis and parakeratosis in erythema annulare centrifugum	• Tumid lupus erythematosus: Dermal mucin • Polymorphous light eruption: Papillary dermal edema

5.7 Panniculitis

SEPTAL

TABLE 5.7.1 SEPTAL PANNICULITIS

Forms	Features	Differential Diagnosis/Pearls
Erythema nodosum *Figure 5.7.1*	Early • Septal edema • Mixed inflammatory infiltrate with neutrophils, eosinophils, histiocytes Late • Widened septa with fibrosis, lymphocytes, multinucleated histiocytes • Miescher radial granuloma (histiocytes surrounding central cleft)	• Infection: Typically neutrophilic; check bug stains • Drug-induced: Typically neutrophilic and eosinophilic; correlate with clinical history • Erythema induratum: Lobular, centered around vessels
Deep morphea (morphea profunda) *Figure 5.7.2*	• Septal thickening • Mixed inflammation with lymphocytes, plasma cells, and eosinophils	• Eosinophilic fasciitis: Involves fascia but indistinguishable on punch biopsy
Necrobiosis lipoidica *Figure 5.7.3*	• Layers of histiocytes with altered collagen and fibrosis • Admixed lymphocytes and plasma cells	• Deep granuloma annulare: Palisading, increased mucin • Morphea: Thickened collagen bundles

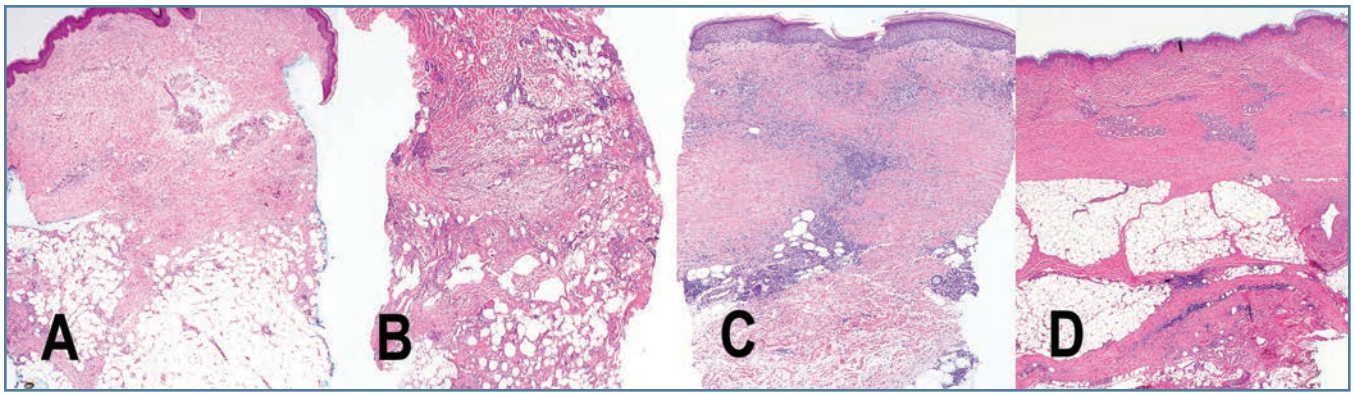

Figure 5.7.4 Differential diagnosis of septal thickening.

Erythema nodosum (EN) (A), lipodermatosclerosis (LDS) (B), necrobiosis lipoidica (NL) (C), and deep morphea (morphea profunda) (D) can all present with thickened and/or fibrotic septa within the subcutis. While NL and morphea typically have dermal involvement, the findings in EN and LDS are confined to the subcutis. EN and NL are both granulomatous, but in EN, the inflammation is confined to the septa rather than involving the dermis with palisading and layering. LDS also has additional features of membranous lipodystrophy. In deep morphea, the fibrosis is typically hypocellular and extends into the fascia.

LOBULAR

TABLE 5.7.2 LOBULAR PANNICULITIS

Forms	Features	Differential Diagnosis/Pearls
Erythema induratum (nodular vasculitis) *Figure 5.7.5*	• Mixed lobular inflammation (neutrophils, lymphocytes, histiocytes, giant cells) in nodular pattern, spills into septae • Medium-vessel vasculitis (inflammation involves vessel walls) at junction of dermis and subcutis	• Polyarteritis nodosa: Inflammation centered around vessel, more focal in appearance
Lupus panniculitis (lupus profundus) *Figure 5.7.6*	• Lymphoplasmacytic lobular panniculitis • Rimming of adipocytes • Lymphoid aggregates • Hyalinized necrosis • ± interface ± superficial and deep periadnexal lymphoplasmacytic infiltrate	• Subcutaneous panniculitis-like T Cell lymphoma: Cytologic atypia, increased CD4/CD8 ratio
Subcutaneous panniculitis-like T Cell lymphoma *Figure 5.7.7*	• Lymphocytic lobular panniculitis • Rimming of adipocytes • Cytologic atypia • Increased CD4+/CD8+ T Cell ratio	• Lupus panniculitis: Normal CD4+/CD8+ T Cell ratio, no cytologic atypia, hyalinized necrosis
Alpha-1 antitrypsin deficiency panniculitis *Figure 5.7.8*	• Neutrophilic panniculitis with dense inflammation • Fat necrosis with lipid-laden foamy macrophages	• Drug-induced panniculitis: Typically has eosinophils
Drug-induced panniculitis *Figure 5.7.9*	• Neutrophils ± eosinophils within the fat lobules	• **Drugs associated with panniculitis: BRAF inhibitors, tyrosine kinase inhibitors**
Lipodermatosclerosis (LDS) *Figure 5.7.10*	• Lipomembranous dystrophy ("arabesque" sign—fatty cysts lined by eosinophilic feathery border) • Septal thickening and sclerosis	• Erythema nodosum: More inflammatory (although early LDS can be quite inflamed) • Deep morphea: Thickened collagen bundles, no lipomembranous dystrophy

TABLE 5.7.2 LOBULAR PANNICULITIS CONTINUED

Forms	Features	Differential Diagnosis/Pearls
Pancreatic panniculitis *Figure 5.7.11*	• Basophilic material + mixed inflammation (neutrophils, giant cells, foamy histiocytes) • Ghost fat cells	
Calciphylaxis *Figure 5.7.12A-B*	• Calcium deposition within small blood vessels in the fat • **Need von Kossa calcium stain**	• Must see deposition in small vessels
Subcutaneous fat necrosis of the newborn *Figure 5.7.13*	• Fat necrosis • Radially arranged needle-like crystals within fat cells • Mixed inflammation including giant cells • Late lesions have calcification and fibrosis	• Sclerema neonatorum: Similar findings but no inflammation • Poststeroid panniculitis: Need clinical history

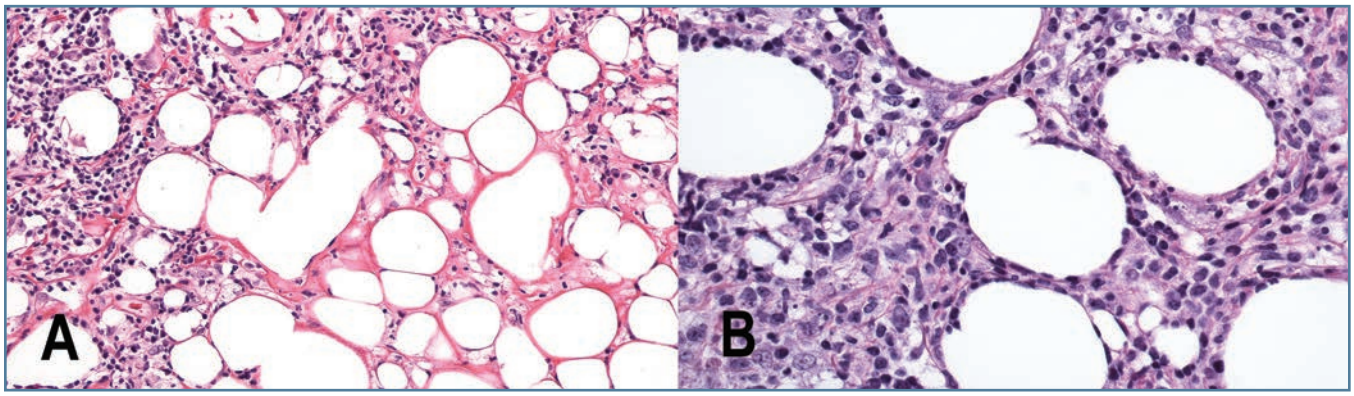

Figure 5.7.14 Lymphocytic lobular panniculitidies.
Lupus panniculitis (lupus profundus) (A), subcutaneous panniculitis-like T Cell lymphoma (SPLTCL) (B) both have findings of lymphocytic lobular panniculitis. Lupus panniculitis shows hyalinized fat necrosis; SPLTCL shows marked cytologic atypia and rimming of atypical lymphocytes around the periphery of adipocytes.

5.8 Infections/Infestation

BACTERIAL

TABLE 5.8.1 BACTERIAL INFECTIONS

Name	Special Features	Differential Diagnosis/Pearls
Botryomycosis *Figure 5.8.1*	• Large blue collection of bacterial cocci (staph) in the dermis surrounded by an abscess (large collection of neutrophils)	• Mycetoma (usually larger, filamentous)
Chancroid *Figure 5.8.2*	• Ulcerated epidermis • Granulation tissue and numerous plasma cells • Gram stain and culture useful	• Cause: *Haemophilus ducreyi*
Ecthyma gangrenosum *Figure 5.8.3*	• Skin ulceration and dermal necrosis • Abundant neutrophilic inflammation in the reticular dermis • Necrotizing vasculitis with thrombosis and numerous gram-negative bacteria in the dermis and around small blood vessels	• *Pseudomonas aeruginosa* infection

TABLE 5.8.1 BACTERIAL INFECTIONS CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Erythrasma *Figure 5.8.4*	• Thin vertical rods seen at the surface of the stratum corneum	• *Corynebacterium* • Gram stain helps to visualize organisms
Granuloma inguinale	• Pseudoepitheliomatous hyperplasia (PEH) with large collections of neutrophils (abscesses) • Donovan bodies—histiocytes containing the organisms • Caused by: *Klebsiella granulomatis*	• PEH with pus DDx includes: Blastomycosis, chromomycosis, cocci, granuloma inguinale, halogenoderma, sometimes leishmaniasis
Impetigo *Figure 5.8.5*	• Neutrophilic serum crust • Clusters of cocci • Bullous impetigo will show a subcorneal blister	• Impetiginization, often only a secondary finding • DDx for bullous impetigo is staphylococcal scalded skin syndrome and pemphigus foliaceus—neither of which has bacterial colonies

Leprosy
Figure 5.8.6
	• Tuberculoid leprosy:
	  ▸ Epithelioid granulomas surrounding neurovascular bundles in the dermis (lesions are anesthetic)
	  ▸ **Oriented "east-west" and resembling "sausages"**
	  ▸ Paucibacillary—may not always see organisms
	• Lepromatous leprosy:
	  ▸ Perivascular and diffuse lymphohistiocytic inflammation in the dermis
	  ▸ A grenz zone may be seen
	  ▸ Globi with mycobacterial collections
	  ▸ Stains strongly with Fite stain
		Leprosy reactions:
		• Type 1: Reversal reaction—starts after treatment, reflects stronger cellular immunity against *Mycobacterium leprae*
		• Type 2: Erythema nodosum leprosum—immune complex–mediated vasculitis of the skin and other organs
		• Type 3: Lucio's phenomenon—massive amount of organisms with thrombosis of the arterioles and infarction

Pitted keratolysis *Figure 5.8.7*	• Dells or pits in the stratum corneum on acral skin • On high power, thin rods or cocci are seen on the surface of the cornified layer	• Causes: *Kytococcus sedentarius* and Corynebacterium)
Rhinoscleroma	• Sheets of lymphocytes and plasma cells in the dermis • **Russell bodies—"constipated plasma cells"—the cytoplasm is filled with bright pink immunoglobulins** • **Mikulicz cells—histiocytes that have engulfed large collections of bacilli**	• Caused by: *Klebsiella rhinoscleromatis*
Suppurative folliculitis *Figure 5.8.8*	• Acute neutrophilic inflammation within or around a hair follicle • Multiple hair follicles may be affected • Epidermal serum crust may be seen	• DDx: Acne, hot tub folliculitis, and fungal folliculitis (don't forget to look for organisms)
Tuberculosis	• Poorly formed nodular granulomas with central caseous necrosis	• AFB stain to look for organism in tissue

AFB = acid-fast bacillus.

SPIROCHETAL

TABLE 5.8.2 SPIROCHETAL INFECTIONS

Name	Special Features	Differential Diagnosis/Pearls
Lyme disease *Figure 5.8.9*	• Erythema migrans: Perivascular lymphocytic inflammation, often with subtle interface change • ± plasma cells and eosinophils • Spirochetes highlighted with a silver stain (in theory), but **test is not sensitive**	• Density of infiltrate can be quite varied • DDx: Arthropod reaction, drug eruption, viral exanthema, other gyrate erythemas
Syphilis	• Primary syphilis is an ulcer with granulation tissue and numerous plasma cells • Secondary syphilis: See Section 5.3 • Tertiary syphilis is granulomatous and organisms may not be present	• Silver stain or IHC for spirochetes to demonstrate bacteria

IHC = immunohistochemistry.

PROTOZOAN

TABLE 5.8.3 PROTOZOAN INFECTIONS

Name	Special Features	Differential Diagnosis/Pearls
Acanthamoeba	• Vascular invasion by amoebic trophozoites • Necrosis of deep vessels	• Organisms are as large as histiocytes
Leishmaniasis *Figure 5.8.10*	• Diffuse granulomatous inflammation in the dermis with admixed lymphocytes and plasma cells • The organisms are intracellular—can be randomly distributed or line up at the periphery (marquee sign) • ***Leishmania* organisms lack a capsule and have a peripheral kinetoplast** • **Amastigotes stain with CD1a immunostain**	• Histoplasmosis—the organisms have a capsule and are always randomly/evenly distributed inside the histiocyte, not CD1a positive

FUNGAL

TABLE 5.8.4 FUNGAL INFECTIONS

Name	Special Features	Differential Diagnosis/Pearls
Blastomycosis *Figure 5.8.11*	• Pseudoepitheliomatous hyperplasia • Suppurative and granulomatous inflammation • Small organism (7-15 µm) with refractile wall • Broad-based budding may be seen	• Caused by Blastomyces *dermatitidis* • Stain with GMS
Candidiasis *Figure 5.8.12*	• Vertically oriented pseudohyphae in the stratum corneum • May also see hyperkeratosis and neutrophils	• Readily seen on H&E, may also use PAS stain
Chromomycosis *Figure 5.8.13*	• Pseudoepitheliomatous hyperplasia with intraepidermal collections of neutrophils • Organisms are brown (5-12 µm), found in groups within multinucleated giant cells. This is known as a Medlar body (or "copper pennies")	• DDx: PEH with pus

TABLE 5.8.4 FUNGAL INFECTIONS CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Coccidioidomycosis *Figure 5.8.14*	• Granulomatous inflammation with **large (10- to 80-μm) grayish spherules filled with endospores** • May also present with pseudoepitheliomatous hyperplasia with neutrophilic abscesses	• DDx: PEH with pus
Cryptococcosis *Figure 5.8.15*	• Granulomatous inflammation with numerous oval yeasts (5-15 μm) that contain a clear gelatinous capsule • **The capsule stains with mucicarmine and Alcian blue**	• *Cryptococcus neoformans* • Blastomycosis, which has broad-based budding, doesn't have double-layered gel capsule
Histoplasmosis *Figure 5.8.16*	• Sheets of histiocytes with randomly distributed organisms with pseudocapsule • Similar in size (2-3 μm) to leishmaniasis, but *Histoplasma* lacks a kinetoplast • Subtype: African histoplasmosis species is much larger and can sometimes be confused with Cryptococcus and Lobomycosis	• *Histoplasma capsulatum* (misnomer, as the organism lacks a true capsule) • DDx: Leishmaniasis, which has marquee sign of peripherally distributed amastigotes
Lobomycosis (keloidal blastomycosis)	• Granulomatous inflammation with numerous organisms, sometimes arranged in pop bead—like formation • Similar in size to African histoplasmosis species (6-12 μm)	• Caused by *Lacazia loboi*
Paracoccidioides infection (South American blastomycosis)	• Granulomatous inflammation with narrow-based budding yeast (5-60 μm) • Absent refractile wall • Best seen with GMS stain • Mariner's wheel budding pattern is characteristic	• Caused by *Paracoccidioides brasiliensis*
Phaeohyphomycosis (Shown with Fontana Masson stain) *Figure 5.8.17*	• Pigmented fungal infection caused by black molds • Granulomatous inflammation with neutrophils • **Brown pigment can be seen in the hyphal wall**	• Most common culprit isolated in tissue is *Exophiala jeanselmei* • In immunocompromised patients, the causative agent is *Bipolaris spicifera*
Sporotrichosis	• Palisading granulomatous inflammation with collections of neutrophils and pleomorphic yeast organisms, some of which can be cigar shaped • Stellate abscesses	• DDx: Cat scratch fever, tularemia, lymphogranuloma venereum, and *Mycobacterium marinum* infection
Tinea capitis *Figure 5.8.18*	• Fungal infection of the hair shaft • Endothrix—spores present inside the hair shaft *(Trichophyton tonsurans)* • Ectothrix—spores on the surface of the hair shaft and not within *(Microsporum canis)*	• More on this in Section 5.10
Tinea corporis *Figure 5.8.19*	• Hyphae in the stratum corneum sandwiched often between basket-weave stratum corneum and compact/parakeratotic stratum corneum • Neutrophilic inflammation and spongiosis may be present	• Readily seen with PAS stain • Subtype: Bullous tinea—will also have massive papillary dermal edema
Tinea nigra *Figure 5.8.20*	• Pigmented hyphae in the stratum corneum on acral skin	• May easily be seen on H&E • Caused by *Hortaea werneckii*
Tinea versicolor *Figure 5.8.21*	• Basket-weave stratum corneum with bluish hyphae and groups of round spores ("spaghetti and meatballs")	• Readily seen on H&E
Onychomycosis (Shown with PAS stain) *Figure 5.8.22*	• Endospores and hyphae in the subungual debris • Parakeratosis and clumps of neutrophils may also be present	• Best seen with PAS or GMS stain
Mycetomas		
Eumycetoma *Figure 5.8.23*	• Stellate abscesses with grains made of radially oriented fungal hyphae with **Splendore-Hoeppli phenomenon at the periphery**	• Splendore-Hoeppli phenomenon at the periphery (accumulation of immunoglobulin)

TABLE 5.8.4 FUNGAL INFECTIONS CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Actinomycetoma *Figure 5.8.24*	• Stellate abscesses with grains made of wispy filamentous bacteria • Also may see Splendore-Hoeppli phenomenon at the periphery	• Not true mycetomas as they are not composed of fungi
Angioinvasive Fungal Infections		
Zygomycosis	• **Large, broad hyphae, WITHOUT septations** • Branch at 90-degree angle • Angioinvasive and cause tissue necrosis	• Sometimes will branch at 45-degree angle, but they lack septations and are larger in diameter when compared with *Aspergillus* • Causes: *Mucor, Rhizopus, Absidia,* etc.
Hyalohyphomycosis *Figure 5.8.25*	• Nonpigmented, narrow hyphae WITH septations and branch at 45-degree angle • Angioinvasive and cause tissue necrosis	• Most common cause: *Aspergillus* spp. and *Fusarium* spp.
Other		
Protothecosis *Figure 5.8.26*	• NOT a fungal infection • The organism is a nonpigmented achlorophyllous algae • The morulae of the organism resemble a soccer ball (3-11 µm)	• Distinct entity
Rhinosporidiosis	• Enormous sporangia (100-400 µm) with numerous endospores • Associated with granulomatous inflammation	• Like *Coccidioides* but **much bigger**

GMS = Grocott-Gomori methenamine-silver nitrate; H&E = hematoxylin-eosin; PAS = periodic acid—Schiff.

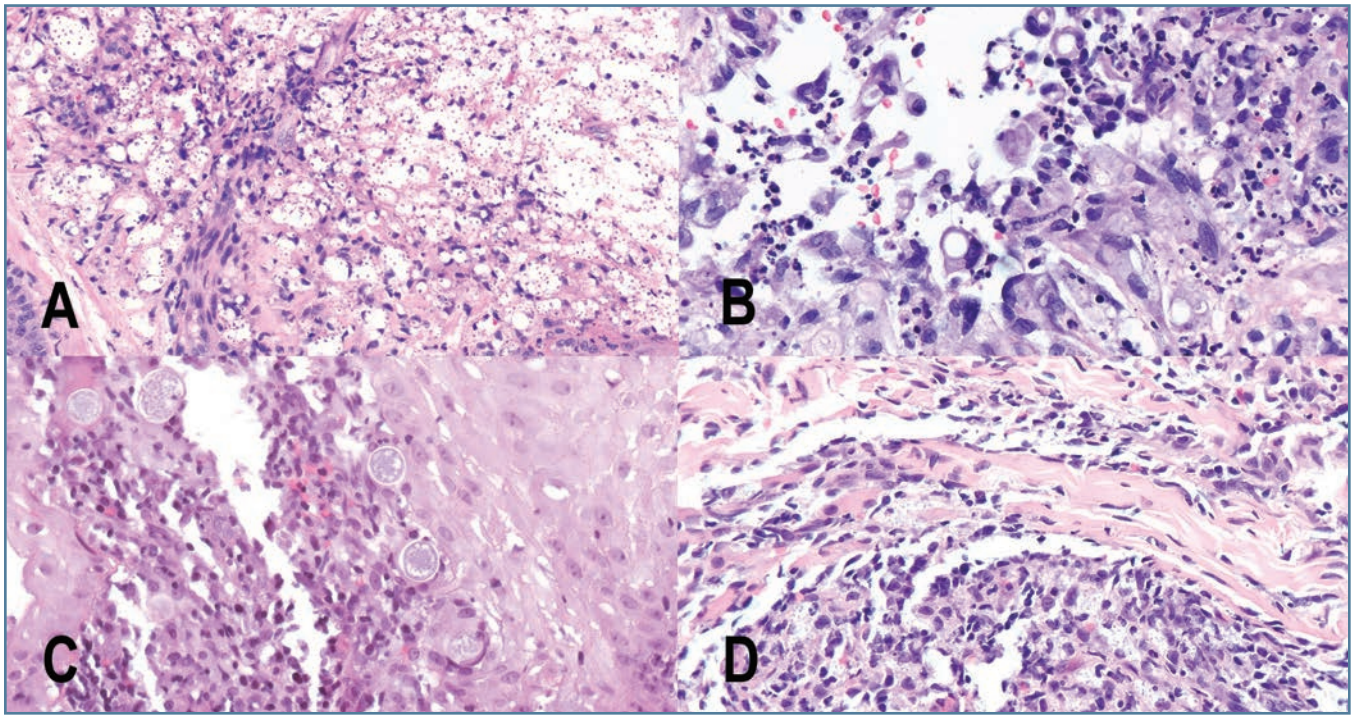

Figure 5.8.27 Comparison of fungal organisms.

A) Cryptococcus has a gelatinous capsule which you often only appreciate as a white space surrounding a nucleus. B) Blastomycosis is approximately the same size and has a refractile cell wall. C) Coccidioidomycosis is much larger and contains endospores. D) Histoplasmosis is small, about the size of leishmania, and is present in parasitized histiocytes.

VIRAL

TABLE 5.8.5 VIRAL INFECTIONS

Name	Special Features	Differential Diagnosis/Pearls
Bowenoid papulosis *Figure 5.8.28*	• Full-thickness atypia with pleomorphic cells and atypical mitotic figures • **Indistinguishable from Bowen's disease**	• Human papillomavirus (HPV) types 16, 18 most common
Condyloma acuminatum *Figure 5.8.29*	• Papillated and acanthotic epidermis with hyperkeratosis, underneath which hypergranulosis and koilocytic changes may be seen • Lacks full-thickness atypia as seen in bowenoid papulosis	• HPV types 6, 11, 16, 18, and many others • Usually softer and rounder in shape than verruca vulgaris
Epidermodysplasia verruciformis *Figure 5.8.30*	• Basket-weave stratum corneum • Epidermis may not be acanthotic • Keratinocytes in the granular layer have a distinct bluish cytoplasm	• HPV types 5, 8, 10, 47, and many others • Mutations in *EVER1* and *EVER2* genes • Associated with immunosuppression/HIV
Heck's disease	• Mucosa with hyperplasia, hyperkeratosis, and parakeratosis • May see epithelial pallor underneath	• HPV types 13, 32
Myrmecial verruca *Figure 5.8.31*	• Endophytic verruca with pink/purple cytoplasmic inclusions • Located on acral skin	• HPV type 1
Verruca plana *Figure 5.8.32*	• Basket-weave stratum corneum • Epidermis may not be acanthotic • Hypergranulosis and koilocytes	• HPV types 3, 10
Verruca vulgaris *Figure 5.8.33*	• Acanthotic epidermis with papillomatosis and in-bending of the rete ridges • Hypergranulosis and variable amount of koilocytes • Parakeratosis at the tips of papillomatosis with dilated blood vessels in the papillary dermis below	• HPV types, 1, 2, 4
Herpetic Infections		

Herpes simplex
Figure 5.8.34
	• May see Cowdry type A bodies
	• The three "M's":
	  ▸ Multinucleation of keratinocytes
	  ▸ Molding of nuclei
	  ▸ Margination of the chromatin peripherally (the nucleus appears more pale in the middle)
		• Herpes simplex virus (HSV)-1/2

Herpes zoster	• As above	• Varicella-zoster virus (VZV)
Cytomegalovirus	• Infects the vascular endothelium • Large endothelial cells with owl's eye nuclei are characteristic	• Immunocompromised patients
Poxvirus and Parapoxvirus Infections		
Molluscum contagiosum *Figure 5.8.35*	• Cup-shaped lesion arising from infected follicular epithelium • Epidermal pallor and numerous pink/purple cytoplasmic inclusions known as Henderson-Paterson bodies	• Distinct entity
Orf *Figure 5.8.36A-B*	• Epidermal necrosis, ballooning of keratinocytes, massive papillary dermal edema • Interface change • Cytoplasmic and nuclear inclusions present	• DDx: Milker's nodule (cowpox) is identical

TABLE 5.8.5 VIRAL INFECTIONS CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Smallpox	• Epidermal necrosis and reticular (lace-like) degeneration • Guarnieri bodies—eosinophilic cytoplasmic inclusions • Paschen bodies—particles of viral aggregates	• Eradicated but not extinct
Dermatoses Associated With Viral Infections		
Gianotti-Crosti syndrome *Figure 5.8.37*	• **Acral skin with interface dermatitis ± spongiosis** • May have intra or subepidermal vesicle formation • Superficial perivascular lymphocytic inflammation • Characteristic distribution and appearance clinically, which helps with the nonspecific pathologic findings	• Associated with hepatitis V virus (HBV) infection in Europe • Associated with Epstein-Barr virus (EBV) infection in the USA • Also associated with enteroviruses
Hand-foot-and-mouth disease *Figure 5.8.38*	• Reticular and ballooning degeneration of the epidermis • Interface dermatitis • Papillary dermal edema • Superficial perivascular lymphocytic inflammation	• Causes: Coxsackie A16, enterovirus A71

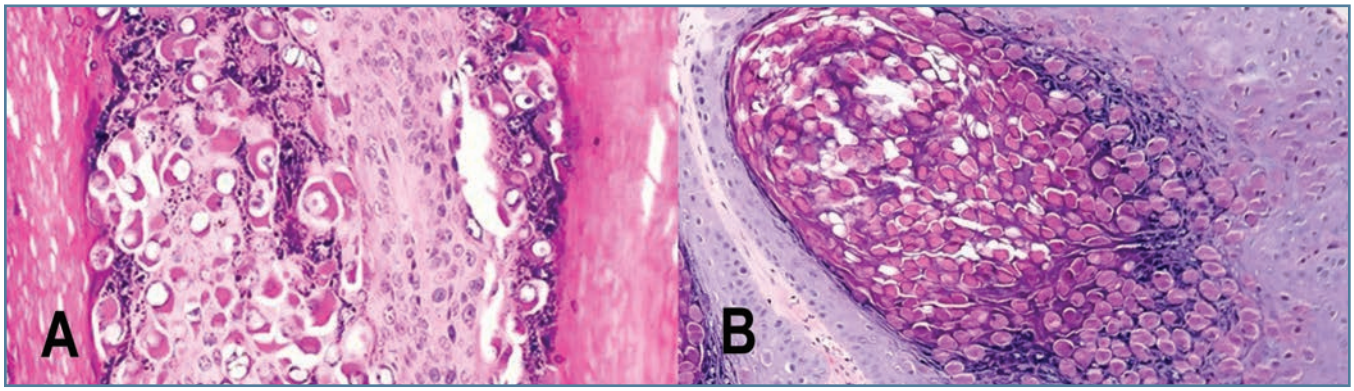

Figure 5.8.39 Intracytoplasmic inclusions in myrmecial verruca vs molluscum contagiosum.
A) Exo and endophytic lesion with hyperkeratosis and hypergranulosis. The keratohyaline granules are coarse, and the intracytoplasmic inclusions are smooth or angulated and do not displace the nucleus. (HPV-1 driven process) B) Endophytic lesion, folliculocentric, large eosinophilic oval intracytoplasmic inclusions that displace the keratinocytic nucleus. (Pox virus driven process).

INFESTATIONS

TABLE 5.8.6 FLUKE, TAPEWORM, ROUNDWORM INFESTATIONS

Name	Special Features	Differential Diagnosis/Pearls
Dirofilariasis	• Granulomatous inflammation • Worm with thick muscular wall	• *Dirofilaria tenuis*
Flatworms	• Cannot excrete waste and will have characteristic calcareous bodies (calcified waste)	• Sparganosis
Onchocerciasis	• Thin microfilaria seen coursing in the dermis	• *Onchocerca volvulus*
Schistosomiasis	• Granulomatous inflammation with stippled ova	• *Schistosoma haematobium* • *S. mansoni* • *S. japonicum*

TABLE 5.8.7 ARTHROPOD INFESTATIONS

Name	Special Features	Differential Diagnosis/Pearls
Arthropod assault *Figure 5.8.40*	• Wedge-shaped mixed infiltrate with eosinophils • Flame figures may be seen	• Urticaria—fewer lymphocytes • Drug reaction—can be indistinguishable
Myiasis *Figure 5.8.41*	• Larva with corrugated pale violet chitinous wall • **Grossly has pigmented spikes, which appear yellow in H&E-stained sections**	• Do not confuse with histologic sections of ticks
Scabies *Figure 5.8.42*	• Mites, ova, and scybala (brown excretions) are seen in the stratum corneum • Chitin scrolls and pigtails, which indicate empty eggshells of Sarcoptes scabiei • Brisk lymphoeosinophilic inflammation in the dermis	• Norwegian scabies will have hyperkeratosis and massive number of mites/ova in the stratum corneum
Tick bite *Figure 5.8.43*	• Wedge-shaped dermal necrosis with mixed inflammation • **Retained tick mouth parts have a yellow-brownish color**	• Be sure to recognize tick on histologic section and not confuse it with myiasis larva
Tungiasis *Figure 5.8.44*	• Multiple organisms on acral skin with striated muscle and numerous red blood cells in the gut cavity	• Note acral location

5.9 Disorders of Collagen and Elastic Tissue

SCLEROTIC

Increased collagen with relative decrease in fibroblasts from normal skin.

TABLE 5.9.1 SCLEROTIC DISORDERS

Name	Special Features	Differential Diagnosis/Pearls
Morphea (localized scleroderma) *Figure 5.9.1A-B*	• Increased collagen with relative decrease in fibroblasts from normal skin • Square biopsy • Sclerosis of the dermis • Adnexal trapping (loss of fat around adnexal structures) • Early lesions have perivascular and interstitial lymphocytic infiltrate ± plasma cells and eosinophils	Variants: • Deep/profunda: Extension into subcutis DDx: • Eosinophilic fasciitis: Fascial involvement, need clinical information • Sclerodermoid graft-versus-host disease: Has interface, need clinical information
Lichen sclerosus (LS) *Figure 5.9.2*	• Compact hyperorthokeratosis • Epidermal atrophy • Dermal homogenization ± edema • Band-like lymphocytic infiltrate, may be patchy or sparse in later lesions	• Lichen planus: Early LS can have similar features

TABLE 5.9.1 SCLEROTIC DISORDERS CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Radiation dermatitis *Figure 5.9.3*	• Dilated blood vessels • Sclerosis of dermis with large, sometimes stellate or triangular fibroblasts • Epidermis may be eroded or hyperkeratotic	• Early lesions exhibit fibrosis
Sclerodermoid graft-versus-host disease (GVHD)	• Vacuolar interface (can be very subtle) • Sclerosis throughout the dermis	• Morphea: Indistinguishable in most cases, but will not have vacuolar interface

FIBROTIC

Increased collagen with relative increase in fibroblasts from normal skin.

TABLE 5.9.2 FIBROTIC DISORDERS

Name	Special Features	Differential Diagnosis/Pearls
Hypertrophic scar	• Parallel or whorled bundles of fibroblasts and thickened collagen	• Fibromatosis (Dupuytren's contracture, Lederhose disease) is more cellular
Keloid *Figure 5.9.4*	• Homogeneous bright pink glassy collagen bundles haphazardly arranged within a scar	• Collagenoma: Does not have pink glassy collagen
Scleromyxedema *Figure 5.9.5*	• Fibrosis of the dermis with increased dermal mucin • Misnomer—there is **NO** sclerosis	• Can look identical to nephrogenic systemic sclerosis
Reactive perforating collagenosis *Figure 5.9.6*	• Cup-shaped epidermal depression • Plug of parakeratotic keratin, collagen, basophilic inflammatory debris	• Elastosis perforans serpiginosa: Pink elastic fibers instead of basophilic collagen
Chondrodermatitis nodularis helicis *Figure 5.9.7*	• Central dell covered by scale-crust • Dermal fibrin, mixed inflammation and small blood vessels • Cartilage may be visible	• Prurigo nodularis/picker's nodule can look identical on the surface

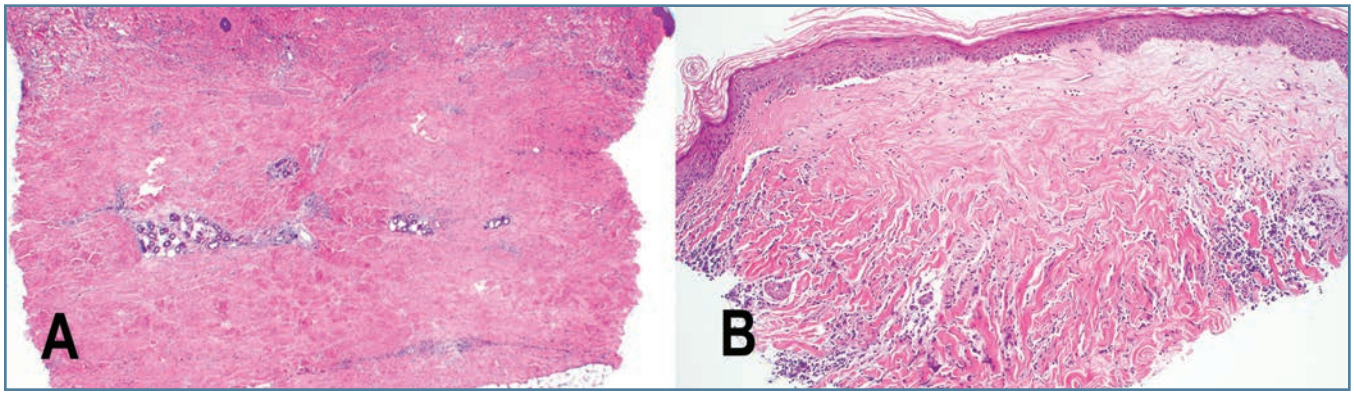

Figure 5.9.8 Sclerotic dermatoses.
Morphea (A) and lichen sclerosus (B) occasionally have overlapping features. Unlike lichen sclerosus, morphea typically has no epidermal change (hyperkeratosis and atrophy), and the dermal changes extend to the junction of the dermis and subcutis, causing an abrupt transition ("square biopsy" appearance). In lichen sclerosus, the dermal collagen is paler, and there is commonly a patchy or lichenoid lymphocytic infiltrate.

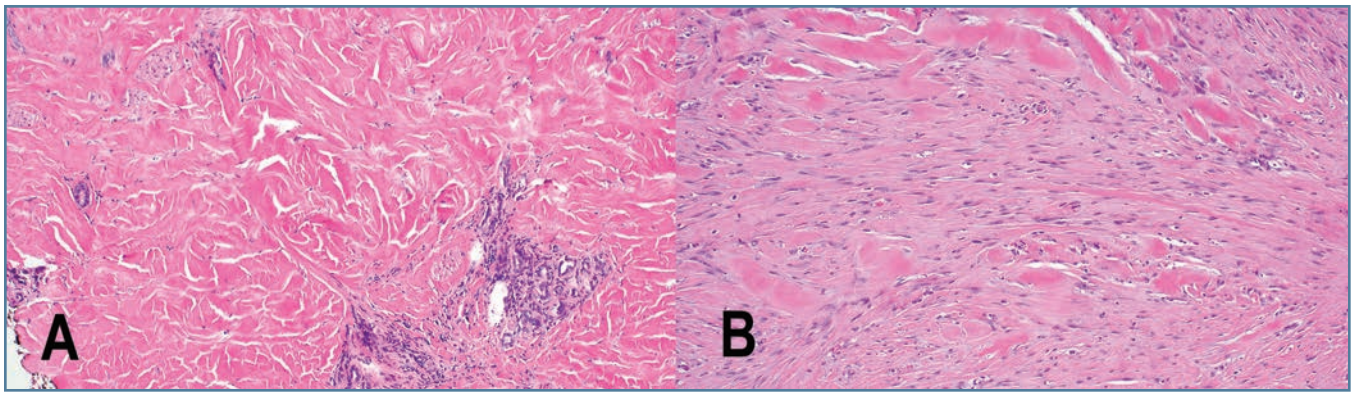

Figure 5.9.9 Sclerosis vs fibrosis.
Sclerosis (A) and fibrosis (B) refer to increased and thickened collagen within the dermis, however, sclerosis is hypocellular while fibrosis has increased numbers of fibroblasts. These two examples are morphea (A) and hypertrophic scar/keloid (B).

ELASTIC

TABLE 5.9.3 ELASTIC DISORDERS

Name	Special Features	Differential Diagnosis/Pearls
Elastosis perforans serpiginosa *Figure 5.9.10A-B*	• Channel through thickened epidermis • Basophilic nuclear debris + eosinophilic fragmented elastic fibers	• Perforating collagenosis: Basophilic collagen
Pseudoxanthoma elasticum *Figure 5.9.11*	• Fragmented distorted calcified elastic fibers ("purple squiggles") within the deep dermis • Fibers stain with von Kossa	• Similar changes may be seen in sites of trauma
Anetoderma *Figure 5.9.12*	• May look normal on H&E stain • Inflammatory changes early • Absent elastic fibers in superficial and mid-dermis on elastic/VVG stain	
Dermal elastolysis (papillary or mid-dermal) *Figure 5.9.13*	• Normal appearance on H&E stain • Loss of elastic fibers in papillary or mid-dermis on elastic/VVG stain	

H&E = hematoxylin-eosin; VVG = Verhoeff–van Gieson stain.

5.10 Alopecia

BIOPSY TECHNIQUES

- Nonscarring alopecia—two 4-mm punch biopsies from unaffected and affected areas, respectively, for horizontal processing
- Scarring alopecia—two 4-mm punch biopsies from affected area for horizontal and vertical processing

APPROACH TO DIAGNOSIS

- Nonscarring alopecia—normal total hair count, retained sebaceous glands
  - Hair counts (total, telogen/catagen, vellus/miniaturized) must be done at isthmus level (sebaceous glands visible)
  - Normal total hair count 25-35 in whites, 21 in blacks, 16 in Asians
  - Telogen/catagen count: Number of telogen + catagen hairs/total hairs, <15% is normal
  - Miniaturized hairs: Diameter of hair shaft < thickness of inner root sheath
  - Normal T (terminal):V (vellus/miniaturized) ratio is >4:1
- Scarring alopecia—decreased total hair count, loss of sebaceous glands
  - Type and distribution of inflammation
  - Epidermal changes (e.g., interface, lichenoid)

CLUES TO DIAGNOSIS

- **Stelae/fibrous streamers—round pink structures within the subcutis containing small blood vessels and plump fibroblasts**
  - **Significance—miniaturization, destruction, telogen/catagen**
  - **Must look at more superficial sections to determine which type**
- **Polytrichia—fusing of follicular infundibula superficially, sign of scarring/inflammation**
- **Pigment casts—trichotillomania versus alopecia areata**
- **Markedly increased telogen count (>50%)—alopecia areata (chronic stage) versus psoriatic alopecia versus nonscarring alopecia of systemic lupus erythematosus versus trichotillomania**
- **Peribulbar inflammation—alopecia areata versus syphilitic alopecia**
- **Miniaturization—androgenetic alopecia versus alopecia areata**

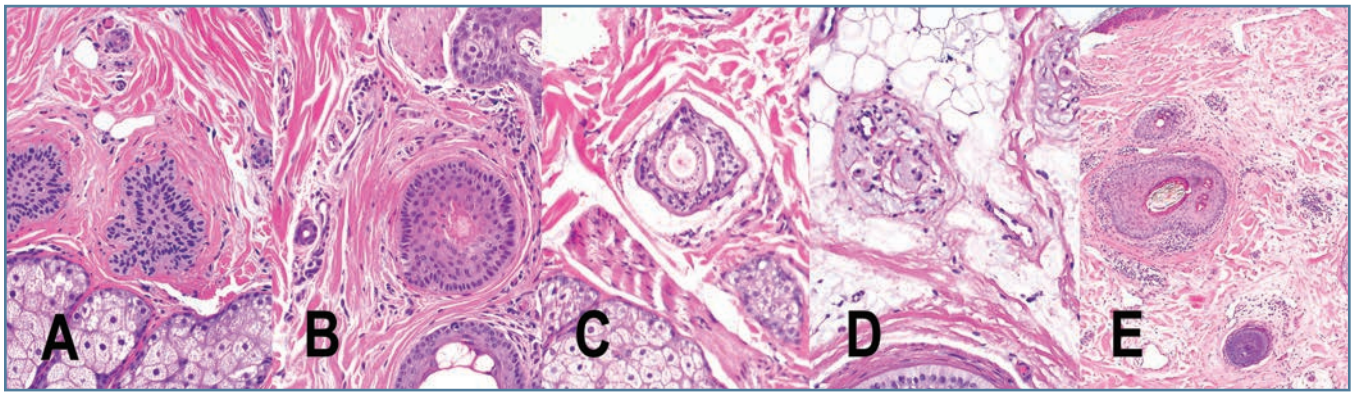

Figure 5.10.1 Notable features of alopecia biopsies.
Telogen (A) follicles have a basophilic stellate appearance, while catagen (B) hairs have a brightly eosinophilic center. In miniaturized and vellus (C) hairs, the diameter of the hair shaft is thinner than the thickness of the inner root sheath. Miniaturized hairs have a fibrous streamer (stela) beneath the shaft while vellus hairs do not. Stelae (D) are loose collections of collagen fibers, plump fibroblasts, and small blood vessels within the fat; these are fibrous streamers that can be seen beneath miniaturized hairs, telogen /catagen hairs, or scarred/destroyed follicles. Perifollicular inflammation associated with loss of sebaceous glands and a total decreased hair count are characteristic of inflammatory scarring alopecias (E).

NONSCARRING

TABLE 5.10.1 NOTABLE FEATURES OF ALOPECIA BIOPSIES

Name	Special Features	Differential Diagnosis/Pearls
Androgenetic alopecia *Figure 5.10.2*	• Slightly elevated telogen count (15-25%) • Increased miniaturization (T:V < 2:1) • Scant inflammation	• Telogen effluvium: Lacks miniaturization • Alopecia areata: Higher telogen count (>50%), peribulbar inflammation
Alopecia areata *Figure 5.10.3A-B*	Acute and subacute: • Increased telogen count • Peribulbar lymphocytic inflammation ("swarm of bees"), occasional eosinophils • Dilated infundibula ("yellow dots" on dermoscopy) Chronic/long-standing: • Markedly elevated telogen count (approaches 100%) • Increased miniaturization • Nanogen hairs (small follicles without hair shafts) • Variable inflammation • Dilated infundibula ("yellow dots" on dermoscopy)	• Psoriatic alopecia: Atrophic sebaceous glands, psoriasiform hyperplasia • Syphilitic alopecia: Peribulbar plasma cells, positive serologies • Nonscarring alopecia of systemic lupus: Increased mucin, periadnexal lymphocytes, vacuolar interface change
Telogen effluvium *Figure 5.10.4*	• Elevated telogen count (typically <50%)	• Acute traction alopecia/trichotillomania: Trichomalacia and higher (>50%) telogen/catagen count • Androgenetic alopecia: Miniaturization • Alopecia areata: Higher telogen count (>50%), miniaturization
Trichotillomania/traumatic alopecia *Figure 5.10.5*	• Trichomalacia (distorted follicular anatomy) • Pigment casts • Perifollicular hemorrhage • Variably increased telogen/catagen count	• Acute traction alopecia: Very similar findings • Alopecia areata: Peribulbar inflammation, no trichomalacia
Traction alopecia	• Acute—increased telogen count, occasional trichomalacia and pigment casts • Chronic—see scarring section below	• Trichotillomania: Very similar findings to acute traction alopecia • Androgenetic alopecia: Miniaturization
Psoriatic alopecia *Figure 5.10.6*	• Markedly elevated telogen count (approaches 100%) • Increased miniaturization • Atrophic sebaceous glands • Psoriasiform and/or spongiotic epidermis • Can have peribulbar inflammation	• Alopecia areata: Normal sebaceous glands, nanogen hairs, normal epidermis • TNF-α inhibitor alopecia: Similar findings but less inflammatory
Syphilitic alopecia	• Increased telogen count (approaches 100%) • Increased miniaturization • **Peribulbar inflammation with plasma cells**	• Alopecia areata: Rare eosinophils in infiltrate

TNF-a = tumor necrosis factor-a.

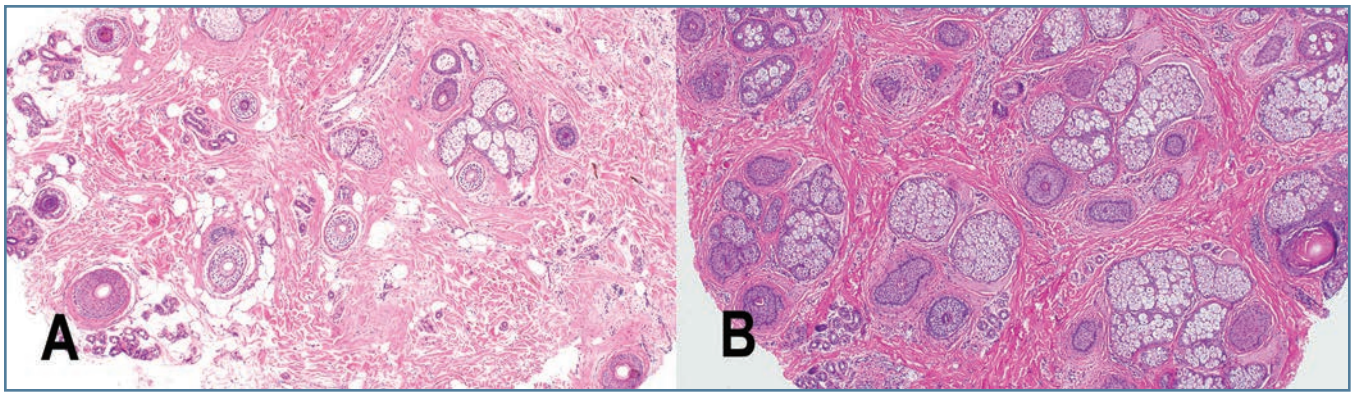

Figure 5.10.7 Nonscarring alopecias.

Androgenetic alopecia (A) and alopecia areata (B) both show increased telogen/catagen hairs and miniaturization. Androgenetic alopecia has a variable degree of miniaturization and only a slightly elevated telogen count, while alopecia areata — particularly, in the chronic phase — has a markedly elevated telogen count, approaching 100%. Peribulbar inflammation is a helpful clue in alopecia areata. In contrast to these entities, telogen effluvium (not pictured) shows a slightly elevated telogen count with no significant miniaturization.

SCARRING

TABLE 5.10.2 SCARRING ALOPECIAS

Name	Special Features	Differential Diagnosis/Pearls
Lichen planopilaris/frontal fibrosing alopecia (LPP/FFA) *Figure 5.10.8*	• Lichenoid inflammation around superficial portions of hair follicles • Concentric perifollicular fibrosis pushes inflammation outward • Interfollicular epidermis may have lichenoid changes	• Discoid lupus: Perieccrine inflammation, dermal mucin, basal vacuolar change
Discoid lupus erythematosus (DLE) *Figure 5.10.9*	• Perifollicular inflammation (involves most levels of hair follicle) • Follicular plugging • **Perieccrine inflammation** • **Increased dermal mucin** • Basal vacuolar change at epidermis • $CD123^+$ cells in large clusters within infiltrate	• LPP/FFA: Lack perieccrine inflammation and dermal mucin, inflammation usually confined to superficial portion of follicles
Chronic traction alopecia *Figure 5.10.10*	• Decreased total hair count + retained sebaceous lobules and vellus hairs • Fibrous tracts at the sites of missing follicles	• Unlike inflammatory scarring alopecias, sebaceous lobules retained
Central centrifugal cicatricial alopecia (CCCA) *Figure 5.10.11*	• Patchy lymphocytic infiltrate around follicles • Fibrosis at the sites of missing follicles • Eccentric epithelial atrophy • **Premature desquamation of the inner root sheath (thin keratinized inner root sheath within follicles beneath the isthmus)**	• Eccentric epithelial atrophy and premature desquamation of inner root sheath are not pathognomonic, but seen more commonly in CCCA than other scarring alopecias

TABLE 5.10.2 SCARRING ALOPECIAS CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Tufted folliculitis/folliculitis decalvans *Figure 5.10.12*	• Fusing of infundibula to form large follicular structures with 3-5 infundibula (polytrichia) • Variably dense mixed inflammation with neutrophils, lymphocytes, and plasma cells • Destruction of hair follicles • Perifollicular fibrosis	• May see this pattern in CCCA as well as other highly destructive inflammatory scarring alopecias
Pseudopelade of Brocq *Figure 5.10.13*	• End-stage scarring alopecia • Markedly decreased total hair count with fibrosis at the sites of missing follicles • ± Naked hair shafts surrounded by granulomatous inflammation • Numerous stelae within the subcutis	• Nonspecific changes in end-stage scarring alopecia • No distinguishing features for LPP vs DLE vs CCCA

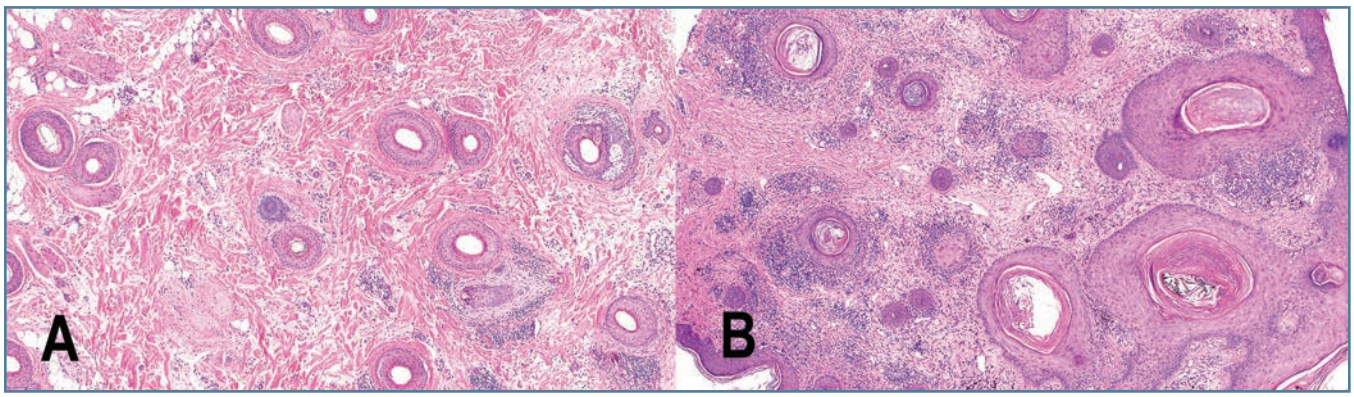

Figure 5.10.14 Inflammatory scarring alopecias.
Both lichen planopilaris/frontal fibrosing alopecia (LPP) (A) and discoid lupus erythematosus (DLE) (B) are characterized by perifollicular lichenoid inflammation and fibrosis. However, LPP tends to be more patchy, and the perifollicular fibrosis is more pronounced, "pushing out" the inflammatory infiltrate. In DLE, additional features include follicular plugging, hyperkeratosis, perieccrine inflammation, and increased mucin.

5.11 Cysts and Deposits

CYSTS

TABLE 5.11.1 HAIR FOLLICLE AND SWEAT GLAND CYSTS

Hair Follicle Cysts		
Arising from:	**Name**	**Characteristics**
Infundibulum	Epidermal inclusion cyst (epidermoid/infundibular cyst) *Figure 5.11.1*	• Epidermis-like epithelium with granular layer, filled with loose keratin, rupture associated with foreign body granulomatous reaction • Variant: **Vellus hair cyst** resembles epidermoid cyst. Numerous small vellus hairs are mixed with loose lamellar keratin • Variant: **Dermoid cyst** resembles epidermoid cyst, but additionally has adnexal structures within the cyst wall
Isthmus	Pilar cyst (trichilemmal, isthmus-catagen cyst) *Figure 5.11.2*	• Granular layer is absent, cyst is filled with dense pink keratin • Variant: Proliferating pilar cyst is a more complex multilobulated cyst with trichilemmal keratinization *Figure 11.3*
Sebaceous duct	Steatocystoma *Figure 5.11.4*	• Lined by an eosinophilic crenulated cuticle (shark tooth lining), sebum falls out during processing, may see sebaceous glands attached to cyst wall on the outside
Hair matrix (bulb)	Pilomatricoma *Figure 5.11.5*	• See Section 5.14
Sweat Gland Cyst		
Name	**Characteristics**	
Hidrocystoma *Image 5.11.6*	• Cyst lining is composed of a double layer of cuboidal epithelial cells • May see apocrine-type decapitation secretion	

TABLE 5.11.2 CYSTS THAT COMMONLY ARISE ON THE NECK

Name	Location	Characteristics
Branchial cleft cyst (failure to obliterate 2nd branchial cleft in embryogenesis)	Lateral part of the neck, anterior to the sternocleidomastoid muscle	• Stratified squamous epithelium or ciliated columnar epithelium • Lymphoid tissue with germinal centers surrounds the cyst
Bronchogenic cyst (remnants of the primitive foregut) *Figure 5.11.7*	Midline lesions, typically in the suprasternal notch	• Ciliated pseudostratified respiratory-type columnar epithelium with goblet cells • May be surrounded by smooth muscle or cartilage
Thyroglossal cyst *Figure 5.11.8*	Deep lesions in the midline of the neck	• Ciliated lining with surrounding thyroid follicles

TABLE 5.11.3 CYSTS WITH DEBRIS

Name	Location	Characteristics
Cutaneous ciliated cyst *Figure 5.11.9*	Lower extremities of women	• Cuboidal or columnar epithelial lining with cilia, cyst lumen is filled with debris
Median raphe cyst *Figure 5.11.10*	Midline lesions, along anogenital raphe	• Pseudostratified columnar epithelium • May have mucus glands and are rarely ciliated • Cyst lumen is filled with debris

TABLE 5.11.4 PSEUDOCYSTS

Name	Location	Characteristics
Digital mucous cyst *Figure 5.11.11*	Base of the nail of a finger or toe (acral location)	• Pseudocyst: A large pool of mucin with fibroblasts • Overlying epidermis is acral, and either atrophic or hyperkeratotic
Pseudocyst of the auricle *Figure 5.11.12*	Upper half or third of the ear	• Intracartilaginous pseudocyst filled with fluid
Mucocele *Figure 5.11.13*	Oral mucosa	• Pseudocyst: Muciphages line a cystic space filled with mucin • Presence of salivary glands and nearby mucosal epithelium is clue to location

DEPOSITS

TABLE 5.11.5 DEPOSITS

Name	Special Features
Calcinosis cutis *Figure 5.11.14*	• Dark purple deposits in the dermis • May have venetian blinds artifact • May be idiopathic, dystrophic, or metastatic
Osteoma cutis *Figure 5.11.15*	• Mature bone in the dermis • Stroma composed of vascular fibrous tissue • May be secondary to trauma or neoplasms. May be perforating
Colloid milium	• Light pink fissured deposits in the papillary dermis • Seen on the face secondary to severe solar degeneration • May stain weakly with amyloid stains
Focal cutaneous mucinosis *Figure 5.11.16*	• Abundant collection of mucin splayed between collagen bundles • Seen in the upper and mid-dermis • Stratum corneum is normal
Follicular mucinosis *Figure 5.11.17*	• Also known as alopecia mucinosa • Mucin is seen in the follicle • If associated with mycosis fungoides, atypical lymphocytes and Pautrier microabscesses are seen
Macular and lichen amyloid *Figure 5.11.18*	• Pink deposits of amyloid in the papillary dermis associated with melanophages • Hyperplastic epidermis is seen in lichen amyloidosis • Associated with MEN 2a • Amyloid is keratinocyte derived

TABLE 5.11.5 DEPOSITS CONTINUED

Name	Special Features
Nodular amyloid *Figure 5.11.19*	• Large nodular deposits of amyloid that involve the dermis and sometimes subcutaneous fat • **Plasma cells are seen around blood vessels at margin of amyloid deposits** • Blood vessel walls may be thickened by amyloid • Amyloid is immunoglobulin light chain derived, typically λ
Papular mucinosis (lichen myxedematosus) Scleromyxedema *Figure 5.11.20*	• Collagen fibers separated by mucin deposits, increased numbers of fibroblasts • Epidermis: Normal, acanthotic, or atrophic • More cellular than pretibial myxedema • Scleromyxedema associated with paraproteinemia (IgG λ)
Pretibial myxedema *Figure 5.11.21*	• Hyperkeratotic epidermis with follicular plugging • Large quantities of mucin, no increase in fibroblasts • **Associated with Graves' disease and thyroid acropachy**
Scleredema of Buschke *Figure 5.11.22*	• Thickened reticular dermis with broadened collagen and loss of subcutaneous fat, no increased fibroblasts, no inflammation • Square biopsy with eccrine gland trapping, mucin tends to be in deeper dermis • **May only see large spaces between the collagen bundles**

MEN 2a = multiple endocrine neoplasia type 2A.

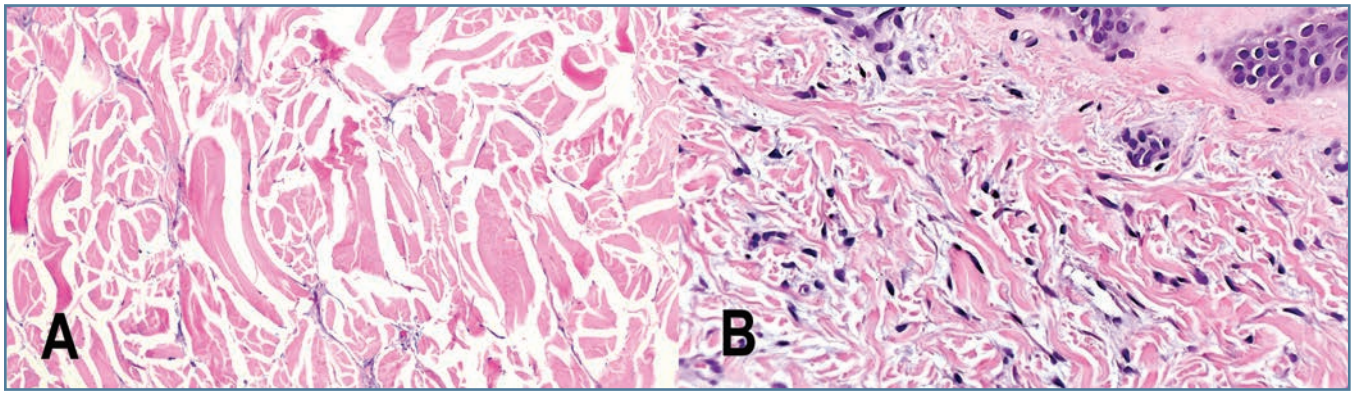

Figure 5.11.23 Mucin deposits.
In scleredema of Buschke A) there are thickened collagen bundles with collections of mucin present between the collagen bundles in the deep reticular dermis. Scleromyxedema B) on the other hand consists of increased dermal mucin with an increased number of fibroblasts.

5.12 Melanocytic Neoplasms

BENIGN

TABLE 5.12.1 BENIGN MELANOCYTIC NEOPLASMS

Name	Special Features	Differential Diagnosis/Pearls
Lentigo *Figure 5.12.1*	• Reticulated epidermal hyperplasia • Basal layer hyperpigmentation • Slight increase in melanocytes at the dermo-epidermal junction (DEJ) • Pigment incontinence	Variants: • Melanotic macule/labial lentigo • Melanotic macule of the nail matrix
Melanocytic nevus *Figure 5.12.2A-C*	• Melanocytes arranged as nests at the DEJ and nests, cords, and strands in the dermis • Junctional (DEJ only), compound (DEJ + dermis), dermal (dermis only) • Maturation with descent: Smaller melanocytes, less abundant cytoplasm, cords and strands rather than large nests • Well circumscribed, symmetric at low power • Junctional nests at tips of the rete ridges • No significant atypia, no mitotic figures • HMB-45 shows gradient pattern of expression with loss in dermal component	Variants: • Halo: Lymphocytes obscure portions of nevus • Balloon cells: Round to oval melanocytes with abundant pale or clear bubbly cytoplasm • Persistent/recurrent: Nevus in and around scar, may have atypical junctional component above scar • Congenital: Melanocytes wrap around adnexal structures
"Dysplastic" nevus (nevus with architectural disorder, Clark's nevus) *Figure 5.12.3*	• May be junctional or compound • Bridging of rete ridges by nests of melanocytes • Papillary dermal fibroplasia • Compound lesions have "shoulder": Junctional component extends beyond dermal component • Random atypia • If atypia is present it is graded by some (mild, moderate, severe) based on cytology, symmetry, circumscription, presence of focal pagetoid spread	**Clues to dysplastic nevus vs melanoma:** • **Well circumscribed** • **Symmetric** • **Nests at tips and sides of rete ridges but not in between** • **Absent to focal pagetoid spread** • **Nonconfluence of melanocytes at DEJ** • **Normal maturation** • **No dermal atypical mitoses**
Blue nevus *Figure 5.12.4A-B*	• Dermal proliferation • Spindled and elongated ("dendritic") melanocytes • Melanin pigment throughout, within cells and dermis • Often forms "lens" shape in the dermis • Cells stain diffusely with MART-1/Melan-A, HMB-45, and SOX-10	Variants: • Cellular blue: Larger, deeper proliferation of round and dendritic melanocytes with focal pigment • Combined blue: Has conventional nests as well as dendritic melanocytes • Sclerotic/amelanotic blue: Dendritic melanocytes with only focal pigment, can mimic dermatofibroma

TABLE 5.12.1 BENIGN MELANOCYTIC NEOPLASMS CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Spitz nevus *Figure 5.12.5A-B*	• May be junctional, compound, or dermal • Epidermal hyperplasia (hyperkeratosis, hypergranulosis, acanthosis) • Dome-shaped lesion • Spindled and epithelioid cells, some enlarged and polygonal • Abundant cytoplasm with fine melanization • Not heavily pigmented • Maturation with descent • Nests can be dyscohesive with clefting, vertically oriented ("bunches of bananas") • Kamino bodies: Pink globules within the epidermis	Variants: • Pigmented Spitz/spindle cell nevus: Junctional or compound, all spindled cells with heavy pigmentation in cytoplasm • Desmoplastic Spitz: Dermal proliferation of large polygonal melanocytes set within sclerotic stroma • Atypical Spitz tumor: Cytologic and architectural atypia
Pigmented spindle cell nevus *Figure 5.12.6*	• Junctional or compound • Spindled melanocytes with heavy pigment deposition within cells and within dermis • Nests often vertically oriented ("bunches of bananas")	• Considered by some a pigmented variant of Spitz nevus
Deep penetrating nevus *Figure 5.12.7A-B*	• Wedge-shaped deep proliferation of spindle and epithelioid cells • May extend into subcutis • Often surrounds adnexal structures and nerves	• Cellular blue: Dumbbell-shaped proliferation of dendritic and round melanocytes
BAPoma *Figure 5.12.8A-B*	• Combined nevus with conventional component and large polygonal epithelioid cells • May have "spitzoid" appearance • Loss of BAP1 by IHC in the epithelioid cells (nuclear stain) • Typically have BRAF V600E mutation as well by IHC or molecular studies	• *BAP1* loss may be sporadic or germline • **Germline loss of BAP1 associated with cancer syndrome including melanocytic nevi, cutaneous melanoma, uveal melanoma, renal cell carcinoma, and mesothelioma**
Special site nevus *Figure 5.12.9*	• Typically junctional or compound • May have mild atypia or lentiginous spread • Occasional focal pagetoid spread OK	Special sites: • Scalp • Flexural/intertriginous • Genital • Acral

BAP1 = BRCA1-associated protein 1; HMB-45 = human melanoma black-45 antigen; IHC = immunohistochemistry; MART-1 = melanoma antigen recognized by T cells 1.

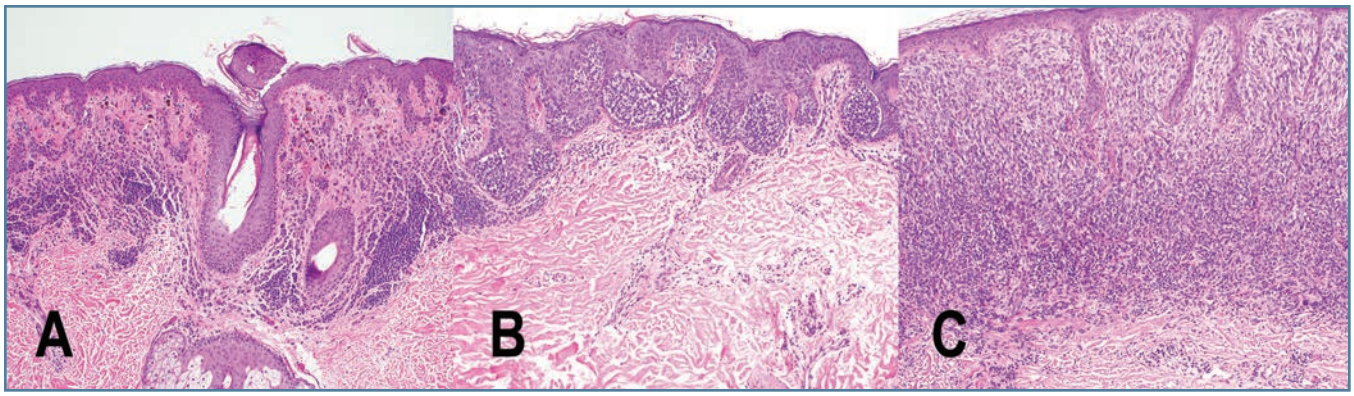

Figure 5.12.10 Comparison of conventional nevus, dysplastic nevus and nevoid melanoma.

Conventional melanocytic nevi, like this compound melanocytic nevus (A), are typically well-nested, with nests at the tips of the rete ridges, and show maturation with descent as the melanocytes become smaller with less abundant cytoplasm and are arranged in cords and strands. Dysplastic nevi (B) show mild architectural and cytologic atypia with bridging of the rete ridges by larger nests, papillary dermal fibroplasia, and a shoulder (junctional component extends beyond dermal component). In contrast, nevoid melanoma (C) shows a sheet-like growth pattern with "pseudo-maturation." At low power, there appears to be maturation, however, at higher power, the cells look fairly similarly from top to bottom, and there are often dermal mitotic figures. This lesion also shows attenuation of the epidermis as the melanocytic proliferation pushes up against the epidermis.

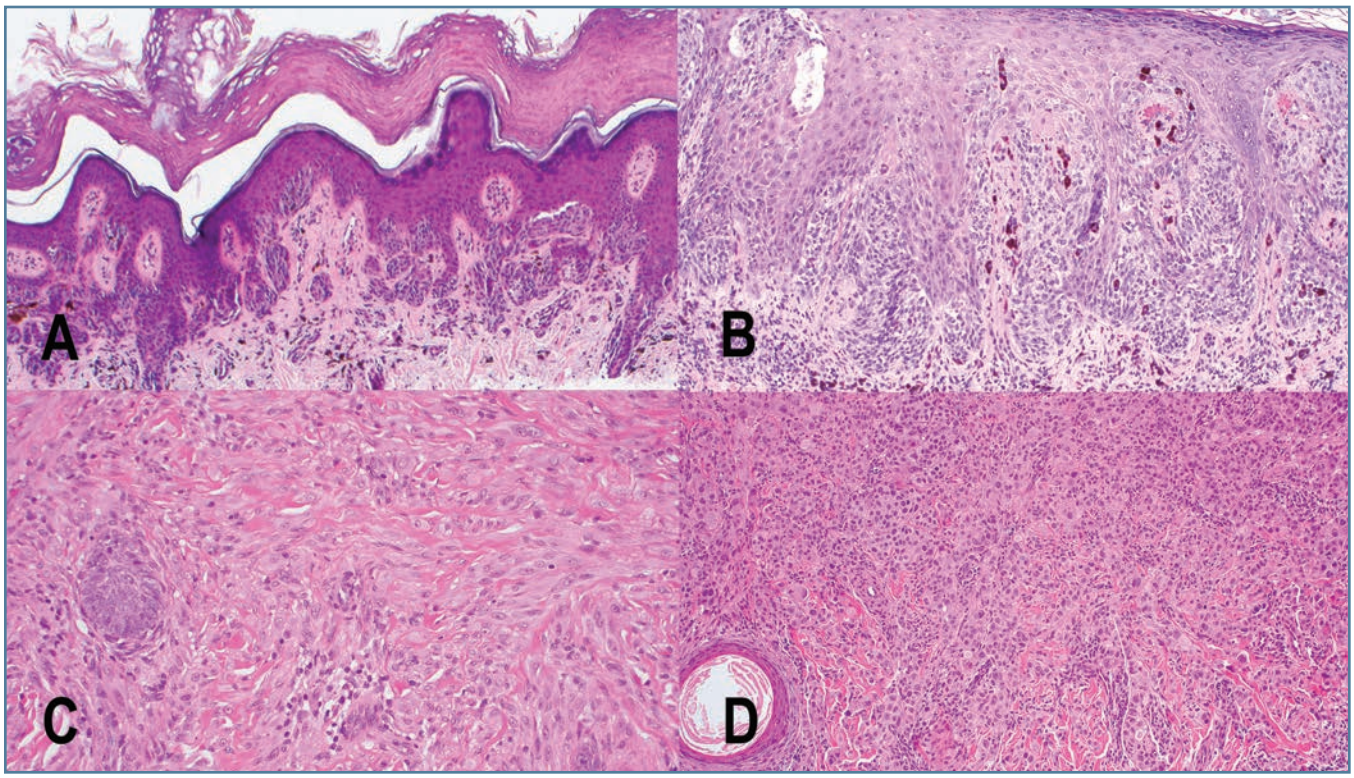

Figure 5.12.11 Spitzoid melanocytic neoplasms.

Pigmented spindle cell nevus (of Reed) (A) is also referred to as a pigmented variant of a Spitz nevus; there are pigmented spindled melanocytes arranged in a vertical or horizontal pattern at the dermo-epidermal junction and sometimes also within the dermis. Spitz nevus can be junctional, compound (B), or intradermal (C). There is epidermal hyperplasia and nests of spindled and epithelioid cells. In the dermal variant, the cells may be more polygonal and set within a desmoplastic stroma (C). Spitzoid melanoma (D) has sheets of markedly atypical spindled and/or epithelioid cells with mitotic figures and deep invasion.

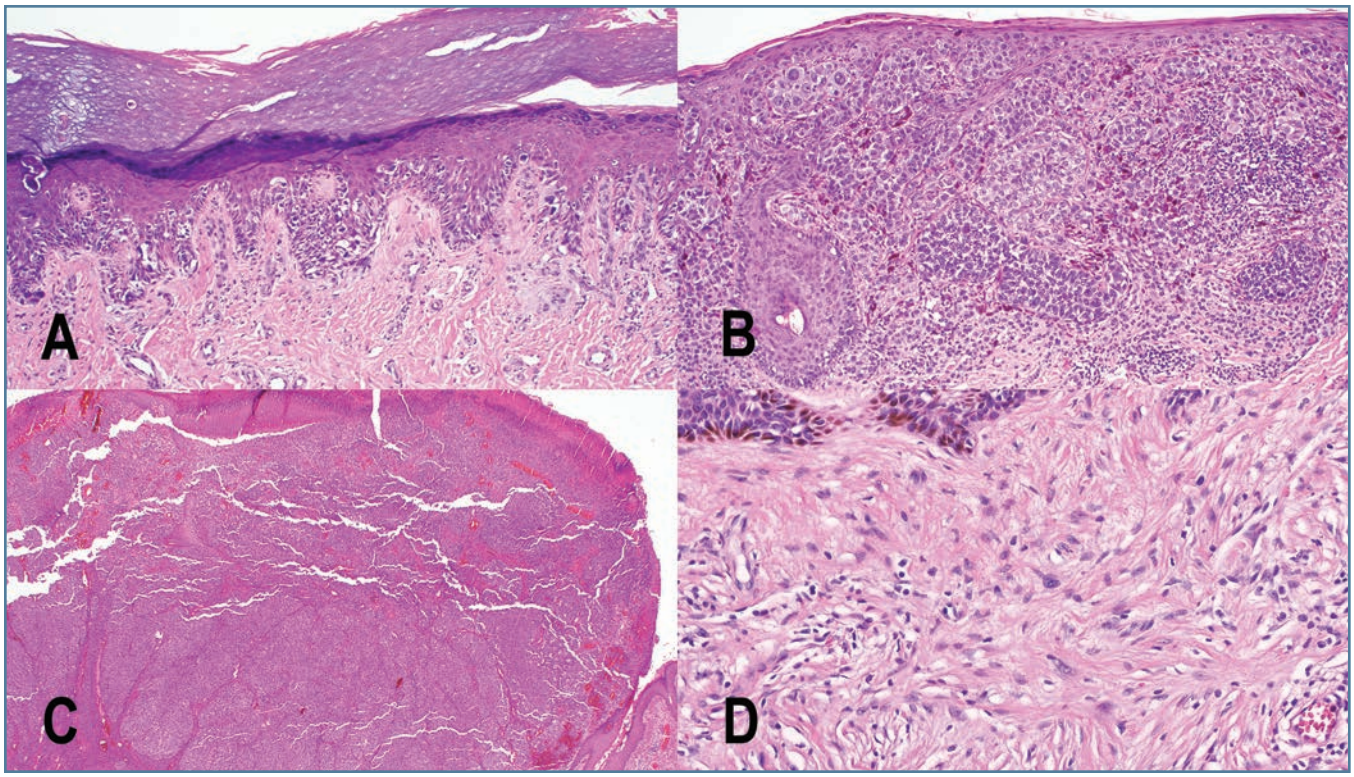

Figure 5.12.12 Malignant melanoma.

Melanoma variants all have in common enlarged atypical melanocytes arranged as nests, sheets or nodules within the epidermis and/or dermis. Acral lentiginous melanoma in situ (A) has a single-cell growth pattern with confluence of melanocytes at the dermo-epidermal junction. Superficial spreading melanoma (B) has atypical melanocytes arranged as nests within the epidermis and dermis with pagetoid spread and lack of maturation. Nodular melanoma (C) is a nodular proliferation with sometimes minimal overlying epidermal involvement. This case is ulcerated. Desmoplastic melanoma (D) is a proliferation of atypical spindle cells within a desmoplastic (sclerotic) stroma; there may not be an obvious in situ component.

MALIGNANT

TABLE 5.12.2 MALIGNANT MELANOCYTIC NEOPLASMS

Name	Special Features	Differential Diagnosis/Pearls
Melanoma in situ (MIS) *Figure 5.12.13A-B*	• Broad, poorly circumscribed, asymmetric • Confluent spread of melanocytes at dermo-epidermal junction • Pagetoid spread throughout lesion • Consumption of the epidermis with ulceration • Melanocytes atypical with nuclear pleomorphism • Variably sized and shaped nests • May be lentiginous (lentigo maligna) or have nested pattern (superficial spreading)	• Melanocytes populate and track down hair follicles • Lentigo maligna (LM) can be insidious, with smaller melanocytes and little to no pagetoid spread • **Lentiginous proliferations that are not well nested on heavily sun-damaged skin should make you think LM!**
Invasive melanoma *Figure 5.12.14A-F*	• Broad, poorly circumscribed, asymmetric • MIS component as well as atypical melanocytes in the dermis • Nests may be variably sized and shaped, or there may be sheets of melanocytes • Lack of dermal maturation • Atypical mitotic figures • **HMB-45 may be retained throughout dermal component** • **Increased proliferative rate with Ki-67 IHC**	Variants: • Lentigo maligna melanoma: Sun damage, lentiginous component • Superficial spreading: Nested in epidermis and dermis • Nodular: May be exophytic, often quite deep • Desmoplastic: Spindle cells within sclerotic or fibrotic dermis, often amelanotic, MIS component may be subtle or nonexistent, clue is lymphoid aggregates within deep dermis • Spindle cell: Component of spindle cells, some lump this with desmoplastic • Nevoid: Mimics compound nevus on low power, but lacks maturation and has mitotic figures and/or clear MIS • Spitzoid: Mimics Spitz nevus with epithelioid and spindle cells

SYNOPTIC REPORTING FOR MELANOMA

- Histologic type: See above for main subtypes of melanoma
- Breslow depth/thickness: Measure from granular layer to deepest portion of lesion (excluding adnexal structures), perpendicular to epidermis
- Ulceration: Full-thickness disruption of epidermis secondary to consumption by melanocytes
- Mitotic rate: Per 1 mm2 (no longer contributory to staging per AJCC [American Joint Committee on Cancer] Cancer Staging Manual, 8th edition)
- Microsatellitosis: One or more discontinuous nest(s) of atypical melanocytes at least 0.3 mm in diameter and at least >0.05 mm away from primary tumor with intervening normal tissue
- Lymphovascular invasion: Presence of atypical melanocytes within lymphovascular spaces
- Neurotropism: Presence of atypical melanocytes around or within nerves
- Tumor-infiltrating lymphocytes: Presence of lymphocytes within the lesion, admixed with melanocytes, not simply surrounding neoplasm (reported as either brisk, nonbrisk, or not present)
- Tumor regression: Patchy dermal fibrosis with melanophages and lymphocytes, decreased or absent melanocytes in overlying epidermis

IMMUNOHISTOCHEMISTRY

TABLE 5.12.3 IMMUNOHISTOCHEMISTRY

Stain	Characteristics	Uses/Pitfalls
Melan-A/MART-1	• Melanocyte marker that recognizes specific cytoplasmic protein in formation of melanosomes • Cytoplasmic stain	• Architecture of lesion (where the melanocytes are, particularly at DEJ) • Recognition of melanocytes in areas of inflammation • Often negative in desmoplastic melanoma • May have high background in areas with melanophages
HMB-45	• Melanocyte marker that recognizes melanosomal glycoprotein (gp100) • Cytoplasmic stain	• Shows gradient pattern of expression in benign nevi with loss of expression with vertical descent (stains epidermal melanocytes but loses expression in dermis) • Stains all melanocytes in blue nevi (common and cellular) • May be helpful in cases with questionable maturation, e.g., nevus vs nevoid melanoma
SOX-10	• Marker for cells derived from neural crest (Schwann cells, melanocytes, myoepithelial cells) • Nuclear stain	• Increasing use for differentiating melanoma in situ from melanocytic hyperplasia given clean nuclear staining • More sensitive than Melan-A/MART-1 for desmoplastic melanoma • Not as specific as a marker; positive in neural tumors (malignant peripheral nerve sheath tumor, neurofibroma) and some carcinomas
S-100	• Marker for cells derived from neural crest • Cytoplasmic and nuclear stain	• Sensitive marker, but not specific • Used for unclear etiology—is a lesion melanocytic or not? (e.g., atypical spindle cell tumor) • Like SOX-10, cannot reliably distinguish between desmoplastic melanoma and malignant peripheral nerve sheath tumor • Also stains apocrine and eccrine glands, adipocytes, dendritic cells, Langerhans cells
MITF	• Melanocyte marker • Nuclear stain	• Can use similarly to SOX-10 • Also stains macrophages/histiocytes, mast cells, osteoclasts, perivascular epithelioid cells

MOLECULAR/GENOMIC ABERRATIONS

- Conventional melanocytic nevus
  - Activating BRAF V600E/K mutations
  - Activating NRAS mutations
- Blue nevus
  - Activating GNAQ and GNA11 mutations (also in uveal melanoma)
- Spitz nevus
  - Activating HRAS mutation
  - Gain of 11p
- BAPoma
  - Loss of 3p (BAP-1 locus)
  - Activating BRAF V600E mutation
- Melanoma
  - Loss of 9p21 (CDKN2A), 10q, 6q, 8p
  - Gain of 7q, 8q, 6p, 1q
  - Activating BRAF V600E/K mutations
  - Activating NRAS mutations
  - Activating KIT mutations (in particular on mucosal or acral surfaces)
  - TERT promoter mutations

CLUES

TABLE 5.12.4 CLUES TO BENIGN VERSUS MALIGNANT

Feature	Benign	Malignant
Architecture	• Well circumscribed • Symmetric from side to side • <6-8 mm in size • Well-defined rete ridge pattern throughout the lesion • Consistently sized and shaped nests • Maturation (larger, more nested melanocytes giving way to smaller, more single melanocytes with descent into the dermis)	• Poorly circumscribed/ill-defined • Asymmetric • Broad lesion (>6-8 mm) • Heterogeneously distributed pigment • Variably sized and shaped nests • Dyscohesive nests (also common in Spitz nevus) • Effacement of rete ridges • Ulceration • Lack of maturation (cells look similar from top to bottom, large nests or sheets of cells back-to-back throughout dermis)
Distribution of melanocytes	• Nests at tips of the rete ridges with few melanocytes along sides or between retes • Very little to no pagetoid spread • If pagetoid spread present, only focal and in center of lesion with cells mostly in bottom half of the epidermis • May have lentiginous (single-cell) growth, but no crowding or confluence at DEJ	• Nests along sides and between rete ridges • Confluent growth of melanocytes at DEJ, may lead to clefting at DEJ • Extensive upward spread (pagetoid) throughout lesion • Consumption of the epidermis by melanocytes
Cytology	• Junctional melanocytes about 1-2 times as large as keratinocytes • No significant nuclear pleomorphism • Nucleoli not prominent • If there are mitotic figures within dermis, they are rare, not atypical, and present superficially • No atypical mitotic figures within the dermis • Spitz nevi with epithelioid and spindled morphologies, cells may be larger with mild pleomorphism	• Large melanocytes, 2-3 times as large as keratinocytes • Nuclear pleomorphism • Prominent "cherry-red" nucleoli • Numerous mitotic figures within the dermis (particularly if deep), including atypical mitotic figures
Staining patterns	• Gradient pattern of expression with HMB-45 • Low proliferative rate in the dermis with Ki-67	• Confluent or crowded growth and/or pagetoid spread with Melan-A/MART-1 or SOX-10 • Retained or patch expression in the dermal component with HMB-45 • Elevated proliferative rate in the dermis with Ki-67 (>10% or "hotspots") • Mitotic figures in the dermis highlighted by pHH3 (mitotic marker)
Molecular/genomic results	• Few copy number variations • Gain of 11p (Spitz)	• Numerous copy number variations • Loss of 9p21, 10q, 6q, 8p • Gain of 7q, 8q, 6p, 1a • *TERT* promoter mutations

FpHH3 = phosphohistone H3.

5.13 Epidermal Neoplasms

BENIGN

TABLE 5.13.1 BENIGN EPIDERMAL NEOPLASMS

Name	Features	Differential Diagnosis/Pearls
Solar lentigo *Figure 5.13.1*	• Reticulated epidermal hyperplasia (elongated rete) • Basal layer hyperpigmentation ("dirty socks") • Solar elastosis • **NOT A MELANOCYTIC LESION!**	• Lentigo: Hyperpigmentation and increased melanocytes • Ephelis: Basal layer hyperpigmentation with no increase in melanocytes • Macular seborrheic keratosis: More acanthotic and reticulated
Seborrheic keratosis *Figure 5.13.2*	• Acanthosis + horn pseudocysts	Variants: • Clonal: "Nests" of similar-appearing cells within epidermis, can mimic squamous cell carcinoma in situ • Pigmented: Pigment within and around lesion • Macular: Flat, pigmented, no horn pseudocysts, mimics solar lentigo • Inflamed: Chronic inflammation, may have keratinocyte atypia, can mimic squamous cell carcinoma (SCC)
Inverted follicular keratosis *Figure 5.13.3*	• Endophytic epidermal growth • Squamous eddies (whorls of keratinocytes without parakeratosis)	• Likely irritated variant of seborrheic keratosis or verruca vulgaris • Can mimic trichilemmoma but does not have cuticle
Epidermal nevus *Figure 5.13.4*	• Epidermal hyperplasia and hyperpigmentation	• SK: Often need clinical information to distinguish
Benign lichenoid keratosis *Figure 5.13.5*	• Irregular acanthosis • Lichenoid infiltrate • Often can see remnants of a solar lentigo or SK being consumed by the lichenoid infiltrate at the periphery of the lesion • May have parakeratosis	• Lichen planus: Wedge-shaped hypergranulosis, no parakeratosis • Lichenoid drug eruption: Parakeratosis + eosinophils
Clear cell acanthoma *Figure 5.13.6*	• Abrupt transition to adjacent normal epidermis • Psoriasiform hyperplasia • Cells with clear/pale cytoplasm • Parakeratosis with neutrophils	• Psoriasis: Thinned suprapapillary plates, dilated superficial blood vessels • Trichilemmoma: Papillomatosis, endophytic, pink cuticle
Prurigo nodularis *Figure 5.13.7*	• Acanthotic and bulbous downgrowths of epidermis • Adnexal epithelial hyperplasia, both vertically and horizontally	• SCC: Atypia, invasion into dermis
Keratoacanthoma *Figure 5.13.8*	• Crateriform lesion with hyperparakeratotic plug • No atypia	• SCC: Atypia

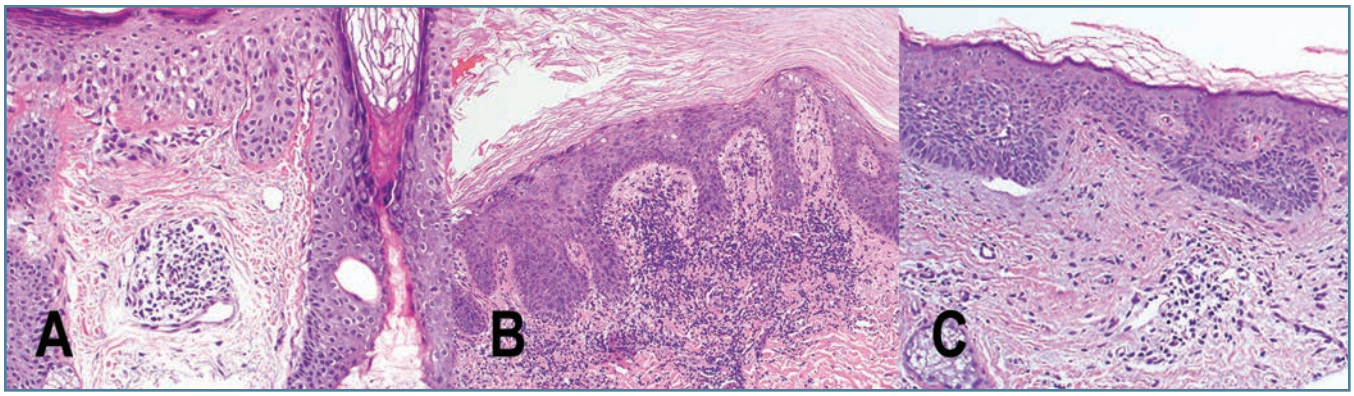

Figure 5.13.9 Comparison of intraepidermal pre-malignant and malignant keratinocyte lesions.

Actinic keratosis (A) classically spares the adnexal structures (follicles). The atypical keratinocytes within the lower half of the epidermis do not involve the adjacent follicles, and the parakeratosis also "skips" over the follicular infundibula. In squamous cell carcinoma in situ (SCCIS) (B), there is full thickness keratinocyte atypia. SCCIS often appears more blue or purple in color because of the increased nuclear to cytoplasmic ratio. Superficial basal cell carcinoma (C) has aggregates of basaloid cells with peripheral palisading of their nuclei emanating from the epidermis, and is surrounded by a fibromyxoid stroma.

PREMALIGNANT AND MALIGNANT

TABLE 5.13.2 PREMALIGNANT AND MALIGNANT EPIDERMAL NEOPLASMS

Name	Features	Differential Diagnosis/Pearls
Actinic keratosis *Figure 5.13.10*	• Alternating parakeratosis that spares the adnexa • Buds of atypical keratinocytes • Solar elastosis	Variants: • Hyperplastic/hypertrophic: Thickened stratum corneum and/or epithelium • Acantholytic
Basal cell carcinoma *Figure 5.13.11A-D*	• Aggregates of basaloid cells • Peripheral palisading • Retraction artifact (clefting) • Myxoid stroma	Variants: • Infiltrative: Angulated strands within fibrotic dermis (cellular) • Morpheaform: Angulated strands within sclerotic dermis (acellular) • Superficial: All aggregates emanating from the epidermis • Fibroepithelioma of Pinkus: Anastomosing strands
Squamous cell carcinoma in situ *Figure 5.13.12*	• Confluent parakeratosis • Full-thickness atypia of the epidermis	Variants: • Pigmented: May be orthokeratotic with subtle atypia • Bowenoid: Buckshot scatter of atypical keratinocytes • Clear cell: Mimics Paget disease and melanoma in situ
Squamous cell carcinoma, invasive *Figure 5.13.13*	• Bulbous aggregates of atypical keratinocytes invading into the dermis • Well, moderately (blue cells with increased nuclear/cytoplasm ratio), or poorly differentiated (spindle cells or plump cells, highly atypical, usually need stains to prove)	Variants: • Acantholytic • Crateriform: Mimics keratoacanthoma, but has atypia • Spindle cell: May not have obvious epidermal connection, stain to prove (CK5/6, pan-keratin, p63, p40)
Merkel cell carcinoma *Figure 5.13.14*	• Aggregates of small blue cells • Salt-and-pepper chromatin • Markers: Synaptophysin, chromogranin, CD56, CK20 and CAM 5.2 (perinuclear dot)	• Basal cell carcinoma: Myxoid stroma, peripheral palisading • Lymphoma: Bottom-heavy, nodular or diffuse pattern • **Metastatic neuroendocrine tumors (small cell): Stains (TTF-1 for lung), history**

TTF-1 = thyroid transcription factor-1.

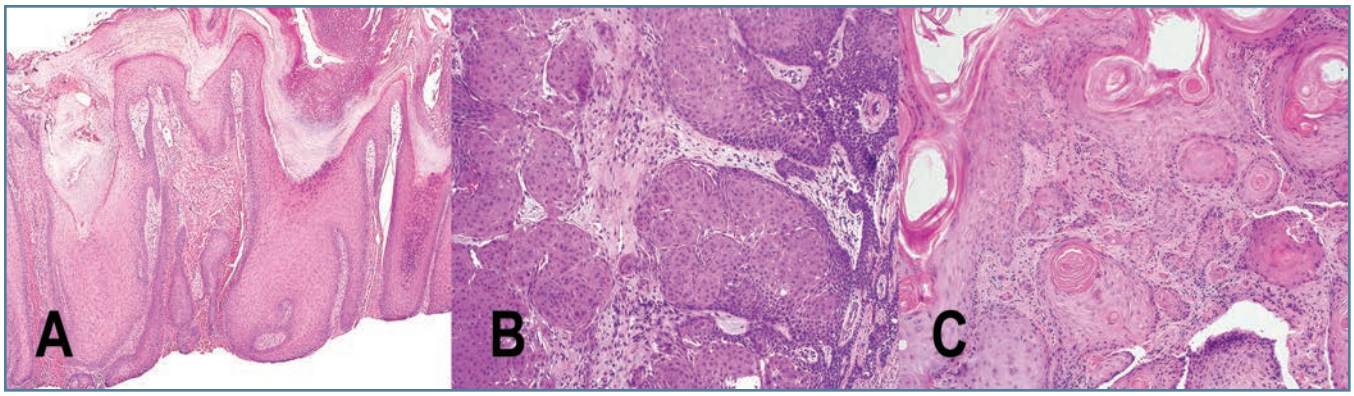

Figure 5.13.15 Comparison of benign and malignant squamous epithelial lesions.

All three lesions pictured above have squamous epithelial hyperplasia. Prurigo nodularis (A) has bland cytology with large keratinocytes with pale glassy cytoplasm. There is bulbous downgrowth of the rete and adnexal structures. Inverted follicular keratosis (B) can have verrucous and/or seborrheic keratosis-like features. Most important, there are "squamous eddies," which are whorls of bland keratinocytes. In comparison, invasive squamous cell carcinoma (C) shows cytologic atypia with an infiltrative architectural pattern and presence of "keratin pearls," which are collections of compact keratin and parakeratin.

5.14 Adnexal Neoplasms

FOLLICULAR

TABLE 5.14.1 FOLLICULAR ADNEXAL NEOPLASMS

Name	Features	Differential Diagnosis/Pearls
Trichoepithelioma *Figure 5.14.1*	• Basaloid islands • Peripheral palisading • Pale pink stroma with plump fibroblasts • Clefting within stroma • Papillary mesenchymal bodies (primitive hair bulbs)	DDx: • Basal cell carcinoma (BCC): Necrotic cells, clefting between cells and stroma Syndromes: • Rasmussen: Trichoepithelioma (TE), cylindroma, milia • Rombo: TE, milia, BCC, vermiculate atrophy • Brooke-Spiegler: TE, cylindroma, spiradenoma
Desmoplastic trichoepithelioma *Figure 5.14.2*	• Dense pink sclerotic stroma • Angulated islands • Calcifications • Horn cysts	• Infiltrative/morpheaform BCC: Mucin, retraction artifact, perineural ± deep involvement • Microcystic adnexal carcinoma: Ductal + follicular, vertically oriented aggregates, perineural involvement
Trichoblastoma *Figure 5.14.3*	• On spectrum with trichoepithelioma • Larger aggregates and deeper invasion • If filled with lymphocytes, referred to as "lymphadenoma"	• BCC: Clefting, myxoid stroma
Trichofolliculoma *Figure 5.14.4*	• Central dilated "mother" hair follicle with "daughter" follicles radiating outward	• May have sebaceous differentiation

TABLE 5.14.1 FOLLICULAR ADNEXAL NEOPLASMS CONTINUED

Name	Features	Differential Diagnosis/Pearls
Tumor of the follicular infundibulum *Figure 5.14.5*	• Plate-like growth from epidermis • Anastomosing strands of pink or basaloid epithelial cells	• Superficial BCC: Clefting, myxoid stroma • Actinic keratosis: Atypia of basal keratinocytes
Dilated pore of Winer *Figure 5.14.6*	• Cystically dilated infundibulum with slightly hyperplastic epithelium	• Pilar sheath acanthoma: Thicker epithelium, ductal structures
Pilar sheath acanthoma *Figure 5.14.7*	• Central dilated infundibulum with surrounding hyperplastic epithelium with ductal structures	• Dilated pore of Winer: Thinner epithelium
Trichilemmoma *Figure 5.14.8*	• Verrucous, endophytic growth • Clear/pale cells • Thick pink cuticle • May have desmoplastic stroma	• Verruca: Hypergranulosis, koilocytic change • Clear cell acanthoma: Abrupt transition to normal skin, no cuticle
Fibrofolliculoma *Figure 5.14.9*	• Perifollicular orb-like stroma • Thin radiating epithelial strands	• On spectrum with trichodiscoma • Seen in Birt-Hogg-Dubé syndrome
Trichodiscoma *Figure 5.14.10*	• Epidermal collarette surrounding bland spindle cells in loose stroma	• Spindle-cell variant, also known as neurofollicular hamartoma: Bland spindle cells in myxoid stroma, "mitt-like" sebaceous glands
Pilomatricoma *Figure 5.14.11*	• Dermal nodule • Pale pink shadow cells + surrounding purple-indigo matrical cells • Calcification and/or ossification common	Syndromes: • Gardner: Follicular cyst with pilomatrical features • Rubinstein-Taybi: Multiple pilomatricomas

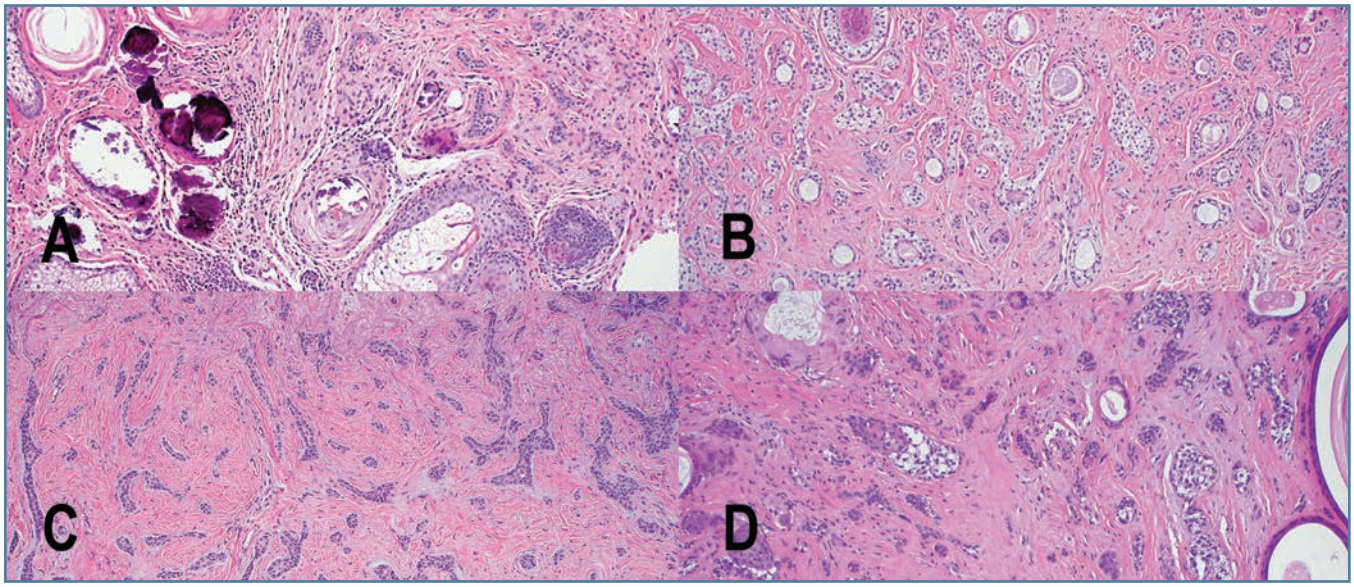

Figure 5.14.12 "Paisley-tie" differential diagnosis.

These four lesions all have small basaloid aggregates of cells ("paisley-tie" appearance) with follicular and/or ductal differentiation. Desmoplastic trichoepithelioma (DTE) (A) has follicular differentiation, calcifications, and horn pseudocysts without deep infiltration or perineural involvement. Syringoma (B) — in this case, clear cell — has ductal structures only, but like DTE, there is no deep infiltration or perineural involvement. Morpheaform basal cell carcinoma (C) shows focal retraction artifact (clefting) between neoplastic aggregates and the surrounding stroma. Deep infiltration is common and there may be perineural involvement. Microcystic adnexal carcinoma (D) has follicular and ductal differentiation as well as deep infiltration and perineural invasion.

DUCTAL

TABLE 5.14.2 DUCTAL ADNEXAL NEOPLASMS

Name	Features	Differential Diagnosis/Pearls
Syringocystadenoma papilliferum *Figure 5.14.13*	• Papillary (frond-like) projections into cystic spaces • Apocrine differentiation • Plasma cells in stroma • Epidermal connection	• Hidradenoma papilliferum: Maze-like configuration, primarily dermal, fewer plasma cells, on vulva/perineum
Hidradenoma papilliferum *Figure 5.14.14*	• Dermal nodule with papillary (frond-like) projections into cystic spaces, apocrine differentiation, maze-like, no epidermal connection	• Syringocystadenoma papilliferum: Epidermal configuration, plasma cells, on head and neck
Syringoma *Figure 5.14.15*	• "Tadpole" or "paisley tie" duct-like epithelial structures	• Clear cell variant associated with diabetes
Microcystic adnexal carcinoma *Figure 5.14.16*	• Purely ductal (sclerosing sweat duct carcinoma) or ductal + follicular • Vertically oriented angulated epithelial strands • Deep infiltration into fat + perineural invasion	• Infiltrative/morpheaform BCC: Follicular only, myxoid stroma • Desmoplastic trichoepithelioma: Follicular only, horizontally arranged, superficial • Syringoma: ductal only, superficial
Poroma + variants *Figure 5.14.17A-B*	• Monomorphous basaloid and/or squamoid epithelial cells with duct-like structures	Variants: • Eccrine poroma: Epidermis and dermis • Hidroacanthoma simplex/intraepidermal poroma: Intraepidermal only, mimics clonal seborrheic keratosis • Dermal duct tumor/dermal poroma: Dermal only
Hidradenoma (poroid, nodular) *Figure 5.14.18*	• Circumscribed dermal nodule • Monomorphous basaloid and squamoid cells • Admixed ducts and cystic spaces	Variants: • Apocrine/clear cell: Cells have pale/clear cytoplasm
Mixed tumor (chondroid syringoma) *Figure 5.14.19*	• Mesenchymal (cartilage or bone) + epithelial (usually ductal) components • Cuboidal cells with pink cytoplasm • Tubule formation set in chondroid (basophilic) stroma	• Apocrine type usually has long branching tubules • Eccrine type tends to have round uniform, non-branching tubules
Cylindroma *Figure 5.14.20*	• Dermal neoplasm with islands of basaloid cells in "jigsaw" or "mosaic" pattern • Pink hyaline basement membrane surrounding basaloid islands	• Associated with Brooke-Spiegler syndrome • Can occur with spiradenomas or in overlap lesions
Spiradenoma *Figure 5.14.21*	• "Blue balls in the dermis" • Light and dark cells • Admixed lymphocytes • Deposits of pink hyaline material	• Associated with Brooke-Spiegler syndrome • Can occur with cylindromas or in overlap lesions

TABLE 5.14.2 DUCTAL ADNEXAL NEOPLASMS CONTINUED

Name	Features	Differential Diagnosis/Pearls
Adenoma, variants *Figure 5.14.22*	• Benign dermal ductal neoplasms • Described based on architecture (solid, cystic, tubular, papillary; can use more than 1 descriptor) and differentiation (eccrine or apocrine)	
Extramammary Paget's disease *Figure 5.14.23*	• Large pale cells with blue-gray cytoplasm at all levels of the epidermis • Tends to spare basal layer • Whole cells "spit" into stratum corneum • Cells stain with CK7, CEA, mucicarmine, CAM 5.2	• Squamous cell carcinoma in situ: Keratinocytes with pink cytoplasm, full-thickness atypia, intracellular bridges, stain with CK5/6 or p63 but not with CK7 • Melanoma in situ: More of a buckshot appearance of pagetoid cells in the epidermis, confluent melanocytes at the DEJ, stain with MART-1/Melan-A or SOX-10

CAM = cytokeratin-specific antibody, monoclonal; CEA = carcinoembryonic antigen; CK = cytokeratin; MART-1 = melanoma antigen recognized by T cells 1.

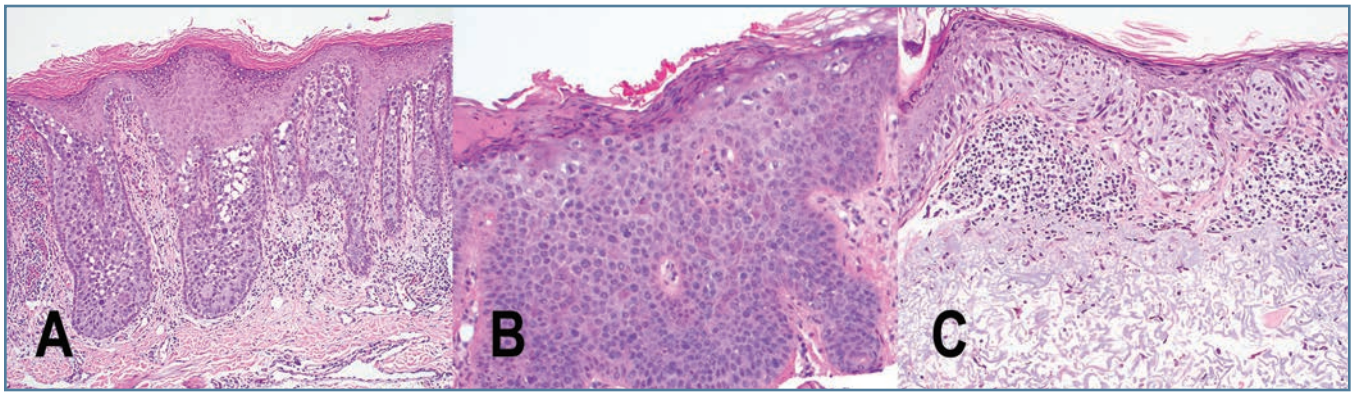

Figure 5.14.24 Comparison of "pagetoid" intraepidermal malignancies.

All three lesions pictured above have malignant cells involving the epidermis ("pagetoid" growth). In extramammary Paget's disease (EMPD) (A), the cells are pale with blue/gray cytoplasm and spare the basal keratinocytes, occasionally leading to a crushed appearance of the basal layer. Squamous cell carcinoma in situ (SCCIS) (B) has a pale or clear cell variant that mimics EMPD. However, the cells in SCCIS still retain their intercellular bridges and are present throughout the full-thickness of the epidermis. Lastly, melanoma in situ (MIS) (C) can mimic either EMPD or SCCIS occasionally, although the melanocytes are typically nested and often have melanin pigment, although this may be scant or absent in clinically amelanotic lesions.

SEBACEOUS

TABLE 5.14.3 SEBACEOUS ADNEXAL NEOPLASMS

Name	Features	Differential Diagnosis/Pearls
Folliculosebaceous cystic hamartoma *Figure 5.14.25*	• Cystically dilated infundibula • "Mitt-like" sebaceous lobules • Rudimentary follicles • Loose fibromyxoid stroma with adipocytes and apocrine glands	• Nevus sebaceus: Papillomatosis, sebaceous glands increased but not changed in morphology
Nevus sebaceus (of Jadassohn) *Figure 5.14.26*	• Papillomatosis • Abortive hair follicle formation • Absence of terminal anagen follicles • Increased sebaceous glands • Dilated apocrine glands	• Secondary tumors occur: Trichoblastoma, syringocystadenoma papilliferum, trichilemmoma

TABLE 5.14.3 SEBACEOUS ADNEXAL NEOPLASMS CONTINUED

Name	Features	Differential Diagnosis/Pearls
Sebaceous adenoma *Figure 5.14.27*	• Well-circumscribed lobules of mature sebocytes • Not associated with follicles • Slightly increased basaloid germinative cells • >50% mature sebocytes	• Associated with Muir-Torre syndrome
Sebaceoma (formerly sebaceous epithelioma) *Figure 5.14.28*	• Circumscribed dermal neoplasm of sebocytes and basaloid germinative cells • >50% germinative cells • May see scattered mitoses	• Associated with Muir-Torre syndrome
Sebaceous carcinoma *Figure 5.14.29*	• Infiltrative, haphazardly arranged atypical sebocytes and basaloid germinative cells • Numerous mitoses + apoptotic cells • May involve epidermis, presenting as carcinoma in situ	• Associated with Muir-Torre syndrome • Periorbital lesions in elderly not usually part of Muir-Torre syndrome

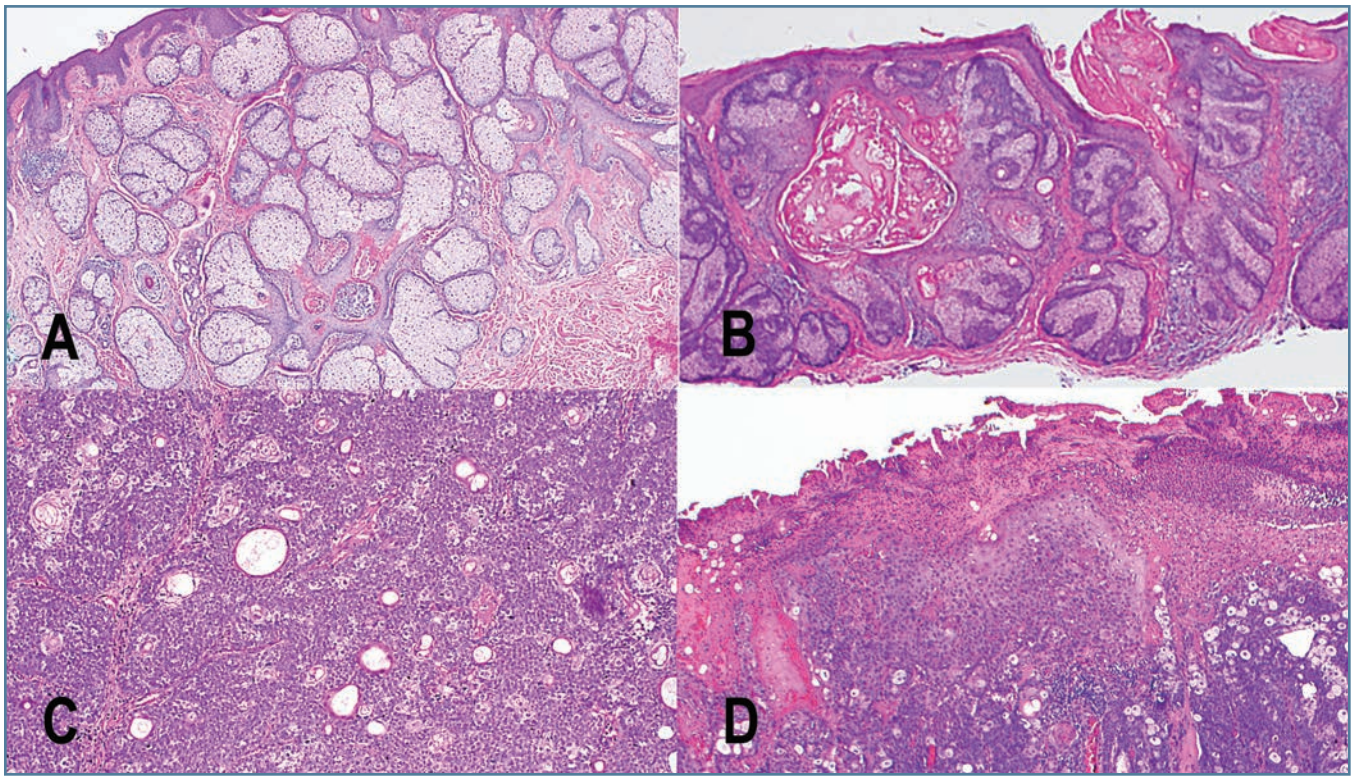

Figure 5.14.30 Sebaceous neoplasms.

All sebaceous neoplasms are comprised of a combination of mature sebocytes and basal germinative epithelial cells. Sebaceous hyperplasia (A) shows an increased number of normal sebaceous lobules. In sebaceous adenoma (B), there is a slight increase in basal germinative cells and the lobules are not associated with a follicle but rather open directly to the epidermis. Sebaceoma (C) is often large and well-circumscribed and is predominantly composed of basal germinative cells. Sebaceous carcinoma (D) has an infiltrative architecture with numerous atypical cells and a haphazard arrangement of mature sebocytes and basal germinative cells. There is often an in situ component as well.

5.15 Fibrohistiocytic Neoplasms

BENIGN

TABLE 5.15.1 BENIGN FIBROHISTIOCYTIC NEOPLASMS

Name	Features	Differential Diagnosis/Pearls
Angiofibroma *Figure 5.15.1*	• Dome-shaped papule • Thickened collagen bundles replace solar elastosis • Dilated blood vessels with "onion-skinning" fibrosis • Scattered plump stellate fibroblasts	Clinical variants all with similar histopathology: • Fibrous papule of the face • Adenoma sebaceum and Koenen tumors (in tuberous sclerosis) • Pearly penile papules • Acquired digital fibrokeratoma/acral fibrokeratoma: On acral skin, no nerve bundles
Sclerotic fibroma *Figure 5.15.2*	• Dome-shaped papule • Thickened collagen with whorled, storiform, or laminated pattern ("wood grain") • Hypocellular with bland delicate spindle cells that stain with factor XIIIa	• When multifocal, think Cowden's disease
Pleomorphic fibroma *Figure 5.15.3*	• Dome-shaped papule • Thickened collagen • Admixed bizarre pleomorphic stellate cells • Cells stain with CD34	• Clinically, indistinguishable from other fibromas
Myxoma *Figure 5.15.4*	• Delicate spindle cells set within loose myxoid stroma • May have overlying basaloid follicular induction • Increased blood vessels + extension into subcutis = superficial angiomyxoma	• **Associated with Carney's complex** • Focal mucinosis is less cellular
Superficial acral fibromyxoma *Figure 5.15.5*	• Acral location • Spindled and stellate cells within myxoid stroma • Cells stain with CD34, EMA and CD99	
Dermatofibroma *Figure 5.15.6A-C*	• Overlying epidermal hyperplasia: Hyperpigmentation, flattening ("table top") of rete ridges, basaloid follicular induction (mimics superficial basal cell carcinoma) • Dermal proliferation of plump spindled and stellate cells • Collagen trapping at periphery of lesion • Denser in center than at periphery • Pushes fat downward but does not typically infiltrate fat or destroy adnexa • Cells stain with factor XIIIa and stromelysin-3, but not CD34	Variants: • Cellular: Dense and deep proliferation, scattered atypia/mitotic figures • Angiomatoid/aneurysmal (sclerosing hemangioma): Dilated blood vessels, hemosiderin deposition within macrophages (siderophages), mimics vascular neoplasm • Monster cell: Scattered large pleomorphic cells
Epithelioid cell histiocytoma *Figure 5.15.7*	• Polypoid lesion with epidermal collarette • Sheets of epithelioid cells with abundant cytoplasm • Cells stain with factor XIIIa, ALK	• May have granular cytoplasm and/or increased degree of vascularity

TABLE 5.15.1 BENIGN FIBROHISTIOCYTIC NEOPLASMS CONTINUED

Name	Features	Differential Diagnosis/Pearls
Dermatomyofibroma *Figure 5.15.8*	• Horizontally oriented proliferation of spindle cells • Spares papillary dermis	• Dermatofibroma: More haphazard arrangement of plump spindle cells, collagen trapping, factor XIIIa positive • Scar: Vertically oriented vessels, thickened collagen
Nodular fasciitis *Figure 5.15.9*	• Unencapsulated deep mass of spindle cells • Haphazard arrangement of cells within loose myxoid stroma ("tissue culture appearance") • Thin-walled blood vessels with numerous extravasated erythrocytes • Positive with SMA, but negative with desmin	• Rapidly growing reactive proliferation • Cells are myofibroblasts: Myofibroblastic differentiation = SMA+, typically desmin−
Fibrous hamartoma of infancy *Figure 5.15.10*	• Poorly defined deep dermal proliferation • Fibrotic collagen with spindle cells (hypocellular) • Loose aggregates of oval or stellate cells (hypercellular) • Admixed mature fat	• Shoulder, axilla, or upper arms in males <2 years old
Digital fibromatosis of childhood (infantile digital fibromatosis) *Figure 5.15.11A-B*	• Interlacing bundles of spindle cells in dense collagen • Brightly eosinophilic round intracytoplasmic inclusions within cells = aggregates of actin	• **Inclusion bodies stain with PTAH (purple), Masson trichrome (red), actin**
Myofibromatosis *Figure 5.15.12*	• Well-circumscribed nodular proliferation • Short fascicles of plump spindle cells • Central vascular spaces • May have bluish appearance in areas due to mucin deposition	• May be solitary in infants and adults or congenital with or without visceral involvement
Giant cell tumor of the tendon sheath *Figure 5.15.13*	• Deep dermal tumor on acral site, often • Histiocytes with foamy cytoplasm (xanthomatous) and/or hemosiderin (siderophages) • Osteoclast-like giant cells = purplish cytoplasm with angulated nuclear borders • Cells stain with CD68	

ALK = anaplastic lymphoma kinase; PTAH = phosphotungstic acid-hematoxylin; SMA = smooth muscle actin.

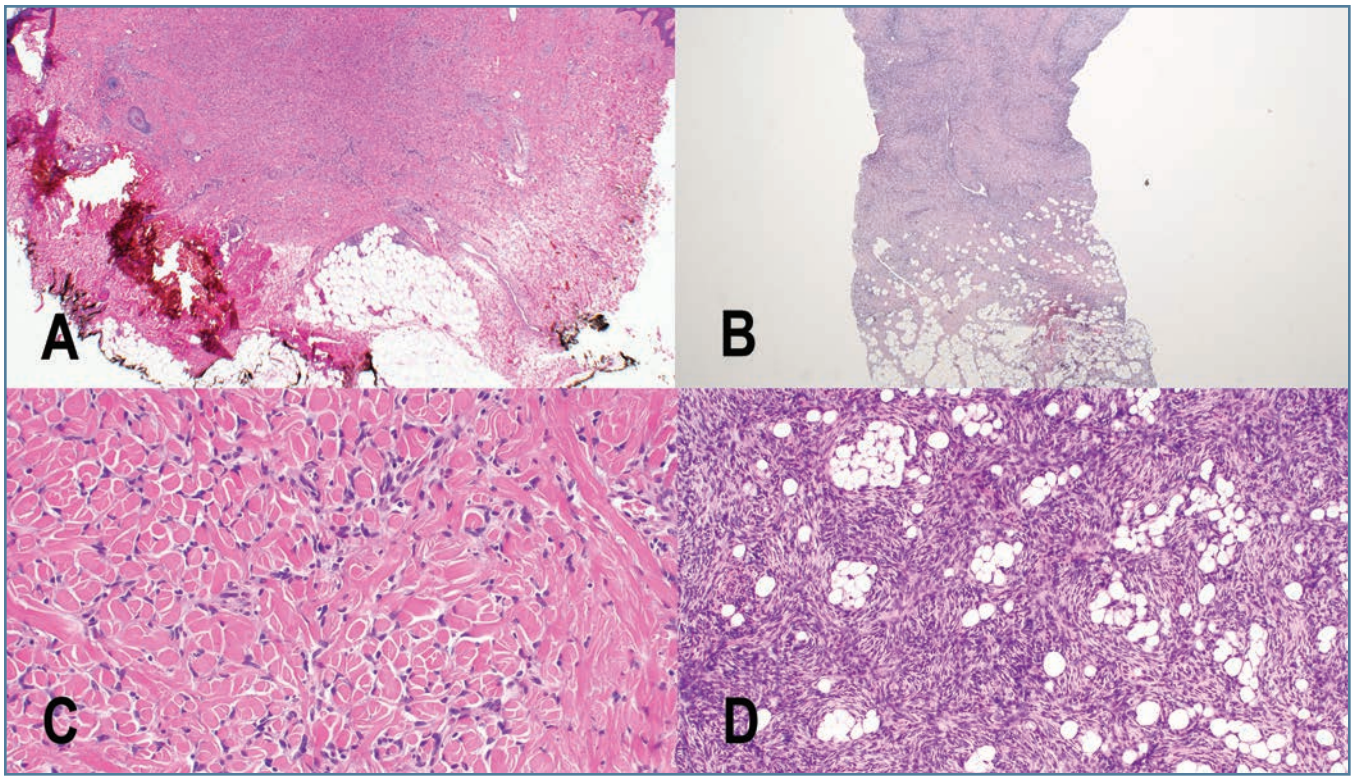

Figure 5.15.14 Comparison of dermatofibroma and dermatofibrosarcoma protuberans.

At low power, both dermatofibroma (DF) (A) and dermatofibrosarcoma (DFSP) (B) are spindle cell proliferations within the dermis. In DF, the proliferation expands the dermis, pushing down the fat, while DFSP invades the fat in a "honeycomb" fashion and often tracks down the septa. At higher power, in DF (C), there are plump spindle cells intersecting between collagen bundles, leading to "collagen trapping," especially at the periphery. In DFSP (D), the cells are smaller, more monomorphous, and are organized in a storiform or "cartwheel" pattern. There are trapped fat cells, demonstrating how a DFSP can infiltrate invisibly into the subcutaneous tissue.

MALIGNANT

TABLE 5.15.2 MALIGNANT FIBROHISTIOCYTIC NEOPLASMS

Name	Features	Differential Diagnosis/Pearls
Dermatofibrosarcoma protuberans *Figure 5.15.15A-B*	• Dense diffuse proliferation of small bland-appearing spindle cells • Storiform ("cartwheel") pattern of cells • Infiltrates into fat in "honeycomb" pattern • Destroys adnexal structures • Stains with CD34	• Typically more cellular than dermatofibroma • Myxoid variant can mimic neurofibroma • **t(17;22)(q22;q13) leads to fusion of collagen type 1 a_1 (COL1A1) and platelet-derived growth factor B-chain (PDGFB)**
Atypical fibroxanthoma (AFX) *Figure 5.15.16*	• Often ulcerated • Vaguely fascicular proliferation of atypical spindle cells • Numerous pleomorphic and multinucleated cells, some with foamy cytoplasm (very bizarre looking) • Diagnosis of exclusion: Stains with CD10, CD99, procollagen, but negative with cytokeratins, melanocyte markers, smooth muscle markers	• Spindle cell squamous cell carcinoma: Keratinization, connection to epidermis, stains with cytokeratins (CK5/6, pan-keratin) and p63/p40 • Leiomyosarcoma: Fascicular, stains with smooth muscle markers (SMA, desmin, h-caldesmon) • Angiosarcoma: Slit-like irregular vascular channels, stains with CD34 and CD31 • Desmoplastic melanoma: May have junctional component (melanoma in situ) above it. Stains with S-100 and/or SOX-10

Pleomorphic dermal sarcoma	• Histopathologic findings identical to AFX with additional features:
	  ▸ Extension into subcutis
	  ▸ Lesional necrosis
	  ▸ Lymphovascular invasion
		• Previously called malignant fibrous histiocytoma or undifferentiated pleomorphic sarcoma

Epithelioid sarcoma *Figure 5.15.17A-B*	• Deep dermal proliferation • Epithelioid cells + spindle cells + granulomatous inflammation • Pleomorphism and mitotic figures • Central "geographic" necrosis • Vascular invasion • Cells stain with vimentin, EMA, CAM 5.2	• Granulomatous dermatitis: No atypia, palisading around altered collagen, often myxoid • Infection: May be neutrophilic as well, need bug stains

CAM = cytokeratin-specific antibody, monoclonal; EMA = epithelial membrane antigen; h-caldesmon = high molecular weight form of caldesmon.

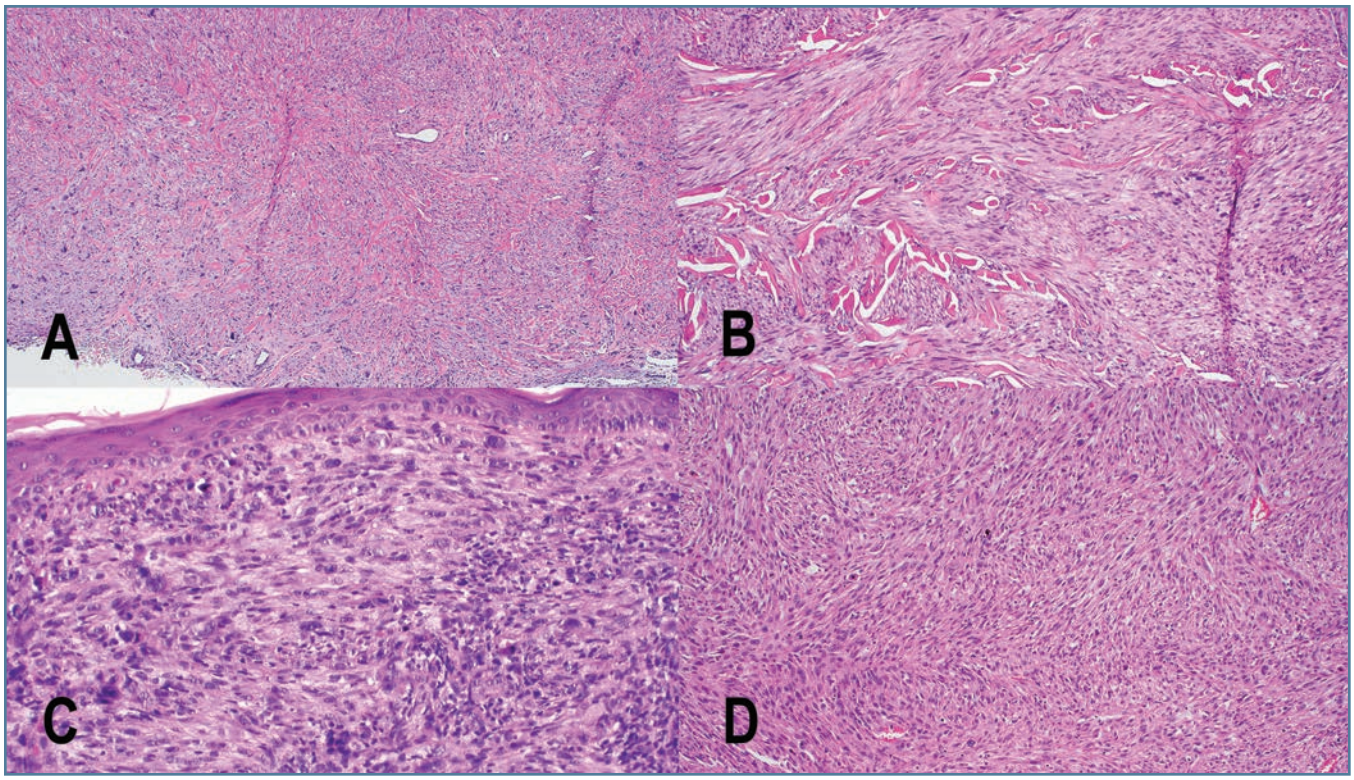

Figure 5.15.18 Differential diagnosis of cutaneous spindle cell malignancies.

These four lesions are composed of atypical spindle cells within the dermis. Atypical fibroxanthoma (AFX) (A) has bizarre pleomorphic multinucleated cells and is often ulcerated. Leiomyosarcoma (LMS) (B) has a fascicular architecture; the smooth muscle cells are tapered or blunt-ended with a "cigar-shape" appearance. Spindle cell melanoma (MM) (C) may or may not have melanin deposition and/or an in situ component. Spindled squamous cell carcinoma (SCC) (D) is composed of spindle cells with pink cytoplasm. A clue to the diagnosis is overlying squamous cell carcinoma in situ or well-differentiated invasive squamous cell carcinoma on the edges of the lesion. Immunohistochemical stains are typically needed to differentiate between these entities: AFX - CD10, CD99; LMS - smooth muscle actin, desmin, h-caldesmon; MM - S100, Sox-10; SCC - CK5/6, pan-cytokeratin, p63, p40.

5.16 Lipomatous/Smooth Muscle/Neural Tumors

LIPOMATOUS TUMORS

TABLE 5.16.1 LIPOMATOUS TUMORS

Name	Special Features	Differential Diagnosis/Pearls
Lipoma *Figure 5.16.1*	• Mature adipocytes • Lacks fibrous septa • Fibrolipoma has prominent mature collagen bundles	• Normal fat: Has fibrous septa
Angiolipoma *Figure 5.16.2*	• A lipoma with capillary-sized blood vessels • Luminal fibrin microthrombi always present	• **Only fatty tumor with no chromosomal abnormality**

TABLE 5.16.1 LIPOMATOUS TUMORS CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Spindle cell lipoma *Figure 5.16.3*	• Well circumscribed • Mature fat + bland spindle cells + ropey collagen + mucin • **CD34$^+$**	• Myxoid liposarcoma: Lipoblasts and pleomorphic cells
Hibernoma *Figure 5.16.4*	• Deep benign tumor, resembles normal brown fat • "Mulberry cells"—nuclei appear scalloped due to multiple vacuoles present in cytoplasm (increased mitochondria)	• Brown fat: Seen in children
Liposarcoma *Figure 5.16.5*	• Lipoblasts • Hyperchromatic, pleomorphic cells	• Clear cell melanoma: Will be S100+ and HMB-45+
Nevus lipomatosus *Figure 5.16.6*	• Mature adipocytes replacing much of the dermis	• Superficial lipoma • Fibroepithelial polyp with prominent adipocytes: Has a stalk • Goltz syndrome: Typically epidermis is right on top of fat and dermis is missing

HMB-45 = human melanoma black-45 antigen.

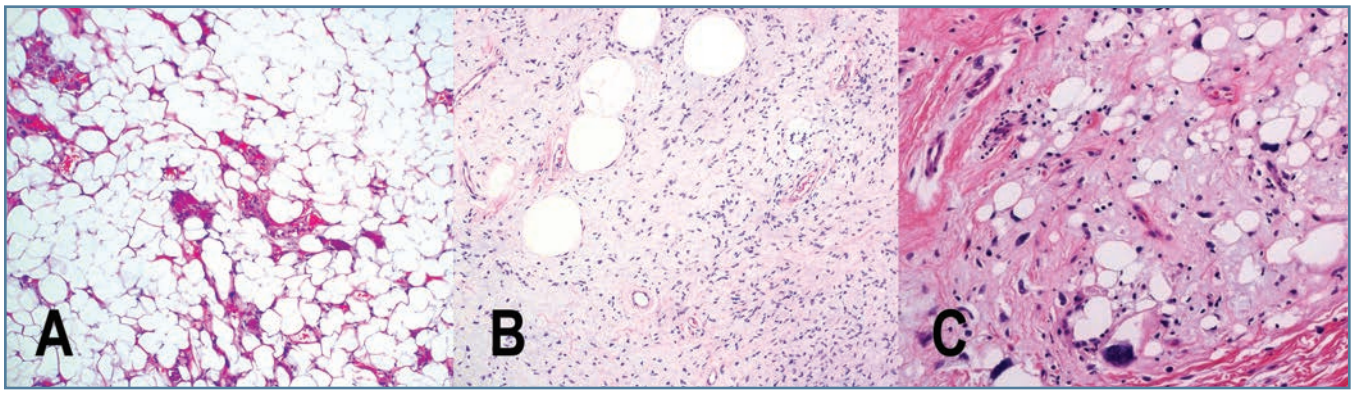

Figure 5.16.7 Lipomatous tumors.
In angiolipoma A) there are an increased number of small blood vessels, many of which are filled with fibrin. In spindle cell lipomas B) there is a proliferation of uniform spindled cells intimately associated with mature adipocytes, which may or may not have prominent mucin. In contrast, liposarcomas C) consist of adipocytes with atypical and pleomorphic nuclei.

SMOOTH MUSCLE TUMORS

TABLE 5.16.2 SMOOTH MUSCLE TUMORS

Name	Special Features	Differential Diagnosis/Pearls
Piloleiomyoma *Figure 5.16.8*	• Interlacing bundles/fascicles of smooth muscle (cells with eosinophilic cytoplasm and cigar-shaped nuclei, with perinuclear clearing) • Mitoses are absent • Derived from arrector pili smooth muscle in the dermis • Multiple lesions seen in Reed's syndrome	• Smooth muscle hamartoma: Distributed in a patch or plaque-like lesion, may also contain terminal hair follicles
Angioleiomyoma *Figure 5.16.9*	• Well-circumscribed tumor • Derived from vascular smooth muscle cells • Numerous small vessels within the lesion with small slit-like spaces	• Angiomyolipoma: Will also contain prominent adipose tissue
Leiomyosarcoma *Figure 5.16.10*	• **Hypercellular smooth muscle tumor with pleomorphism** • **Necrosis and mitotic figures**	• Leiomyoma—less cellular and no nuclear pleomorphism • If poorly differentiated—spindle cell squamous cell carcinoma, spindle cell malignant melanoma, atypical fibroxanthoma: Need immunohistochemical staining

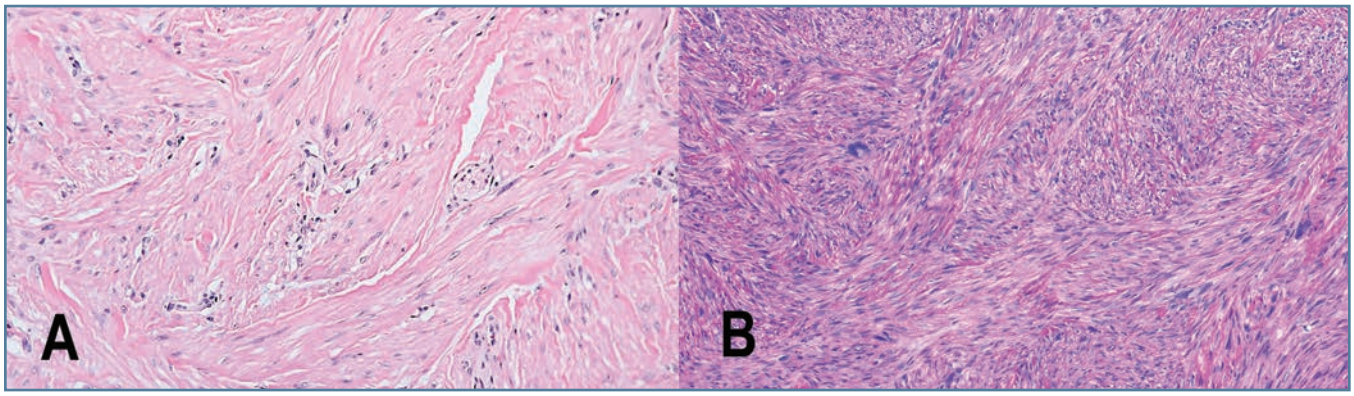

Figure 5.16.11 Smooth muscle tumors.
In Leiomyoma A) there are fascicles of spindled cells with oval, blunt ended nuclei and a conspicuous perinuclear clearing (white space). Leiomyosarcoma B) conversely are much more cellular, have pleomorphic nuclei with atypia and mitotic figures. They are often quite well differentiated and retain the perinuclear clearing characteristic of smooth muscle cells, in which case the density of the cells is the most distinguishing feature.

NEURAL TUMORS

TABLE 5.16.3 NEURAL TUMORS

Name	Special Features	Differential Diagnosis/Pearls
Neurofibroma (NF) *Figure 5.16.12*	• Well defined, nonencapsulated dermal proliferation of wavy spindle cells, scattered mast cells • Diffuse neurofibroma may extend into subcutaneous fat	• Amelanotic blue nevi and neurotized dermal nevi: Will be Melan-A$^+$ • DFSP and diffuse NF may look alike and both are CD34$^+$, but S100 will only be positive in NF
Schwannoma (neurilemmoma) *Figure 5.16.13*	• Encapsulated, deep dermal or subcutaneous lesion, biphasic Antoni A (hypercellular, Verocay bodies) and Antoni B (hypocellular, myxoid stroma) areas • S100 positive	• **Neuroma will have more mature-appearing nerve bundles as opposed to Verocay bodies**
Traumatic neuroma *Figure 5.16.14*	• Nonencapsulated • Numerous haphazardly arranged individual nerve fascicles embedded in fibrous scar tissue	• Supernumerary digit: Not associated with a scar
Palisaded encapsulated neuroma *Figure 5.16.15*	• Well-circumscribed dermal nodule but **nonencapsulated** (misnomer) • Cells are arranged in short fascicles separated by artifactual clefting	• **Looks like a thumbprint**
Supernumerary digit *Figure 5.16.16*	• Located near the base of the fifth digit • Polypoid lesion with acral skin and numerous nerve bundles in the dermis • Bone/cartilage may be present	• Acral fibrokeratoma (acquired digital fibroma): Lacks nerve bundles, has longitudinal collagen streaking and stellate cells
Nerve sheath myxoma (formerly known as myxoid neurothekeoma) *Figure 5.16.17*	• Multiple multilobulated myxoid areas with sparse spindle cells • S100 positive	• Looks like schwannoma with mucin
(Cellular) Neurothekeoma *Figure 5.16.18*	• Now thought to be of fibrohistiocytic origin • Vaguely nested-appearing cells of various morphology, often with sclerotic background • S100$^-$, NKI-C3$^+$, MITF$^+$, S100A6$^+$	• Plexiform fibrohistiocytic tumor: Both are positive for NKI-C3, but this one is MITF negative
Granular cell tumor *Figure 5.16.19*	• Round cells with distinctly granular cytoplasm • S100$^+$ • PAS$^+$ lysosomal inclusions called pustulo-ovoid bodies of Milian	• Granular cytoplasm is slightly more coarse than "ground glass"-appearing cytoplasm
Malignant peripheral nerve sheath tumor (MPNST)	• Malignant transformation of plexiform neurofibromas • Hypercellularity > atypia • Mitoses may not be prominent • S100 focal and weak	• Desmoplastic melanoma: Diffuse S100 staining

MITF = microphthalmia-induced transcription factor; PAS = periodic acid—Schiff.

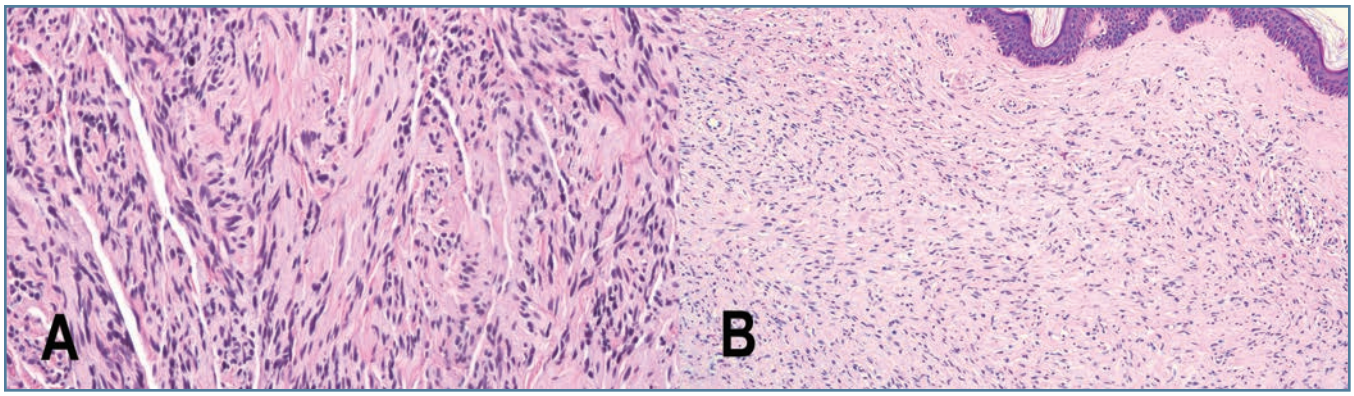

Figure 5.16.20 Comparison of neural neoplasms.

In neuromas such as this palisaded encapsulated neuroma A) there are fascicles of nerve cells that resemble mature nerve bundles seen normally in the skin. In neurofibromas B) there is a loose wavy proliferation of nerve cells with spindled nuclei that blends smoothly into the surrounding collagen. In schwannomas C) there are usually prominent verocay bodies (antoni A) where spindled cells palisade around a smooth eosinophilic zone (looks like mitotic figures in telophase).

5.17 Vascular Neoplasms

TABLE 5.17.1 VASCULAR NEOPLASMS

Name	Special Features	Differential Diagnosis/Pearls
Angiokeratoma *Figure 5.17.1*	• Dilated and congested capillaries in the superficial dermis right beneath an acanthotic and hyperkeratotic epidermis	• Often traumatized and therefore showing features of a Masson's tumor (intravascular papillary endothelial hyperplasia)
Cherry angioma *Figure 5.17.2*	• Proliferation of capillary-sized blood vessels with pink hyalinized vessel walls	• "Cherry" is clinical; pathologists call them hemangiomas
Infantile hemangioma *Figure 5.17.3*	• Early lesions are highly cellular, the vascular lumina are nonapparent and slit-like • With regression, fibrosis and replacement with fat is seen • **GLUT1 positive**	• Kaposiform hemangioendothelioma: Does not involute, GLUT1 negative, associated with Kasabach-Merritt phenomenon
Pyogenic granuloma *Figure 5.17.4*	• Lobular dermal mass of small capillaries separated by fibrous septa • Early lesions are hypercellular and edematous (overly vascularized granulation tissue) • Epidermal collarette may also be seen	• Bacillary angiomatosis: Has clouds of organisms in perivascular space or deep dermal neutrophils
Bacillary angiomatosis *Figure 5.17.5 A-B*	• Proliferation of capillaries with bluish clouds of organisms adjacent to vessels • **Neutrophils present** • Not distinctly lobular • May be ulcerated	• Pyogenic granuloma: Lacks neutrophils and clouds of organisms

TABLE 5.17.1 VASCULAR NEOPLASMS CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Lymphangioma *Figure 5.17.6*	• Widely dilated, irregularly shaped spaces in the dermis lined by a layer of bland endothelial cells • Filled with lymph, very few erythrocytes • D2-40 positive	• Lymph-hemangioma: Hybrid lesion
Venous lake *Figure 5.17.7*	• Big dilated thin-walled vessel in the dermis filled with blood • Commonly seen on the lips and ears	• Distinct entity
Intravascular papillary endothelial hyperplasia (Masson's tumor) *Figure 5.17.8*	• Thrombosed vessel filled with pink fibrin and numerous endothelial cells forming papillary projections in the process of recanalization • No atypia	• Angiosarcoma: Has atypia
Arteriovenous hemangioma *Figure 5.17.9*	• Vascular proliferation with thick (arterial) and thin (venous) blood vessels • Commonly see mast cells between vessels	• Arteriovenous malformation: Congenital lesion, deep involvement
Glomus tumor *Figure 5.17.10*	• Uniform round cells around delicate vascular spaces • Stains with SMA, muscle-specific actin and myosin	• Nodular hidradenoma or poroma: Makes ducts and not vessels
Glomangioma	• The vascular component is more prominent than the solid component seen in glomus tumor	
Angiolymphoid hyperplasia with eosinophilia *Figure 5.17.11*	• Also known as epithelioid hemangioma • Lobulated mass of numerous thick-walled vascular channels lined by round endothelial cells that are protruding into the vessel lumen (hobnail-like) • Prominent inflammatory infiltrate: Lymphocytes (nodular aggregates), eosinophils, and histiocytes	• Kimura's disease: Lacks hobnail endothelium, has many deep lymphoid nodules
Targetoid hemosiderotic hemangioma (hobnail hemangioma) *Figure 5.17.12*	• Dilated vascular channels with hobnail endothelial cells in the upper dermis • More slit-like vessels at the periphery with prominent RBC extravasation and hemosiderin	• Kaposi sarcoma: HHV-8 positive • Pearl: The target shape is created by the red (dilated blood vessels) in the center and brown (extravasated erythrocytes and hemosiderin) at the periphery
Glomeruloid hemangioma *Figure 5.17.13 A-B*	• Capillary loops within a dilated vascular space (resembles a glomerulus) • Endothelial cells filled with pink globules that are immunoglobulins (M-protein) • **Associated with POEMS syndrome**	
Microvenular hemangioma *Figure 5.17.14*	• Branching venules between collagen bundles • No atypia • Surrounding SMA+ pericytes • HHV-8 negative	• Kaposi sarcoma: HHV-8 positive
Acroangiodermatitis	• Exaggerated stasis changes with proliferation of thickened vessels • Extravasated red blood cells, hemosiderin and fibrosis	• Kaposi sarcoma: HHV-8 positive

TABLE 5.17.1 VASCULAR NEOPLASMS CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Kaposi sarcoma *Figure 5.17.15 A-B*	• Patch: Increased number of dilated dermal vessels, plump but monomorphous-appearing endothelial cells, admixed lymphocytes and plasma cells, may see hemosiderin deposits. Promontory sign: New vessels forming around other vessels • Plaque: More obvious and extensive dermal vascular proliferation with prominent inflammation • Nodular: Well-circumscribed dermal (relatively monomorphous) spindle cell proliferation with slit-like vascular spaces and prominent red blood cells • HHV-8 positive	• Acroangiodermatitis: HHV-8 negative
Angiosarcoma *Figure 5.17.16*	• Irregular dilated vascular channels dissecting through collagen bundles ("dry riverbed") • Atypia and pleomorphism of the endothelial cells • May have spindled areas • CD31, CD34, and ERG positive	• Kaposi's sarcoma: Endothelial cells are more monomorphous and spindled

ERG = ETS-related gene (transcription factor); GLUT1 = glucose transporter 1; HHV-8 = human herpesvirus type 8; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; SMA = smooth muscle actin.

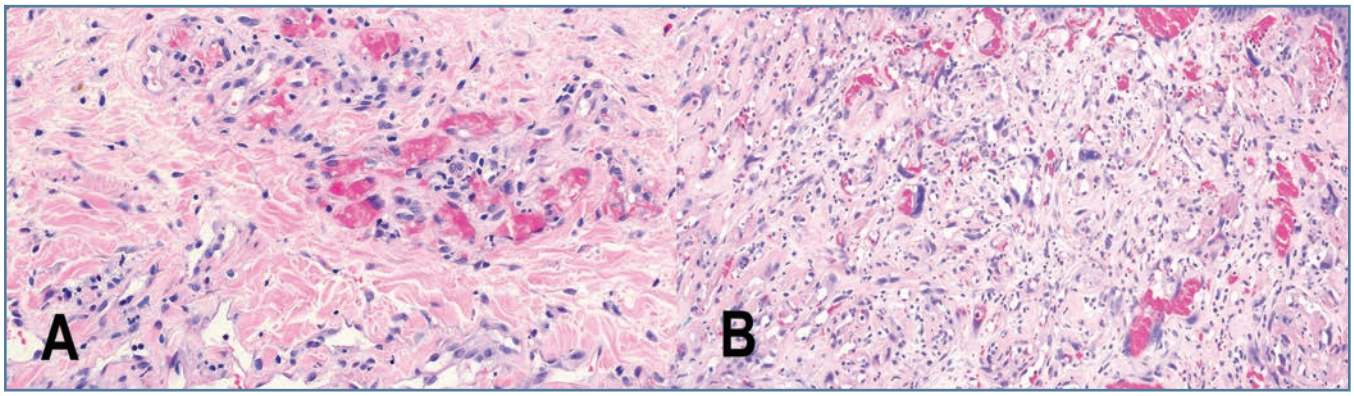

Figure 5.17.17 Vascular neoplasms.

A) Kaposi's sarcoma is not a true sarcoma. In all stages of the disease including the patch stage featured here, the endothelial cells are plump and oval, but relatively monomorphous. B) Angiosarcoma on the other hand has true atypia of the endothelial cells. Both entities may have promontory sign (cross section of a vessel within a vessel) and plasma cells so look closely at the endothelial cells!

5.18 Lymphoid and Leukemic Infiltrates

BASIC STAINING PATTERNS

T cells

- Normal markers: CD2, CD3, CD5, CD7; also stain with CD43 and bcl-2
- Normal CD4:CD8 ratio approximately 2-3:1
- Cytotoxic: CD8+/TIA1+/granzyme+/perforin+
- Reactive T cells: Stain with all normal markers and have normal CD4:CD8 ratio
- Loss of markers suggestive of T Cell dyscrasia; loss of CD7 particularly associated with cutaneous T Cell lymphoma (CTCL)
- Increased CD4:CD8 ratio in mycosis fungoides (MF) subtypes, but may be CD8+ predominant

B cells

- Normal markers: CD20, CD79a, Pax5
- bcl-2 in nongerminal center B cells and marginal zone lymphoma as well as systemic follicular lymphomas
- bcl-6 in germinal center B cells and follicle center cell lymphoma
- CD10 in precursor B cells and follicular lymphoma
- CD23 in mantle zone B cells and chronic lymphocytic leukemia/small lymphocytic lymphoma

Plasma Cells

- Normal markers: CD138, CD79a, MUM1
- Normal κ:λ ratio for polyclonality approximately 2:1
- Light chain restriction: Either κ:λ significantly > 2:1 or significantly < 2:1

Natural Killer (NK)/T Cells

- Normal markers: CD3 (cytoplasmic), CD56, TIA1, granzyme, perforin
- Variable staining with CD4, CD8

Plasmacytoid Dendritic Cells

- Normal markers: CD123, CD303 (BDCA-2)
- Blastic plasmacytoid dendritic cell neoplasm: CD4, CD56, CD123, TCL1, BDCA-2

Myeloid Cells (Includes Neutrophils, Macrophages, Histiocytes)

- CD68, CD43, myeloperoxidase

PSEUDOLYMPHOMA

TABLE 5.18.1 PSEUDOLYMPHOMA

Name	Special Features	Differential Diagnosis/Pearls
Cutaneous lymphoid hyperplasia *Figure 5.18.1*	• Variably dense infiltrate of lymphocytes • Can mimic B Cell lymphoma, but may also be T Cell rich • May see lymphoid follicles • Eosinophils and plasma cells common, but not consistent • Mixed B cells ($CD20^+$), T cells ($CD3^+$, normal CD4:CD8 ratio), histiocytes ($CD68^+$); germinal centers stain $CD10^+/bcl\text{-}2^-$; plasma cells polyclonal • No evidence of IgH clonal rearrangements	• Presence of eosinophils does not reliably distinguish from lymphoma • May be bottom-heavy and involve subcutis • Clinical history important • May see CD30+ reactive cells • Etiologies: Drug, bug, idiopathic

T CELL INFILTRATES

TABLE 5.18.2 T CELL INFILTRATES

Name	Special Features	Differential Diagnosis/Pearls
Cutaneous T Cell Lymphoma		
Mycosis fungoides (MF) *Figure 5.18.2A-C*	• Lymphocytic infiltrate with atypia • Epidermotropic aggregates of atypical lymphocytes within epidermis (Pautrier's microabscesses) or lining up at DEJ ("string of pearls") • Remarkably little tissue reaction in the epidermis (i.e., little to no spongiosis or interface change) • Enlarged hyperchromatic nuclei with irregular contours • Typically markedly increased CD4:CD8 ratio (>5:1), but may be CD8 positive (hypopigmented MF) • CD7 expression may be diminished • Patch stage: May be subtle with minimal inflammation, sclerotic dermal collagen, Pautrier's microabscesses rare • Plaque stage: Denser inflammation within dermis • Tumor stage: Dermal infiltrate, may have minimal epidermotropism, admixed eosinophils • Folliculotropic: Involvement of follicular epithelium, may have follicular mucinosis • Hypopigmented CD8+ variant: Very subtle with pigment incontinence and sparse infiltrate • Large-cell transformation (LCT): 25% of infiltrate composed of large cells (>4 times the size of normal lymphocyte), may have CD30 positivity • Sézary syndrome: Similar to patch stage, can be very subtle	• Spongiotic dermatitis: Spongiosis with randomly distributed exocytosis of small lymphocytes, eosinophils common, normal CD4:CD8 ratio • Drug eruption: May have interface, spongiotic or psoriasiform features, exocytosis common, small lymphocytes, conspicuous eosinophils, normal CD4:CD8 ratio • Lichenoid eruptions: Dense lichenoid band that obscures DEJ, pigment incontinence, necrotic keratinocytes, normal CD4:CD8 ratio but may see skewing in some processes • Pityriasis lichenoides: "Dirty scale," interface with exocytosis of small lymphocytes, necrotic keratinocytes in all levels of epidermis, may have CD4/CD8 skewing or monoclonal T Cell gene rearrangement • Lymphomatoid papulosis: Wedge-shaped infiltrate of large $CD30^+$ cells; type B can be indistinguishable from MF
Subcutaneous panniculitis-like T Cell lymphoma (SPTCL) *Figure 5.18.3*	• Lymphocytic lobular panniculitis with cytologic atypia, no epidermal/dermal involvement • Rimming of adipocytes by enlarged atypical lymphocytes • Cytotoxic phenotype: $CD3^+$/**$CD8^+$/TIA1+/granzyme$^+$**; $CD4^-$/$CD56^-$	• Lupus panniculitis: Similar findings in the subcutis + hyalinized necrosis, lymphoid aggregates, plasma cells, ± interface change, perivascular and periadnexal inflammation
CD30-Positive Lymphoproliferative Disorders		
Lymphomatoid papulosis (LyP) *Figure 5.18.4A-C*	• Wedge-shaped dermal infiltrate of enlarged atypical cells with variable CD30 positivity and mixed inflammatory cells (eosinophils usually present) • Type A: Classic, wedge-shaped, background of inflammatory cells • Type B: Mimics MF, cells $CD4^+$ with admixed larger $CD30^+$ cells • Type C: Mimics ALCL with more diffuse collection of large $CD30^+$ cells without significant inflammation • Type D: Epidermotropism of large atypical CD8+/$CD30^+$ cells • Type E: Angiocentric variant	• ALCL: Need clinical correlation; LyP type C most similar to ALCL • Bug bite: Dense mixed dermal infiltrate, may see scattered reactive CD30+ large cells • Scabies and molluscum lesions with dense inflammation may have CD30+ cells that can mimic LyP, but additional sections may reveal mite/eggs/scybala or molluscum bodies, respectively • PLEVA: Does not typically have admixed eosinophils and neutrophils

TABLE 5.18.2 T CELL INFILTRATES CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Primary cutaneous anaplastic large-cell lymphoma (PC-ALCL) *Figure 5.18.5A-B*	• Dense dermal infiltrate • Sheets of markedly atypical enlarged cells • Cells stain with CD30 (typically >75% of cells) • Primary disease: **EMA$^-$/ALK$^-$**	• LyP type C: Need clinical correlation, typically presents with crops of lesions that come and go vs localized lesions in ALCL • MF with LCT: Can be CD30$^+$ but typically not the majority of cells, may see epidermotropism, clinical correlation needed
NK/T Cell Lymphoma		
Extranodal NK/T Cell lymphoma, nasal type *Figure 5.18.6*	• Diffuse or angiocentric dermal infiltrate that may also involve subcutis • Variably sized lymphocytes • May see invasion of vessel walls with fibrinoid necrosis • Admixed inflammatory cells common • NK/T Cell phenotype: CD3$^+$/**CD56$^+$/TIA1$^+$/granzyme$^+$** • Negative with CD4 and CD8 • Uniformly **EBV$^+$** (EBER in situ hybridization positive)	• SPTCL: Infiltrate confined to subcutis • Lymphomatoid granulomatosis: Also EBV-positive, but B Cell process with CD20 positivity • EBV-associated posttransplant lymphoproliferative disorders: Variable immunophenotypes, need clinical history

ALCL = anaplastic large-cell lymphoma; ALK = anaplastic lymphoma kinase; DEJ = dermo-epidermal junction; EBER = Epstein-Barr virus–encoded small RNA; EBV = Epstein-Barr virus; EMA = epithelial membrane antigen; PLEVA = pityriasis lichenoides et varioliformis acuta; TIA1 = T cell–restricted intracellular antigen-1.

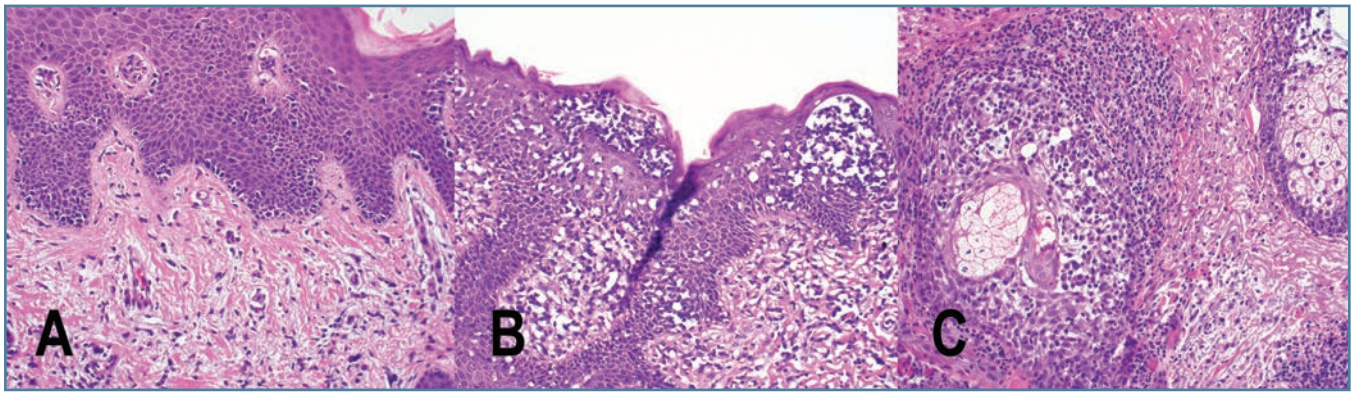

Figure 5.18.7 Mycosis fungoides.

Three variants of mycosis fungoides (MF) are shown here. In the early or patch stage (A) of MF, atypical lymphocytes with enlarged hyperchromatic nuclei line up at the dermo-epidermal junction and are present as single cells and within the overlying epidermis. In the plaque stage (B), there are clusters of atypical lymphocytes within the epidermis (Pautrier's microabscesses). In folliculotropic MF (C), atypical lymphocytes are present within and around the follicular epithelium; there is often increased mucin with the follicle as well.

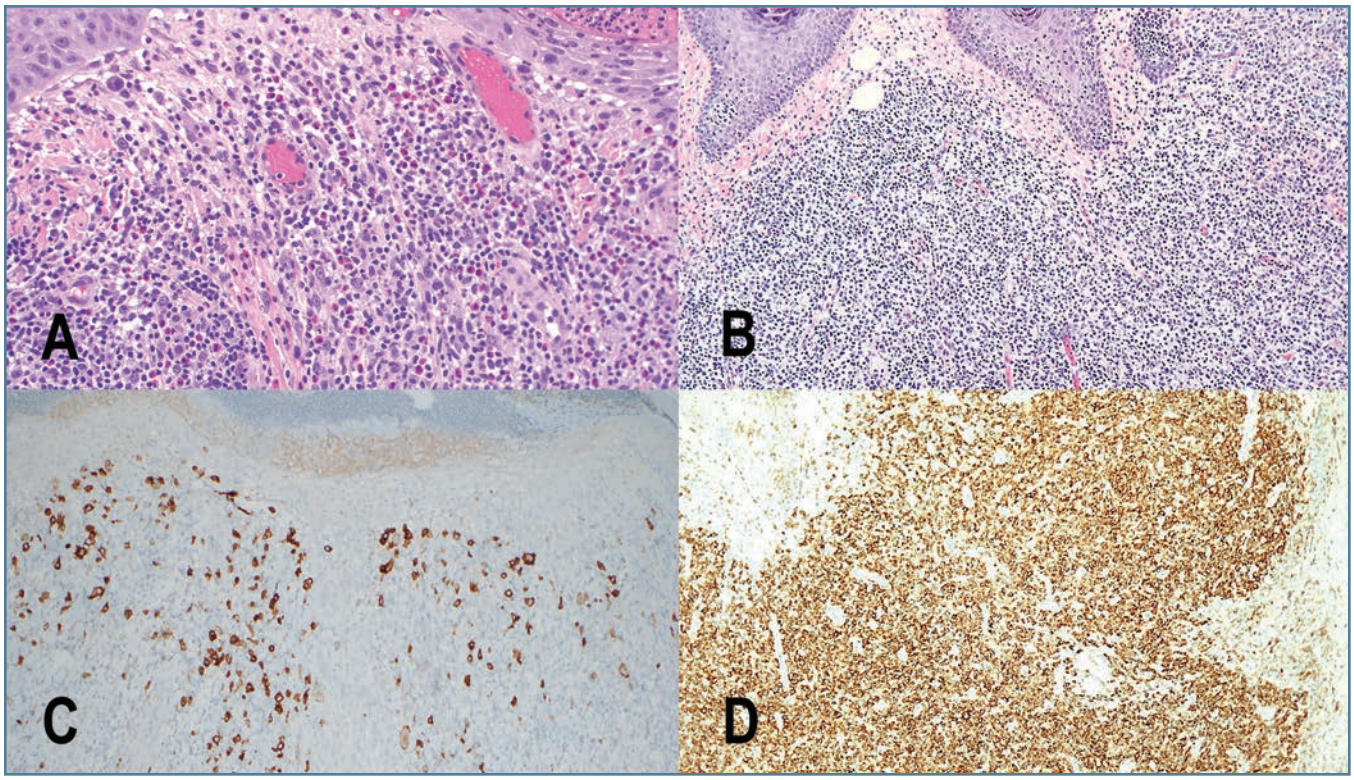

Figure 5.18.8 Comparison of lymphomatoid papulosis and anaplastic large cell lymphoma.

Lymphomatoid papulosis (LyP) (A and C) and anaplastic large cell lymphoma (ALCL) (B and D) are composed of sheets of lymphocytes. LyP has scattered enlarged atypical cells, and typically has a background of other inflammatory cells, such as eosinophils. In ALCL, there is a greater proportion of enlarged atypical cells. In both entities, the atypical cells stain with CD30 (C and D).

B CELL INFILTRATES

TABLE 5.18.3 B CELL INFILTRATES

Name	Special Features	Differential Diagnosis/Pearls
Primary cutaneous marginal zone lymphoma (PC-MZL) *Image 5.18.9A-B*	• Nodular or diffuse dermal infiltrate of small lymphocytes • May be "bottom-heavy" • Plasma cells common surrounding reactive lymphoid follicles • May have admixed eosinophils and numerous reactive T lymphocytes ($CD3^+$) • Neoplastic cells: $CD20^+/CD79a^+/$**$bcl\text{-}2^+$** and $bcl\text{-}6^-/CD5^-/CD10^-$ • Clonal rearrangements of immunoglobulin heavy chain (IgH) genes • Plasma cells often κ-restricted (using κ and λ IHC or in situ hybridization)	• Cutaneous involvement by systemic MZL: Need systemic work-up • Pseudolymphoma: Polyclonality with κ/λ, no clonal *IgH* rearrangements • PC-FCL: Typically $bcl\text{-}6^+/bcl\text{-}2^-$, plasma cells not prominent • Plasmacytoma: Lymphocytes are reactive, not as many $CD20^+$ cells in infiltrate
Primary cutaneous follicle center cell lymphoma (PC-FCL) *Figure 5.18.10*	• Dermal infiltrate of small lymphocytes without epidermal involvement • May be "bottom-heavy" • May have follicular or diffuse pattern • Neoplastic cells: $CD20^+/CD79a^+/CD43^+/CD10^+/$**$bcl\text{-}6^+$** • Clonal rearrangements of immunoglobulin heavy chain *(IgH)* genes in 50% of cases	• Cutaneous involvement by systemic follicular lymphoma: Need systemic work-up, but often $bcl\text{-}2^+$ • PC-MZL: $bcl\text{-}2^+/bcl\text{-}6^-$, monoclonal plasma cells • Pseudolymphoma: Often need clinical correlation
Diffuse large B Cell lymphoma (DLBCL), leg type *Figure 5.18.11A-C*	• Diffuse dermal infiltrate of large lymphocytes • Mitoses common • Neoplastic cells: $CD20^+/CD79a^+/bcl\text{-}6^+/MUM1^+/bcl\text{-}2^+$	• PC-FCL, diffuse type: May mimic DLBCL, but $bcl\text{-}2^-/MUM1^-$ • Cutaneous involvement by systemic DLBCL: Need systemic work-up
Intravascular large B Cell lymphoma *Figure 5.18.12*	• Intravascular proliferation of large atypical lymphoid cells • May be found on "blind biopsy" • Neoplastic cells: **$CD20^+/CD79a^+$**$/CD3^-$ • Variable staining with CD5, CD10, bcl-6, bcl-2, MUM1	• Metastatic adenocarcinoma with intravascular involvement: Cells stain with CK7 or CK20 and other organ-specific markers, but negative with lymphocyte markers • Intralymphatic histiocytosis; reactive condition, cells stain with CD68
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) *Figure 5.18.13A-B*	• Variable dermal infiltrate of small lymphocytes • Importantly, may surround nonmelanoma skin cancers (basal cell carcinoma, squamous cell carcinoma) in patients with CLL/SLL • Neoplastic cells: **$CD20^+/CD5^+/CD43^+$**$/CD10^-$	• Reactive lymphocytic infiltrate: Should be predominantly composed of $CD3^+$ T cells with rare/scattered $CD20^+$ B cells

CK = cytokeratin; IHC = immunohistochemistry; MUM1 = multiple myeloma 1.

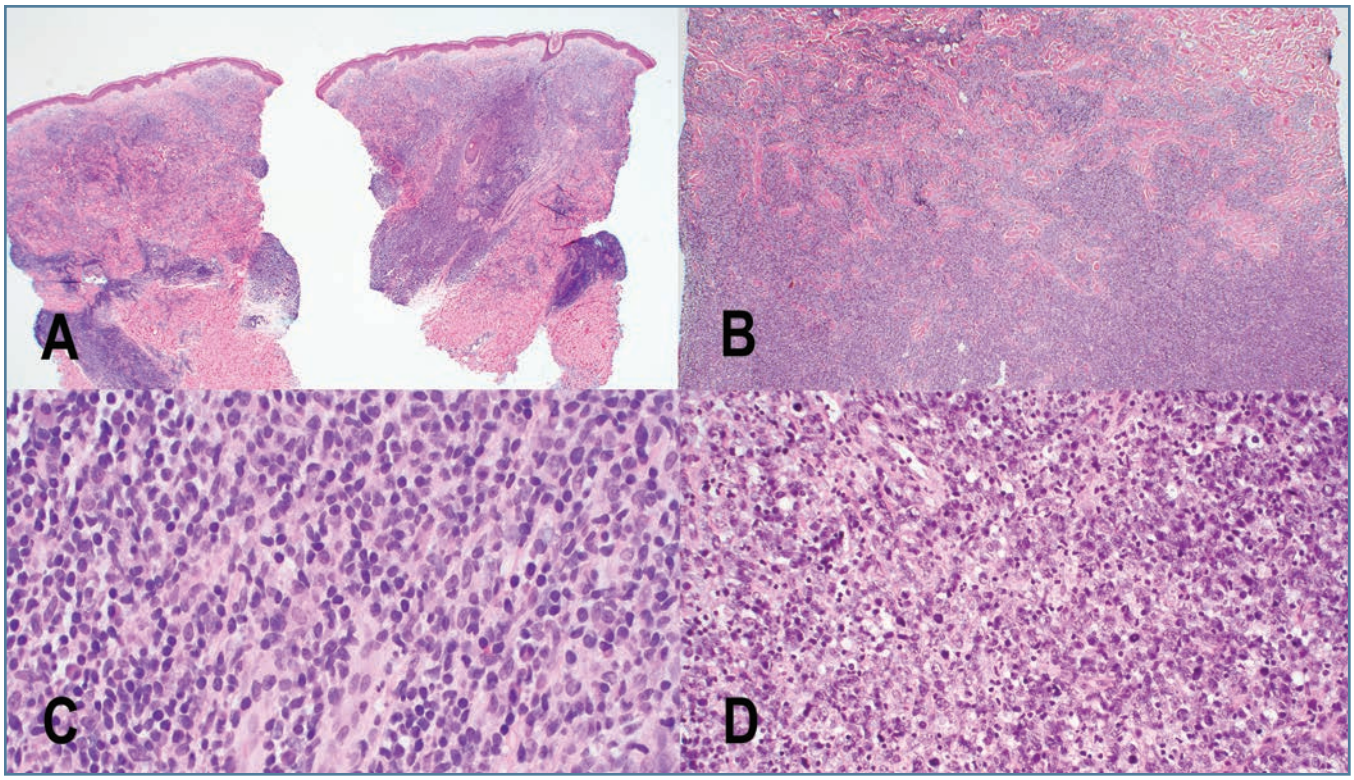

Figure 5.18.14 B cell lymphoma.

Low-grade B cell lymphoma (marginal zone lymphoma, MZL) (A and C) and high-grade B cell lymphoma (diffuse large B cell lymphoma, DLBCL) (B and D) are both diffuse infiltrates of B cells within the dermis. Low-grade B cell lymphoma tends to have a nodular pattern, but may be diffuse, and is often "bottom-heavy," while high-grade lesions are typically diffuse, deeply infiltrative, and bottom-heavy. In low-grade B cell lymphoma, the infiltrate is composed of mature appearing, somewhat monomorphous lymphocytes, with admixed inflammatory cells, including plasma cells and eosinophils (C). In high-grade B cell lymphoma, there is increased pleomorphism and large atypical cells with few admixed inflammatory cells.

MYELOID/PRECURSOR INFILTRATES

TABLE 5.18.4 MYELOID/PRECURSOR INFILTRATES

Name	Special Features	Differential Diagnosis/Pearls
Myeloid leukemia cutis *Figure 5.18.15A-B*	• Diffuse dermal infiltrate of atypical mononuclear cells • Often with grenz zone separating infiltrate from epidermis • Has more jagged infiltrative pattern as opposed to nodular round shapes seen in lymphomas • May see cells in single-file pattern between collagen bundles • Mitotic figures and apoptotic bodies common	• CD68 and lysozyme most sensitive markers, but not specific • Myeloperoxidase specific to myeloid lineage, but not always positive • High discordance between blood and skin IHC markers
Blastic plasmacytoid dendritic cell neoplasm	• Dermal infiltrate of monomorphic medium-sized cells with scant cytoplasm and smudgy-appearing nuclei • No epidermal involvement • Neoplastic cells: **$CD4^+/CD56^+/CD123^+/TCL1^+$**	• Myeloid leukemia cutis: typically $CD4^-/CD56^-$ and $CD68^+$/lysozyme$^+$ • NK/T Cell lymphoma: EBV^+, vascular invasion • Cutaneous T Cell lymphoma: $CD56^-/CD123^-$

TCL1 = T Cell leukemia/lymphoma 1.

5.19 Nonlymphoid Infiltrates

NEUTROPHILIC INFILTRATES

Cellular Features

- Multilobulated nucleus (2-5 distinct lobes)
- Finely granular cytoplasm
- Stains: Myeloperoxidase

Associations

- Infection
- Purpura
- Autoimmune/autoinflammatory diseases

TABLE 5.19.1 NEUTROPHILIC INFILTRATES

Name	Special Features	Differential Diagnosis/Pearls
Sweet syndrome *Image 5.19.1*	• Marked papillary dermal edema • Sheets of neutrophils in superficial dermis • Nuclear debris • May have scattered eosinophils • May have mild vasculitic change, but not frank leukocytoclastic vasculitis (LCV) • Histiocytoid variant has small mononuclear cells set within papillary dermal edema	• Leukocytoclastic vasculitis: Neutrophils centered around vessels without significant interstitial component, papillary dermal edema not common • Early pyoderma gangrenosum: Diagnosis of exclusion • Infection: Denser neutrophilic inflammation without edema; need bug stains
Pyoderma gangrenosum (PG) *Figure 5.19.2*	• Often ulcerated epidermis • Dense neutrophilic infiltrate throughout dermis • May have granulomatous component	• Infection: Need bug stains and culture to differentiate • Ruptured cyst or follicle: Similar findings but typically more granulomatous with remnants of follicular epithelium
Other neutrophilic dermatoses *Figure 5.19.3*	• Similar to above (Sweet syndrome and PG) but less dense	• Associated with inflammatory bowel disease (BADAS), rheumatoid arthritis, systemic lupus erythematosus, other autoimmune diseases
Urticaria *Figure 5.19.4*	• Sparse infiltrate of neutrophils ± eosinophils • Perivascular and interstitial • Can mimic normal skin at low-power magnification	• Sweet syndrome: Denser inflammation in papillary dermis • Dermal hypersensitivity reaction/drug: Many more lymphocytes, few neutrophils • Still's disease: Can be indistinguishable on pathology
Palisaded neutrophilic and granulomatous dermatitis *Figure 5.19.5*	• **Features of granuloma annulare (palisaded histiocytes around altered collagen) + interstitial histiocytes and neutrophils** • May have features of LCV	• Sweet syndrome: Predominantly neutrophilic with dermal edema • Rheumatoid vasculitis: Usually deeper with necrotizing features

BADAS = bowel-associated dermatosis-arthritis syndrome.

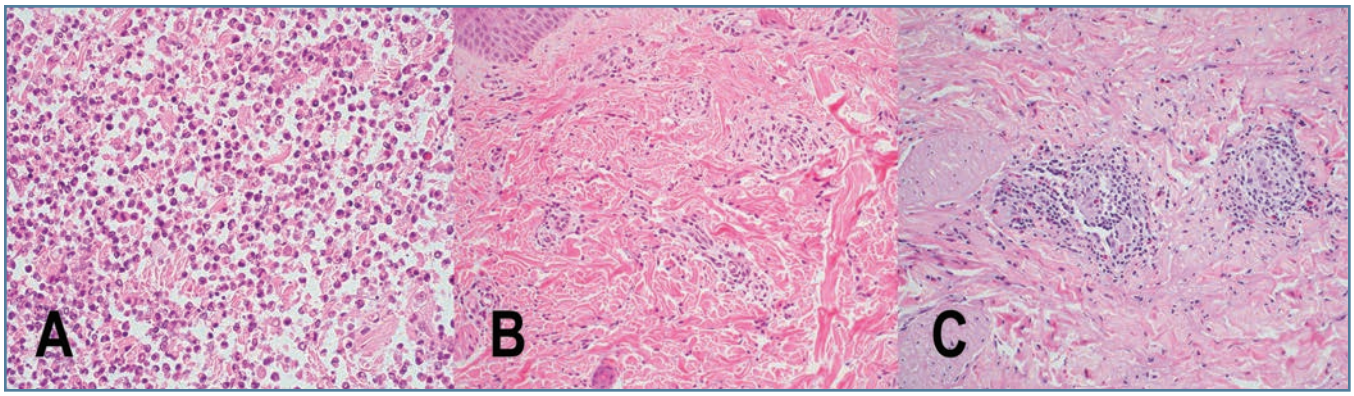

Figure 5.19.6 Neutrophilic and eosinophilic dermal infiltrates.

Sweet syndrome (similar to other neutrophilic dermatoses) (A) is composed of sheets of neutrophils within the superficial dermis, often accompanied by papillary dermal edema. In urticaria (B), the infiltrate is much more sparse with neutrophils (and occasional eosinophils) present around blood vessels and between collagen bundles. In contrast, a dermal hypersensitivity reaction pattern (C), caused by a drug or bug typically, is predominantly composed of lymphocytes around blood vessels within the superficial and deep dermis. There are a variable number of eosinophils within the infiltrate.

EOSINOPHILIC INFILTRATES

Cellular Features

- Bilobed nucleus
- Red granular cytoplasm
- Stains: Sirius red

Associations

- Hypersensitivity reactions
- Parasitic infections
- Infestations
- Some neoplasms (Squamous cell carcinoma, Keratoacanthoma)

TABLE 5.19.2 EOSINOPHILIC INFILTRATES

Name	Special Features	Differential Diagnosis/Pearls
Dermal hypersensitivity reaction *Image 5.19.7*	• Superficial and deep perivascular and interstitial lymphocytic infiltrate with eosinophils • Eosinophils may be abundant or sparse, but predominant cell type is lymphocyte (remember, it's a delayed-type hypersensitivity) • May have scattered neutrophils early on • May have mild overlying spongiosis, but typically no significant epidermal change	• Allergic contact dermatitis: Spongiosis + dermal eosinophils, may have eosinophils in epidermis • Urticarial bullous pemphigoid: Eosinophils predominantly at DEJ; DIF+ • Urticaria: Sparse, predominantly neutrophilic • Pruritic urticarial papules and plaques of pregnancy: Can have similar findings, need history
Wells' syndrome (eosinophilic cellulitis) *Figure 5.19.8*	• Dense perivascular and interstitial dermal infiltrate of eosinophils • Flame figures = eosinophilic material surrounded by histiocytes, consist of eosinophil granule major basic protein	• If primarily involving the subcutis, referred to as eosinophilic panniculitis • Flame figures not pathognomonic and may be seen in other entities with numerous eosinophils
Eosinophilic pustular folliculitis *Figure 5.19.9*	• Aggregates of eosinophils within and around hair follicles • Eosinophilic pustulosis: Clusters of eosinophils within the dermis	• Suppurative folliculitis: Primarily neutrophilic infiltrate within dilated follicular infundibulum

DEJ = dermo-epidermal junction; DIF = direct immunofluorescence.

MAST CELL INFILTRATES

Cellular Features

- Centrally placed round/oval/fusiform nucleus
- Abundant cytoplasm with basophilic granules
- "Fried egg" appearance
- Stains: CD117 (c-kit) and tryptase (IHC); Leder, toluidine blue, Giemsa (metachromatic = stains granules a different color than stain itself)

Associations

- Neurofibromas and other neural tumors
- Scars and chronic inflammation

TABLE 5.19.3 MAST CELL INFILTRATES

Name	Special Features	Differential Diagnosis/Pearls

Cutaneous mastocytosis
Figure 5.19.10A-B
	• Dermal infiltrate of mast cells
	• Typically with admixed eosinophils
	• Tryptase or c-kit/CD117 helpful
	• Solitary mastocytoma: Dense aggregates extending into dermis
	• Urticaria pigmentosa: Variably dense aggregates + basal layer hyperpigmentation
	• Telangiectasia macularis eruptiva perstans: Subtle increases in mast cells around dilated blood vessels, can look like normal skin
	• Diffuse cutaneous: Need clinical information, may be bullous
		• WHO categories:
		  ▸ Maculopapular
		  ▸ Diffuse
		  ▸ Mastocytoma
		• Low-power DDx:
		  ▸ Melanocytic nevus: Nested with maturation
		  ▸ Normal skin: Need stains
		• Urticaria: Predominantly neutrophilic

PLASMA CELL INFILTRATES

Cellular Features

- Eccentrically placed nucleus
- "Clock-face" chromatin pattern with coarse granules around periphery of nucleus
- Basophilic cytoplasm with perinuclear clearing (hof)
- May see pink intracytoplasmic inclusion = Russell body (immunoglobulin accumulation)
- Stains: CD79a, CD138, κ/λ (for clonality)

Associations

- Normal on mucous membranes, head and neck, sun-damaged skin
- Syphilis
- Fibrosing disorders
- Rosacea
- Lupus
- Neoplasms
- Any long-standing inflammatory process

TABLE 5.19.4 PLASMA CELL INFILTRATES

Name	Special Features	Differential Diagnosis/Pearls
Plasmacytosis mucosae (Zoon's balanitis, Zoon's vulvitis, plasma cell cheilitis, vulvitis/balanitis circumscripta plasmacellularis) *Image 5.19.11*	• Dense band-like infiltrate of plasma cells in superficial dermis • May see admixed lymphocytes, mast cells, eosinophils, and neutrophils • Attenuation of epidermis, rare ulceration	• Syphilis (primary chancre): *Treponema pallidum* IHC necessary to distinguish • Lichen planus: Predominantly lymphocytes with rare scattered plasma cells
Cutaneous plasmacytoma *Figure 5.19.12*	• Circumscribed dense infiltrate of plasma cells of variable maturation • Typically monoclonal (can demonstrate by κ/λ staining)	• Secondary: Associated with underlying multiple myeloma or extramedullary plasmacytoma, poor prognosis • Primary: Exceedingly rare, poor prognosis

IHC = immunohistochemistry.

HISTIOCYTIC INFILTRATES

Cellular Features

- Mononuclear cells with abundant pale cytoplasm
- Macrophage: CD45/CD68/CD163/lysozyme+, S100/CD1a/factor XIIIa−
- Dermal dendrocyte: factor XIIIa/CD45/CD68+, S100/CD1a−
- Indeterminate cell: CD45/S100/CD1a+, Birbeck granules absent
- Langerhans cell: CD45/S100/CD1a+, factor XIIIa−, Birbeck granules present

Associations

- Heterogeneous group of dermatoses and neoplasms
- Granulomatous infiltrates, Langerhans cell histiocytosis, xanthomatous diseases, reactive infiltrates

TABLE 5.19.5 HISTIOCYTIC INFILTRATES

Name	Special Features	Differential Diagnosis/Pearls
Non-Langerhans Cell		
Xanthogranuloma (XG) (juvenile or adult) *Figure 5.19.13*	• Early: Dense dermal nodular infiltrate of mononuclear cells with abundant cytoplasm • Late: Touton giant cells (wreath-like arrangement of nuclei with abundant foamy cytoplasm around periphery), admixed inflammatory cells (eosinophils, neutrophils, lymphocytes, plasma cells) • Cells stain with CD68, factor XIIIa	• Reticulohistiocytosis: "Ground glass" cytoplasm, not foamy cytoplasm • Cellular neurothekeoma: Nests of mononuclear cells in the dermis, not foamy but can mimic early XG • Similar histopathology: Benign cephalic histiocytosis, progressive nodular histiocytosis, generalized eruptive histiocytosis, xanthoma disseminatum
Reticulohistiocytosis (multicentric reticulohistiocytosis, reticulohistiocytoma) *Figure 5.19.14*	• Dermal nodular infiltrate of mononuclear and multinucleated cells with abundant "ground glass," pink/purple "two-tone" cytoplasm • Cells stain with CD68, ± factor XIIIa	• XG: Touton cells + admixed inflammatory cells, foaminess more pronounced rather than "ground glass" appearance ("ground glass" looks hazy, like fine sand)
Necrobiotic xanthogranuloma *Figure 5.19.15*	• Broad zones of necrobiosis (altered eosinophilic collagen) • Dense granulomatous inflammation with histiocytes, foam cells, multinucleated giant cells (Touton and foreign body) • ± Cholesterol clefts • Deep infiltration of dermis, may involve subcutis	• Deep Granuloma annulare: May have giant cells, but typically not Touton cells or significant foaminess, no cholesterol clefts
Cutaneous Rosai-Dorfman disease (RDD) *Figure 5.19.16*	• Dense dermal infiltrate of large polygonal histiocytes with abundant pale cytoplasm, set in a background of lymphocytes and plasma cells (can look like a starry night) • Emperipolesis = whole inflammatory cells within cytoplasm of histiocytes • Cells stain with S100, CD68 but are negative with CD1a	• Langerhans cell histiocytosis: No emperipolesis, cells stain with CD1a

TABLE 5.19.5 HISTIOCYTIC INFILTRATES CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Langerhans Cell		
Langerhans cell histiocytosis (LCH) *Figure 5.19.17*	• Dermal infiltrate of mononuclear cells with reniform nuclei and abundant pale cytoplasm • **Admixed eosinophils** • Often with marked papillary dermal edema leading to "floating cells" • May have epidermotropism of Langerhans cells • Cells stain with CD1a, S100, langerin (CD207)	• Congenital self-healing histiocytosis: Identical findings, need clinical information • Langerin (CD207) staining distinguishes from indeterminate cell histiocytosis • Activating mutations in *BRAF* V600E in about 50% of cases (can use VE1 IHC)
Xanthomatous		
Xanthoma *Figure 5.19.18A-B*	• Dermal infiltrate of foamy histiocytes • Xanthelasma: On eyelid skin = vellus hairs and/or skeletal muscle at base of biopsy • Eruptive: Extracellular lipid + foamy histiocytes • Tuberous: Sheets/nodules of foamy histiocytes in dermis • Tendinous: Similar to tuberous	• Granuloma annulare: cells are not foamy • Balloon cell nevus: Has features of typical melanocytic nevus
Verruciform xanthoma *Figure 5.19.19*	• Verrucous architecture with papillomatosis and hyperkeratosis • Characteristic hypereosinophilic compact hyperparakeratosis with invagination into dermis ("crotch sign") • Foamy histiocytes within dermal papillae	• Verruca: Parakeratosis at tips of papillomatous areas, no foamy histiocytes • Warty dyskeratoma: Has acantholysis + dyskeratosis, no foamy histiocytes

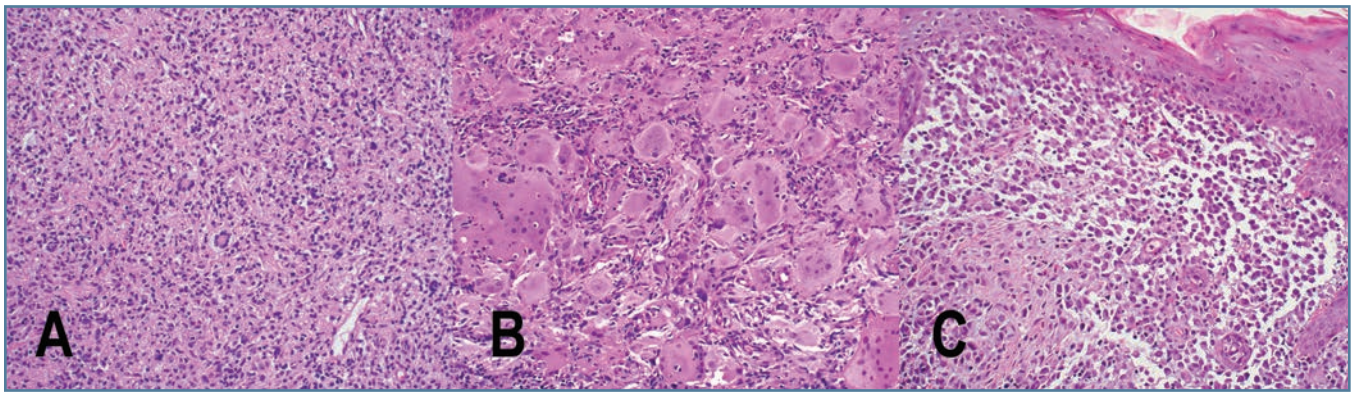

Figure 5.19.20 Histiocytic infiltrates.

Xanthogranuloma (A) is composed of sheets of foamy histiocytes with numerous Touton giant cells and admixed eosinophils. Reticulohistiocytoma (B) has a similar appearance, however, instead of Touton giant cells, there are multi-nucleated cells with "two-tone" cytoplasm that has a fine "ground-glass" rather than foamy appearance. There are fewer admixed inflammatory cells. In Langerhans cell histiocytosis (C), the cells are mononuclear with a reniform nucleus. There is often background edema and typically, eosinophils are conspicuous.

5.20 Miscellaneous Entities

DISORDERS OF EPIDERMAL MATURATION

TABLE 5.20.1 DISORDERS OF EPIDERMAL MATURATION

Name	Special Features	Differential Diagnosis/Pearls
Epidermolytic hyperkeratosis *Figure 5.20.1*	• Compact hyperorthokeratosis • Upper half of the epidermis with granular and vacuolar degeneration of the keratinocytes	• Seen in bullous congenital ichthyosiform erythroderma (BCIE), epidermal nevi (risk for child with BCIE), epidermolytic acanthoma, or just incidental finding
Acantholytic dyskeratosis *Figure 5.20.2*	Acantholysis with: • Corps ronds: Rounded basophilic cells, large nuclei, perinuclear halo (epidermal cells maturing toward granular layer in an unusual fashion, instead of "dyskeratosis") • Grains: Resemble rice grains, flattened nuclei, eosinophilic cytoplasm (the parakeratotic remnants of the dyskeratotic cells)	• Seen in Grover's disease, Darier's disease, acantholytic acanthoma, and focal acantholytic dyskeratosis
Cornoid lamella *Figure 5.20.3*	• Column of parakeratosis above an epidermis with a focus of necrotic keratinocytes and lost granular layer	• Seen in porokeratosis and all of its clinical variants
Papillomatosis *Figure 5.20.4*	• Undulations of the epidermis	• Seen in acanthosis nigricans, epidermal nevus, confluent and reticulated papillomatosis of Gougerot and Carteaud, acrokeratosis verruciformis of Hopf

METASTATIC TUMORS TO THE SKIN

TABLE 5.20.2 METASTATIC TUMORS TO THE SKIN

Name	Special Features	Differential Diagnosis/Pearls
Breast carcinoma *Figure 5.20.5A-B*	• May present with single cells infiltrating in the dermis (single-file boxcar formation or single-file invasive pattern), or as sheets of atypical cells • Glandular formation among the atypical cells • Can rarely demonstrate epidermotropism	• GCDFP-15$^+$, CK7$^+$, ER$^+$ • Inflammatory carcinoma of the breast will show atypical cells within dermal lymphatics
Lung carcinoma *Figure 5.20.6*	• May be squamous, adenocarcinomatous, or small cell type	• TTF1$^+$
Renal carcinoma *Figure 5.20.7*	• Numerous tubules and collections of clear glycogenated cells • Prominent vascular component and extravasated erythrocytes	• RCC antigen and CD10$^+$
Thyroid carcinoma *Figure 5.20.8*	• Nodule in the dermis composed of ductal spaces lined by cuboidal cells and filled with bright pink eosinophilic material	• TTF1$^+$

TABLE 5.20.2 METASTATIC TUMORS TO THE SKIN CONTINUED

Name	Special Features	Differential Diagnosis/Pearls
Colon carcinoma *Figure 5.20.9*	• Atypical columnar cells attempting to make glandular structures in the dermis • Dirty necrosis usually present in the middle	• Typically $CK20^+$, $CDX2^+$
Signet ring carcinoma *Figure 5.20.10*	• Collections of tumor cells with prominent intracytoplasmic mucin, thus nucleus is pushed to the side and resembles a signet ring	• Most commonly of gastrointestinal origin

CDX2 = caudal type homeobox transcription factor 2; CK = cytokeratin; ER = estrogen receptor; GCDFP-15 = gross cystic disease fluid protein-15; TTF1 = thyroid transcription factor 1.

ARTIFACTS AND FOREIGN BODIES

TABLE 5.20.3 ARTIFACTS AND FOREIGN BODIES

Name	Special Features	Differential Diagnosis/Pearls
Electrodesiccation artifact *Figure 5.20.11*	• Elongated keratinocytes, all oriented in the same direction • Smudged cellular appearance	
Freeze artifact *Figure 5.20.12*	• Excessive vacuolization of the keratinocytes	• Can mimic SCCIS or MIS • Key is look for desmosomes to determine if the cell is a keratinocyte or a melanocyte
Tattoo *Figure 5.20.13*	• Clumps of granular pigment deposited in the superficial reticular dermis • Variable colors	• Red tattoo ink most allergenic, may be associated with granulomatous reaction
Ochronosis *Figure 5.20.14*	• Banana-shaped orange/yellow-brownish deposits in the superficial dermis • Represents irreversible binding with collagen bundles	• Exogenous form: Application of hydroquinone or contact with phenol • Endogenous form: Alkaptonuria
Gel foam *Figure 5.20.15*	• Bluish-purplish triangular-shaped substance in lace-like arrangement and associated with granulomatous type of inflammation	• Used for hemostasis
Hyaluronic acid filler *Figure 5.20.16*	• Amorphous, acellular, bluish deposits in the dermis of variable size	• **Hyaluronic acid filler:** A glycosaminoglycan polysaccharide composed of alternating residues of the monosaccharide D-glucuronic acid and *N*-acetyl-D-glucosamine, both normally present in the human body
Calcium hydroxylapatite filler *Figure 5.20.17*	• Calcified spheres in the dermis surrounded with granulomatous type of inflammation	• Radiopaque and can be seen on X-ray and CT
Silicone *Figure 5.20.18*	• Cystic spaces and vacuoles in the reticular dermis of variable size • Surrounded by granulomatous inflammation	• DDx: Paraffinoma—Swiss cheese appearance. Cystic spaces also variable in size, very difficult to distinguish from silicone granuloma. Sometimes more sclerosis. History helps

ECTOPIC PHENOMENA

TABLE 5.20.4 ECTOPIC PHENOMENA

Name	Special Features	Differential Diagnosis/Pearls
Omphalomesenteric duct	• Squamous epithelium adjacent to columnar mucosa with goblet cells	• Seen in the umbilical area
Endometriosis *Figure 5.20.19*	• Glandular spaces surrounded by myxoid concentric fibrous stroma • Stroma may have extravasated red blood cells	• If you see glands filled with blood, think endometrial tissue

5.21 Board Fodder

HISTOPATHOLOGIC CLUES

TABLE 5.21.1 HISTOPATHOLOGIC CLUES

Name	Differential Diagnosis
Looks like normal skin at low power	• Macular amyloidosis = dull pink globules in papillary dermis • Anetoderma = need elastic stain • Argyria = subtle black deposits around vessels and ducts • Atrophoderma = dermal atrophy • Café-au-lait macule = basal layer hyperpigmentation • Connective tissue nevus = haphazard collagen bundles • Dermatophytosis/tinea versicolor = look for organisms in stratum corneum • Graft-vs-host disease = subtle interface • Ichthyosis vulgaris = hypogranulosis • Porokeratosis = cornoid lamellae • Scleroderma/morphea = thickened collagen bundles + eccrine trapping • Scleredema = increased mucin between collagen bundles • Urticaria = interstitial neutrophils • Telangiectasia macularis eruptiva perstans = mast cells around blood vessels • Vitiligo = absent melanocytes
Dome-shaped at low power	• Accessory digit = nerve bundles • Acquired digital fibrokeratoma = hyperkeratosis, pedunculated/dome-shaped • Accessory nipple = smooth muscle bundles • Accessory tragus = vellus hairs • Angiofibroma/fibrous papule = dermal fibrosis + dilated vessels + plump fibroblasts
"Square biopsy"	• Scleromyxedema = increased mucin + increased fibroblasts • Scleredema = increased mucin between collagen • Scleroderma/morphea = thick collagen + eccrine trapping ± inflammation • Necrobiosis lipoidica = layering of histiocytes and altered collagen
Parakeratosis above basket-weave orthokeratosis	• Dermatophytosis • Resolving spongiotic dermatitis

TABLE 5.21.1 HISTOPATHOLOGIC CLUES CONTINUED

Name	Differential Diagnosis
Hyperkeratosis + epidermal atrophy	• Lichen sclerosus = pale dermis ± lichenoid inflammation • Flegel's disease = columns of parakeratosis • Discoid lupus erythematosus = follicular plugging + mucin + superficial/deep inflammation
Regular acanthosis at low power	• Psoriasis = neutrophils in dry stratum corneum • Chronic spongiotic dermatitis = mild spongiosis ± eosinophils, broader rete • Squamous cell carcinoma in situ (SCCIS)/Bowen's = atypical cells, blue hue from low power • Dermatophytosis = hyphae in stratum corneum • Clear cell acanthoma = pale cells, abrupt transition to adjacent normal skin
Epidermal necrosis	• External factors: Burn, frostbite, caustic agent • Internal factors (drug, other): Erythema multiforme (EM)/Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) (basket-weave orthokeratosis, pauci-inflammatory), coma bullae (+ eccrine gland necrosis) • Vascular compromise: Vasculitis, vasculopathy • Infection: Angioinvasive fungus (+ dermal necrosis), herpes simplex virus/varicella-zoster virus (HSV/VZV) (viral cytopathic change)
No epidermis visible = deep biopsy	• Angioleiomyoma = "red ball in the dermis," smooth muscle cells + vessels • Giant cell tumor of the tendon sheath = multinucleated giant cells • Nodular fasciitis = "tissue culture appearance" + RBCs • Rheumatoid nodule = eosinophilic center with palisaded histiocytes • Gout = needle-like clefts • Hibernoma = "mulberry cells"
Pseudoepitheliomatous hyperplasia + abscess (dense neutrophils) or suppurative granulomatous inflammation (neutrophils and histiocytes)	• Blastomycosis = broad-based budding • Paracoccidioidomycosis = mariner's wheel + single yeast cells • Chromoblastomycosis = copper pennies • Coccidioidomycosis = spherules • Sporotrichosis = cigar-shaped organisms (rare to see) • Halogenoderma = need history
Grains	• Botryomycosis = Splendore-Hoeppli reaction • Actinomycosis/nocardiosis = thin filamentous organisms • Eumycetoma = thick hyphae
Giant cells	• Xanthogranuloma = Touton + mixed inflammation • Reticulohistiocytoma/-osis = pale pink/purple, ground-glass cytoplasm • Ruptured cyst = foreign-body + keratin fragments • Giant cell tumor of tendon sheath = osteoclast-like (scalloped nuclei)
Clear cells	• Clear cell SCCIS = full-thickness atypia • Clear cell acanthoma = psoriasiform + abrupt transition to adjacent normal skin • Trichilemmoma = verrucous + pale cells + pink cuticle • Paget's/extramammary Paget's disease (EMPD) = buckshot scatter of pale atypical cells • Melanoma in situ = look for pigment + nests • Metastatic renal cell carcinoma = look for hemorrhage (dermal process) • Hidradenoma = well-circumscribed dermal nodule
Eosinophilic spongiosis	• Allergic contact dermatitis = spongiosis + parakeratosis + eosinophils • Urticarial bullous pemphigoid (BP) = eosinophils line up at dermo-epidermal junction (DEJ) • Incontinentia pigmenti = scattered dyskeratotic cells • Arthropod bite reactions = deep inflammation with eosinophils

HISTOPATHOLOGIC BODIES

TABLE 5.21.2 HISTOPATHOLOGIC BODIES

Name	Features	Associations
Asteroid body	• Eosinophilic amorphous material • Stellate inclusions	• Sporotrichosis • Sarcoidosis • Berylliosis
Schaumann body	• Concentric laminated calcified inclusion	• Sarcoidosis • Other granulomatous disorders
Birbeck granules	• Tennis racquet—shaped cytoplasmic bodies seen on electron microscopy	• Langerhans cells
Dutcher body	• Pseudo-nuclear inclusions of pink material	• Immunoglobulin deposits in plasma cells
Russell body	• Cytoplasmic inclusions of pink material	• Immunoglobulin deposits in plasma cells • Rhinoscleroma • Granuloma inguinale • Syphilis
Caterpillar body	• Pale amorphous pink linear structures in epidermis • Type IV collagen	• Porphyria cutanea tarda
Civatte body	• Dull pink globules in papillary dermis	• Represent apoptotic debris • Lichen planus (LP) and other lichenoid/interface dermatoses
Kamino body	• Pink globules of various sizes in epidermis	• Spitz nevus
Cowdry A body (Lipschütz body)	• Intranuclear eosinophilic globules with margination of chromatin	• Herpesvirus infections
Cowdry B body	• Intranuclear inclusions without margination of chromatin	• Adenovirus • Poliovirus
Guarnieri body	• Eosinophilic cytoplasmic inclusions	• Smallpox
Henderson-Patterson body	• Eosinophilic cytoplasmic inclusions that fill cell	• Molluscum
Negri body	• Neuronal cytoplasmic inclusions	• Rabies
Michaelis-Gutmann body	• Concentric, laminated, calcified bodies within and external to cells	• Malakoplakia
Donovan body	• Rod-shaped intracytoplasmic bacteria • Within histiocytes	• Granuloma inguinale
Leishman-Donovan body	• Intracytoplasmic nonflagellated organism	• Leishmaniasis
Medlar body (sclerotic body)	• Copper-colored round structures within dermis	• Chromoblastomycosis
Papillary mesenchymal body	• Looks like early hair germ/bulb	• Trichoblastoma • Trichoepithelioma
Psammoma body	• Concentric laminated calcified body	• Papillary thyroid carcinoma • Benign nevi (incidental) • Meningiomas
Verocay body	• Palisaded nuclei lining up to form "picket-fence" structure	• Schwannoma/neurilemmoma

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Chapter 6
DERMATOPHARMACOLOGY

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6.1 Drug Vehicles and Absorption Mechanisms of Action

VEHICLES

Penetration of topical medications is determined by the component ingredients of the vehicle as well as the mode of application. Vehicles consist of combinations of powders, oils, and liquids; appropriate selection of vehicles can improve efficacy and compliance. Stratum corneum thickness affects absorption, requiring caution in areas such as the face and intertriginous areas. Applying topical medication to damp skin and judicious use of occlusion can enhance absorption when needed.

- Ointments: Excellent emollient, prevents transepidermal water loss and enhances absorption. Not suitable for hair-bearing areas, and patients may find ointments cosmetically unacceptable
- Creams: Cosmetically acceptable and less potent than ointments
- Lotions: Drying effect during evaporation is useful for moist dermatoses
- Solutions: Aid in drying exudative dermatoses
- Gels: Base contains alcohol. Suitable for hair-bearing areas
- Foams: Cosmetically most appealing and great ease of application. Due to specialized packaging can be cost prohibitive

VOLUME

- Fingertip unit (FTU): Amount of ointment, cream, or other semisolid form expressed from a tube with a 5-mm-diameter nozzle, applied from the distal skin crease to the tip of the index finger of an adult
- One FTU equals 0.5 grams and is enough to treat an area of skin twice the size of the flat of an adult's hand with the fingers together, i.e., a "handprint"
- Rule of hand: The area of the side of one adult hand (palm and fingers) is approximately equal to 1% of body surface area

TABLE 6.1.1 ESTIMATION OF AMOUNT, IN GRAMS, OF TOPICAL AGENT NEEDED FOR A TWICE-DAILY, 14-DAY COURSE

Location	Adult	Older Child	Younger Child	Infant < 1 Year
Arm and hand	60	40	20	15
Back and buttocks	100	70	40	20
Entire body	580	350	190	120
Face and neck	30	30	20	15
Front of chest and abdomen	100	50	30	15
Hand and fingers (front and back)	15	10	7.5	5
Leg and foot	110	60	30	20

TABLE 6.1.2 STEROID CLASS STRATIFICATION

Steroid Potency Group	Examples*
I: Highest	Betamethasone dipropionate augmented (0.05% G, O) Clobetasol (0.05% C, F, G, L, O, S, shmp, spray) Fluocinonide (0.1% C) Flurandrenolide (4 μg/cm^2 tape) Halobetasol (0.05% C, O) Diflorasone diacetate (0.05% O)
II: High	Amcinonide (0.1% O) Betamethasone dipropionate augmented (0.05% C) Betamethasone dipropionate (0.05% O) Desoximetasone (0.25% C, O; 0.05% G) Diflorasone (0.05% O) Diflorasone emollient (0.05% C, O) Fluocinonide (0.05% C, G, O) Halcinonide (0.1% C) Mometasone (0.1% O)

III: High/medium	Amcinonide (0.1% C, L) Betamethasone valerate (0.1% O) Diflorasone (0.05% C, L) Fluticasone (0.005% O) Triamcinolone (0.5% O, C)	Betamethasone dipropionate (0.05% C) Desoximetasone (0.05% C) Fluocinonide emollient (0.05% C) Halcinonide (0.1% O, S)
IV: Medium	Betamethasone valerate (0.12% F) Desoximetasone (0.05% C) Hydrocortisone valerate (0.2% O) Prednicarbate (0.1% O)	Clocortolone (0.1% C) Flurandrenolide (0.05% O) Mometasone (0.1% C, L) Triamcinolone (0.0147% spray; 0.1% C; 0.025% O)
V: Medium/low	Betamethasone dipropionate (0.05% L) Desonide (0.05% O) Flurandrenolide (0.05% C, L) Hydrocortisone butyrate (0.1% C, O, S) Prednicarbate (0.1% C)	Betamethasone valerate (0.1% C, L) Fluocinolone (0.025% C; 0.01% shmp) Fluticasone (0.05% C, L) Hydrocortisone valerate (0.2% C) Triamcinolone (0.025% O; 0.1% C, L)
VI: Low	Alclometasone (0.05% C, O), Fluocinolone (0.01% C, S, oil),	Desonide (0.05% C, F, G, L), Triamcinolone (0.025% C, L)
VII: Lowest	Hydrocortisone (0.5%, 1% C, L, O; 2.5% C, L, S), Methylprednisolone (0.25% O)	

*Key: C = cream; F = foam; G = gel; L = lotion; O = ointment; S = solution; shmp = shampoo.

TABLE 6.1.3 TOPICAL VEHICLES

Vehicle	Components
Liquids	
Lotion/solution	Powder in water (or oil)
Gel	Semisolid emulsion in alcohol base
Foam	Liquid and/or solid materials in gaseous medium
Semisolids	
Ointment	Emulsion of oil with little or no water
Cream	Semisolid emulsion of oil in water, usually with a preservative
Solids	
Powder	Finely divided particles of a solid

6.2 Topical and Systemic Corticosteroids

TOPICAL CORTICOSTEROIDS

- Utilized for their antiinflammatory, antimitotic, immunosuppressive, and vasoconstrictive properties
- Most common adverse effects of topical glucocorticoids are atrophy, striae, and acneiform eruptions
- Allergic sensitization can occur; most commonly to vehicle or preservative, but also to steroid

SYSTEMIC CORTICOSTEROIDS

- Decrease circulating lymphocytes
- Decrease T cell responsiveness to antigens
- Inhibit release of lysosomal enzymes
- Decrease response of macrophages to lymphokines
- Decrease antibody production
- Increase the number of polymorphonuclear leukocytes and diminish the numbers of lymphocytes, eosinophils, and monocytes

- **Cortisone and hydrocortisone are short-acting and have the greatest mineralocorticoid activity; cortisone has the lowest glucocorticoid activity**
- Methylprednisolone and triamcinolone are intermediate-acting
- Dexamethasone and betamethasone are long-acting with virtually no mineralocorticoid activity; dexamethasone and betamethasone have the highest glucocorticoid activity
- Risk of hypothalamic-pituitary-adrenal axis suppression is minimized in acute disease with single morning dosing mimicking normal circadian cortisol production
- **Alternate-day administration of oral steroids is advised during a tapering regimen to reduce complications of systemic therapy; all complications are believed to be reduced by alternate-day dosing except the risk of posterior subcapsular cataracts, osteoporosis, and osteonecrosis**
- Other adverse effects from systemic therapy include increased infection risk, hyperglycemia, hypertriglyceridemia, cushingoid appearance, pancreatitis, sodium retention, potassium wasting, open-angle glaucoma, myopathy, and growth retardation in children

TOPICAL CORTICOSTEROIDS IN PREGNANCY

- The use of potent/ultrapotent steroids in pregnancy has been associated with low birth weight
- Use should be limited to 300 grams with routine obstetric care

6.3 Other Immune-Modulatory Drugs

CRISABOROLE (EUCRISA)

- Topical phosphodiesterase-4 enzyme inhibitor FDA approved for treatment of atopic dermatitis
- Side effects include burning sensation

ZORYVE (ROFLUMILAST)

- PDE4 inhibitor
- Approved for the treatment of plaque psoriasis in patients aged 12 and older

APREMILAST (OTEZLA)

- Oral phosphodiesterase-4 inhibitor approved for plaque psoriasis and psoriatic arthritis. Similar efficacy to methotrexate with PASI-75 (75% or greater reduction from baseline Psoriasis Area and Severity Index score) achieved in 30-35% of patients
- Shows some efficacy for hidradenitis suppurativa
- Side effects include diarrhea, weight loss, depression

TOFACITINIB (XELJANZ)

- A JAK1/3 inhibitor
- Available as a tablet or liquid
- Janus kinase inhibitor FDA approved for psoriatic and rheumatoid arthritis
- Currently being investigated for plaque psoriasis, vitiligo, and alopecia areata

RUXOLITINIB (JAKAFI)

- JAK1/2 inhibitor
- A cream
- Approved for atopic dermatitis (mild to moderate) and vitiligo (non-segmental)
- Can be applied continuously

VTAMA (TAPINAROF)

- Aryl hydrocarbon agonist
- Approved for the treatment of psoriasis in adults.

RUXOLITINIB (OPZELURA)

- JAK1/2 inhibitor
- A cream
- Approved for atopic dermatitis (mild to moderate) and vitiligo (non-segmental)
- Can be applied continuously

UPADACITINIB (RINVOQ)

- JAK1 selective inhibitor
- Once daily tablet
- Approved for atopic dermatitis (moderate to severe)

ABROCITINIB (CIBINQO)

- JAK1 selective inhibitor
- Once daily tablet
- Approved for atopic dermatitis (moderate to severe)

BARICITINIB (OLUMIANT)

- JAK1/2 inhibitor
- Once daily tablet
- Approved for severe alopecia areata

RITLECITINIB (LITFULO)

- JAK3 and TEC Kinase Family inhibitor
- Once daily tablet
- Approved for alopecia areata ages 12 and older

6.4 Sunscreens

- Two main categories: Chemical (organic) filters and physical (inorganic) filters
- Chemical filters absorb ultraviolet light and, in their conversion from a higher energy state back down to the ground state, convert the absorbed energy into longer, lower-energy wavelengths
- Chemical sunscreens further divided into UVA and UVB absorbers
- Most common UVB-absorbing chemicals are padimate O (PABA esters), octyl methoxycinnamate, and octyl salicylate
- Most common UVA-absorbing chemicals are the benzophenones, dibenzoylmethanes, and methyl anthranilate
- Benzophenones, oxybenzone, and dioxybenzone have the broadest spectrum of absorption of the chemical sunscreens with UVB and UVA II absorption
- Avobenzone or Parsol 1789 is a dibenzoylmethane with UVA I absorption

TIP

Allergic contact allergy can occur with *p*-aminobenzoic acid (PABA) and its derivatives, which can cross-react with azo dyes, aniline, procaine, benzocaine, *p*-phenylenediamine, and sulfonamides

- **There have been increasing reports of photoallergy to benzophenones**
- An ounce of sunscreen is required to fully cover the adult body
- Sunscreen should be applied 15-30 minutes before anticipated sun exposure, every 2 hours and after swimming or sweating

SUMMARY OF SUNSCREENS

- UVA blockers
  - Benzophenones (dioxybenzone, oxybenzone, sulisobenzone)
  - Dibenzoylmethane → avobenzone (Parsol 1789), the best UVA/UVB blocker
  - Methyl anthranilate
  - Ecamsule or Mexoryl SX (Anthelios)
- UVB blockers
  - PABA
  - Cinnamates
  - Salicylates
  - Amyl p-dimethylaminobenzoate (padimate A, padimate O → PABA derivatives)
- Physical blockers
  - Titanium dioxide
  - Zinc oxide

6.5 Retinoids

- Synthetic and natural substances with vitamin A—like structure and activity
- Vitamin A exists as retinol, a vitamin A alcohol; retinal, a vitamin A aldehyde; and retinoic acid, a vitamin A acid. These three forms are interconvertible
- Precursors of vitamin A (retinal): Carotenoids, synthesized by plants and when ingested are oxidized to vitamin A
- Retinol is transported in the serum by retinol-binding proteins and transthyretin
- Retinol binds to a cytosolic retinol-binding protein for translocation to the nucleus
- **Keratinocyte differentiation is enhanced by retinoids with increased filaggrin production, increased keratohyalin granules, keratin filaments, and Odland body secretion of lipids**
- Isotretinoin reduces the size of sebaceous glands and decreases differentiation to mature sebocytes
- Retinoids normalize keratinization, leading to decreased follicular occlusion
- Retinoids directly inhibit ornithine decarboxylase and therefore lessen inflammatory hyperplasia
- First-generation synthetic retinoids include tretinoin (all-*trans*-retinoic acid [RA]) and isotretinoin (13-*cis*-RA)
- Tretinoin and isotretinoin downregulate the proliferative keratins, K6 and K16
- Second-generation synthetic retinoids include etretinate, which was replaced by its metabolite acitretin
- Third-generation (polyaromatic) retinoids include the arotinoids, tazarotene, adapalene, and bexarotene. Arotinoids have been developed to interact selectively with specific receptors
- Isotretinoin, acitretin, and bexarotene are water-soluble, with very little lipid deposition. Water-soluble retinoids are undetectable in the serum after 1 month of stopping therapy
- Etretinate is 50 times more lipophilic than acitretin with increased storage in adipose tissue

- Highly lipid-soluble etretinate lasts several years in the fatty tissues; **in the presence of ethanol (alcohol), acitretin is re-esterified to etretinate**
- Etretinate has a half-life of 100 days, in contrast to the half-life of acitretin and isotretinoin, which are 50 and 20 hours, respectively
- Acitretin is used to treat severe, pustular or erythrodermic forms of psoriasis
- Isotretinoin is used to treat nodulocystic or recalcitrant, scarring acne
- Bexarotene is used to treat mycosis fungoides

TIP

Isotretinoin may cause hypertriglyceridemia, which may manifest with eruptive xanthomas

TIP

The recommended period for contraception after acitretin therapy is 3 years

- Retinoids are used for follicular disorders, such as HIV-associated eosinophilic folliculitis, and for disorders of keratinization, such as Darier's disease or lamellar ichthyosis
- The most common serious side effects from systemic retinoids include reduced night vision, back pain, premature epiphyseal closure, elevated serum lipids and transaminases, pseudotumor cerebri **(risk increased with concomitant tetracyclines)**, and myopathy

TIP

Bexarotene has been shown to cause reversible central hypothyroidism

- Retinoid teratogenicity: Microtia, hearing loss, microphthalmia, optic nerve atrophy, acral and axial skeletal abnormalities, cardiovascular defects, hydrocephalus, microcephaly, meningomyelocele, thymic aplasia, and anal and vaginal atresia
- Fourth generation retinoid tifarotene is a RAR gamma selective agonist approved for acne in kids aged 9 and older

TABLE 6.5.1 RETINOIC ACIDS

Drug	Category	Half-Life	Metabolism	Excretion
Tretinoin	First generation	48 min	Hepatic	Bile, urine
Isotretinoin	First generation	20 hr	Hepatic	Bile, urine
Etretinate	Second generation	4 mo	Hepatic	Bile, urine
Acitretin	Second generation	2 d	Hepatic	Bile, urine
Bexarotene	Third generation	7 hr	Hepatic	Hepatobiliary
Tifarotene	Fourth generation	2-9 hours	Hepatic	Feces

TABLE 6.5.2 RECEPTOR SPECIFICITIES OF TOPICAL RETINOIDS

	RAR-α	RAR-β	RAR-γ	RXR-α	RXR-β	RXR-γ
Tretinoin (all-*trans*-RA)	+	+	+	–	–	–
Alitretinoin (9-*cis*-RA)	+	+	+	+	+	+
Adapalene	–	+	+	–	–	–
Tazarotene	–	+	+	–	–	–
Tifarotene	–	–	+	–	–	–

RA = retinoic acid; RAR = retinoic acid receptor; RXR = retinoid X receptor.

TABLE 6.5.3 RECEPTOR SPECIFICITIES OF SYSTEMIC RETINOIDS

	RAR-α	RAR-β	RAR-γ	RXR-α	RXR-β	RXR-γ
Isotretinoin (13-*cis*-RA)	–	–	–	–	–	–
Acitretin	–	–	–	–	–	–
Bexarotene	–	–	–	+	+	+

6.6 Antibiotics

Antibiotics play an essential role in the treatment of infectious and inflammatory dermatologic conditions.

PENICILLINS

- Bactericidal
  - Inhibit bacterial cell wall synthesis by blocking the transpeptidation step
  - Active against a broad spectrum of organisms: Gram-positive and gram-negative cocci, most gram-positive bacilli, and spirochetes
  - Addition of β-lactamase inhibitors (clavulanic acid, sulbactam, or tazobactam) extends spectrum of coverage
  - Most common adverse effects: Hypersensitivity reactions including mild morbilliform eruptions, delayed systemic reactions, acute generalized exanthematous pustulosis, and Stevens-Johnson syndrome
  - A history of immediate-type hypersensitivity reaction, such as urticaria, angioedema, or anaphylaxis, is a contraindication to penicillin use

TABLE 6.6.1 PENICILLINS: SPECTRUM OF ACTIVITY

Category	Name	Spectrum of Activity
Penicillin G	Penicillin G	Gram-positive cocci, gram-positive rods, gram-negative cocci, and most anaerobes
Antistaphylococcal	Nafcillin, oxacillin, cloxacillin, and dicloxacillin	Penicillinase-producing staphylococci
Broad spectrum	Ampicillin and amoxicillin (2nd generation)	*Escherichia coli, Proteus mirabilis, Salmonella, Shigella,* and *Haemophilus influenzae (β-lactamase negative)*
	Carbenicillin (3rd generation)	*Proteus, Enterobacter,* and *Pseudomonas aeruginosa*
	Piperacillin (4th generation)	*Proteus, Enterobacter, Pseudomonas aeruginosa,* and *Klebsiella*
β-Lactamase inhibitor combinations	Amoxicillin-clavulanate	Oxacillin-sensitive *Staphylococcus* aureus and β-lactamase-producing *Haemophilus influenzae*
	Ampicillin-sulbactam (IV)	Oxacillin-sensitive *S. aureus* and β-lactamase-producing *H. influenzae*, Enterobacteriaceae, and anaerobes
	Piperacillin-tazobactam (IV)	β-Lactamase-producing *S. aureus, H. influenzae, Neisseria gonorrhoeae*, Enterobacteriaceae, and anaerobes

CEPHALOSPORINS

- Bactericidal
  - Structure resembles the penicillins, possessing a β-lactam ring
  - Block bacterial cell wall synthesis through inhibition of penicillin-binding proteins that catalyze transpeptidation
  - Treat uncomplicated soft tissue infections caused by staphylococci and nonenterococcal streptococci
  - Variable gram-negative coverage depending on generation
  - **Up to 10% of patients allergic to penicillins may also exhibit similar allergic reactions to cephalosporins**

TIP

Cefaclor has been associated with an increased incidence of serum sickness in children

TETRACYCLINES

- Bacteriostatic
  - Inhibit protein synthesis by binding to the 30S ribosomal subunit
  - Effective against both gram-positive and -negative organisms: *Mycoplasma Chlamydia*, and *Rickettsia* infections
  - Have antiinflammatory properties: Decrease matrix metalloproteinase activity, inhibit leukocyte chemotaxis, and decrease proinflammatory cytokines
  - Absorption of tetracycline, **more so than** minocycline and doxycycline, is impaired by the ingestion of dairy products, calcium, and iron or zinc salts
  - **Doxycycline, excreted by the gastrointestinal (GI) tract, is the only tetracycline for use in patients with renal failure**
  - Demeclocycline and doxycycline are the most phototoxic of all the tetracyclines
  - Sarecycline is a once daily, narrow spectrum tetracycline for acne
  - Onycholysis can accompany tetracycline-induced phototoxicity
  - **Recent evidence has failed to show dental staining in children exposed to doxycycline**
  - Pneumonitis, drug-induced lupus, and serum sickness—like reactions from tetracyclines, especially minocycline, have been reported
  - Minocycline has been reported to cause blue-black pigmentation of the nails, skin (especially shins), scars, and sclerae
  - Minocycline stains the permanent teeth in adults, with a gray-green discoloration of the midportion of the tooth
  - New FDA approved tetracycline only for Acne Vulgaris: Sarecycline A narrow-spectrum tetracycline-class drug indicated for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years of age and older
  - Minocycline also comes formulated as a foam, such as Amzeeq foam 4% for acne qHS and Zilxi 1.5% qHS for rosacea

TABLE 6.6.2 MINOCYCLINE-INDUCED PIGMENTATION

Type	Description of Pigmentation	Cause
I	Blue-black pigmentation in sites of prior inflammation or scars	Iron-containing pigment granules
II	Blue-gray ecchymotic macules and patches, most commonly on the shins	Iron- or melanin-containing pigment granules
III	Diffuse brown pigmentation localizing to sun-exposed areas	Increased melanin in basal layer or dermal melanophages

MACROLIDES

- Bacteriostatic
  - Inhibit the 50S ribosomal subunit during protein synthesis
  - Antiinflammatory properties like tetracyclines
  - Azithromycin and clarithromycin are effective in the treatment of gram-negative soft-tissue infections
  - Erythromycin is effective against acne, pyodermas, erythrasma, and pitted keratolysis
  - Suitable alternative for staphylococcal and streptococcal skin infections in patients allergic to penicillin
  - **Erythromycin is known to interact with many drugs by inhibiting the cytochrome P-450 system, increasing levels of carbamazepine, warfarin, theophylline, phenytoin, and digoxin**

TIP

Cholestatic hepatitis is associated with the estolate form of erythromycin

SULFONAMIDES AND CO-TRIMOXAZOLE

- Block the synthesis of bacterial nucleic acids
- Bacteriostatic vs bactericidal depending on drug concentrations and susceptibility of target organism
- Treat pyodermas due to suspected methicillin-resistant *Staphylococcus aureus* (MRSA)
- Used for *Pneumocystis jirovecii* pneumonia prophylaxis in immunosuppressed patients
- Common cause of cutaneous side effects in patients with HIV
- **Avoid in pregnancy due to folic acid inhibition in first two trimesters and increased risk of kernicterus in the third trimester**
- Hepatic toxicity and anemia have been reported in nursing infants

FLUOROQUINOLONES

- Bactericidal
  - Inhibit DNA gyrase. **DNA gyrase is also known as topoisomerase II**
  - Effective against *Mycobacterium* species, gram-negative infections, particularly Enterobacteriaceae organisms and multiresistant bacteria
  - **Antacids decrease the absorption of fluoroquinolones and should be taken at least 2 hours after the drug**
  - **To be used with caution with medications causing QT prolongation for fear of decreasing arrhythmia threshold**
  - **Contraindicated during pregnancy and in children because of possible deposition in cartilage resulting in arthropathy**

RIFAMPIN

- Inhibits RNA synthesis by inhibiting DNA-dependent RNA polymerase
- Effective in tuberculosis and atypical mycobacterial infections
- Only drug bactericidal to *Mycobacterium leprae*
- Cutaneous leishmaniasis and rhinoscleroma also respond to rifampin
- **Reduces efficacy of oral contraceptives**

TIP

Rifampin causes orange-red discoloration of urine and tears and can permanently stain soft contact lenses

CLINDAMYCIN

- Binds to the 50S ribosomal subunit and inhibits protein synthesis
- Particularly effective against anaerobic and gram-positive organisms, including MRSA, as well as those causing deep tissue infections and toxic shock syndrome
- Evaluate for inducible clindamycin resistance when initial sensitivities show resistance to erythromycin
- Pseudomembranous colitis associated with *Clostridium difficile* toxin has been reported in up to 10% of treated patients, limiting the long-term dermatologic use of clindamycin

6.7 Antivirals

This section focuses on the agents for human herpesvirus infections and HIV-1 infection. Imiquimod and podophyllin are briefly discussed for their use in the treatment of human papillomavirus (HPV) infections.

ACYCLOVIR

- A guanosine analog that is preferentially **phosphorylated by viral thymidine kinase and inhibits viral DNA polymerase,** thereby halting viral DNA synthesis by chain termination
- Relies on the fact that thymidine kinase (TK) is produced at a higher rate in herpes-infected cells than in noninfected cells
- Useful for treatment of herpes simplex virus (HSV) infections, varicella-zoster viral (VZV) infections, and recurrent erythema multiforme eruptions secondary to HSV infection

TIP

Rapid intravenous infusion of acyclovir has been associated with reversible obstructive nephropathy

VALACYCLOVIR

- The **prodrug of acyclovir, the active metabolite,** has enhanced bioavailability and converts rapidly and completely into acyclovir

TIP

Severe and even fatal cases of thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome (HUS) have been reported in AIDS and transplant patients taking high doses of valacyclovir for cytomegalovirus (CMV)

FAMCICLOVIR AND PENCICLOVIR

- Famciclovir is the prodrug of penciclovir, which is a topical preparation
- Considered equivalent in efficacy as acyclovir and valacyclovir for HSV-1, HSV-2, and VZV
- Used for VZV in immunocompetent patients and for recurrent HSV genital infections

GANCICLOVIR

- Used to treat CMV retinitis in immunocompromised patients and for CMV prophylaxis in transplant patients
- CMV isolates resistant to ganciclovir on the basis of DNA polymerase mutations may also be resistant to foscarnet and cidofovir with prolonged therapy
- Intravenous (IV) or oral (per os, PO), but **PO has very poor bioavailability**
- Adverse effects: **Bone marrow suppression**, neutropenia, thrombocytopenia, and nephrotoxicity; worsened by concomitant administration of zidovudine (AZT)

FOSCARNET

- Noncompetitively inhibits viral DNA polymerases at the pyrophosphate-binding site
- **Does not require phosphorylation for antiviral activity**, therefore active against viruses resistant to acyclovir, famciclovir, or ganciclovir on basis of altered kinase activities
- Given only IV and in dilute solutions
- Major use is for CMV retinitis in AIDS patients
- Useful for HSV or VZV infection resistant to acyclovir and for ganciclovir-resistant CMV

TIP

Penile erosions are known to occur when using foscarnet

CIDOFOVIR

- Nucleotide analog
- **Does not require phosphorylation by virus,** but is converted by host cell kinases to a diphosphate
- **Usually active against CMV isolates resistant to ganciclovir and foscarnet**
- IV use only
- Used for CMV retinitis in AIDS patients who have failed treatment with ganciclovir and foscarnet
- Adverse effects include iritis, nephrotoxicity, and gastrointestinal disturbance

TREATMENT OF HIV-1 INFECTION

Nucleoside analogs, nonnucleoside analogs, and protease inhibitors comprise the three major categories of antiretroviral drugs for treatment of HIV-1 infection.

- Zidovudine (AZT)
  - A thymidine analog that is phosphorylated to its active form and preferentially inhibits HIV reverse transcriptase rather than human DNA polymerase
  - Bone marrow suppression with subsequent anemia and granulocytopenia is the most severe adverse effect
  - Can cause **longitudinal melanonychia,** diffuse and oral hyperpigmented macules, and trichomegaly
- Abacavir
  - A nucleoside reverse transcriptase inhibitor
  - Can lead to an abacavir hypersensitivity reaction (AHR) in approximately 5% of treated patients → can be fatal on rechallenge with abacavir
  - Pretreatment screening for *HLA-B*57-01* is recommended to reduce risk of AHR
- Protease Inhibitors
  - Block the protease enzyme responsible for final assembly of new viral proteins
  - The protease inhibitors, especially indinavir (now rarely used), have been associated with **lipodystrophy,** which manifests as abnormal fatty deposits known as the "buffalo hump" and "protease pouch"

TIP

The protease inhibitors have been associated with lipodystrophy

Several HIV medications including indinavir, zidovudine, and lamivudine have been reported to cause periungual/paronychial eruptions resulting in pyogenic granuloma-like lesions

OTHER AGENTS

- Interferons
  - Cytokines with broad antiviral, immunomodulating, and antiproliferative effects
  - Given IV, intramuscularly (IM), intralesional (IL), or subcutaneously (SQ)
  - FDA-approved dermatologic uses: Condyloma, AIDS-associated Kaposi sarcoma, and melanoma
  - Side effects: Fever, chills, headache, myalgia, arthralgia, GI symptoms (these are dose-related); granulocytopenia, thrombocytopenia, various neurotoxicities, alopecia, hepatotoxicity, and autoantibody formation
  - Interferon-induced psoriasis has been reported
- Imiquimod
  - A topical agent
  - Does not exhibit direct antiviral activity, but instead exerts its action through immunomodulation as a Toll-like receptor 7 agonist
  - Induces cytokines, most notably, tumor necrosis factor (TNF)-α, interferon (IFN)-α, IFN-γ, and interleukin (IL)-12, leading to stimulation of a cell-mediated immune response
  - FDA-approved dermatologic uses: Anogenital warts, actinic keratosis, and superficial basal cell carcinomas
  - Off-label uses: Common warts, molluscum contagiosum, lentigo maligna, squamous cell carcinoma in situ, and extramammary Paget's disease
  - Induction of vitiligo after use has been reported
- Podophyllin (Podophyllotoxin)
  - A crude cytotoxic extract from the mayapple plant that is **antimitotic and acts by arresting cells in metaphase by binding to the protein tubulin**
  - Used for the treatment of condyloma acuminatum
  - Side effects include local skin irritation

6.8 Antifungals

TERBINAFINE

- Drug structure class: Allylamine
- Fungicidal
- Inhibits squalene epoxidase and blocks the biosynthesis of ergosterol, a sterol essential to the integrity of the fungal cell membrane
- Does not interfere with synthesis of steroid hormones, prostaglandins, and drug metabolism
- Extensively biotransformed in liver; patients with liver dysfunction slow elimination by 30%
- Clinical use: Onychomycosis due to dermatophytes; tinea corporis, tinea pedis, and to a lesser degree, cutaneous candidiasis
- Side effects: Nausea, dyspepsia, stomach pain

ITRACONAZOLE

- Triazole
- **Inhibits 14α-demethylase**, blocking lanosterol conversion to ergosterol
- Highly lipophilic
- Bioavailability increased postprandially
- Clinical use: Blastomycosis, histoplasmosis, aspergillosis, candidiasis, cryptococcosis, coccidioidomycosis, sporotrichosis, superficial infections with dermatophytes, onychomycosis
- Side effects: Nausea and vomiting, hypertriglyceridemia, edema, hypertension, leukopenia, elevated liver function test (LFT) results, nephrotic syndrome
- Drug interactions: Low affinity for cytochrome P-450 leading to elevation of digoxin, cyclosporine, triazolam, midazolam
- Needs acid environment for absorption

KETOCONAZOLE

- FDA warns against use of oral ketoconazole due to risk of hepatotoxicity and adrenal insufficiency
- Mechanism similar to triazoles
- Absorption enhanced by food intake
- Highly lipophilic and keratinophilic
- Needs acid environment for absorption
- Side effects: Uncommon effects on liver (fulminant hepatitis and transient increases in LFTs)
- Inhibits cytochrome P-450

TIP

Ketoconazole side effects include gynecomastia and impotence, by interfering with androgen and glucocorticoid synthesis

FLUCONAZOLE

- **Inhibits 14α-demethylase**, blocking lanosterol conversion to ergosterol
- Clinical use: Oral, esophageal, vaginal candidiasis, cryptococcal meningitis, candidal prophylaxis in AIDS and transplant recipients, tinea corporis, tinea cruris, tinea pedis, tinea unguium, histoplasmosis, sporotrichosis, tinea versicolor
- Side effects: Nausea, vomiting, diarrhea, abdominal pain, dysgeusia
- Rarely, elevated LFTs
- Alopecia after prolonged use at 400 mg daily
- Drug interactions: Elevates phenytoin, warfarin, nortriptyline, midazolam, triazolam, and tacrolimus

VORICONAZOLE

- **First-line treatment for invasive aspergillosis**
- Dermatologic side effects include **photosensitivity** and increased risk of squamous cell carcinoma and melanoma
- Periostitis may occur with long-term use; FDA recommends discontinuation of treatment in patients with skeletal pain or radiologic findings compatible with periostitis

POSACONAZOLE

- FDA approved for invasive *Aspergillus* and *Candida* prophylaxis

GRISEOFULVIN

- **Disrupts microtubule mitotic spindle formation, causing metaphase arrest**
- Absorption enhanced by fatty meal
- Effective against dermatophytes, but not yeast and bacteria
- Indicated for tinea capitis, but *Trichophyton* is resistant
- Indicated for onychomycosis, but cure rate is low and relapse rate is high

AMPHOTERICIN

- Polyene antifungal
- Disrupts fungal cell wall synthesis through ergosterol binding and pore formation
- **Initial drug of choice for the treatment of mucormycosis**
- Phlebitis may occur due to infusion through small peripheral vein
- Patients should be monitored throughout treatment for nephrotoxicity and electrolyte abnormalities, especially hypokalemia and hypomagnesemia
- 20-50% experience severe headaches
- Photoallergy occurs and may precipitate lupus erythematosus and severe skin reactions
- **Induces** cytochrome P-450
- Ineffective against candidiasis, systemic mycoses, and *Pityrosporum* species
- Has been reported as a potential exacerbator of acute intermittent porphyria and thus is contraindicated in patients with a history of porphyria

6.9 Antiparasitics

PERMETHRIN

- Pyrethroid compound that **disables sodium transport channels in the nerve cell membrane of the parasite, leading to its paralysis**
- FDA approved for infants 2 months and older
- The preferred treatment for pregnant women

LINDANE

- An organochloride that blocks neural transmission, inducing respiratory and muscular paralysis in parasites
- Effective against scabies, pubic lice, head lice, and body lice
- Side effects from lindane include irritant contact dermatitis and neurotoxicity, predominantly **seizures (black box warning)**
- Not recommended for use in children, the elderly, or individuals weighing less than 50 kg

MALATHION

- An organophosphate **cholinesterase inhibitor**
- Used for treatment of scabies and head lice
- **Disadvantages include flammability and high cost**

IVERMECTIN

- **Blocks glutamate-gated chloride ion channels, leading to paralysis of the parasite**
- Used to treat strongyloidiasis, onchocerciasis, and crusted scabies

BENZIMIDAZOLES

- Inhibit polymerization of tubulin and microtubule-dependent glucose uptake
- Used to treat creeping eruption, cutaneous larva migrans, and larva currens

6.10 Antihistamines

- First-generation H_1 antihistamines competitively block histamine from binding to histamine receptors. Class includes diphenhydramine, promethazine, cyproheptadine, chlorpheniramine, and hydroxyzine
  - Cyproheptadine is the histamine of choice for treating cold urticaria
  - Adverse effects of first-generation H_1 antihistamines are sedation, increased appetite, dry mouth, constipation, tachycardia, dysrhythmias, and blurry vision
  - **Chlorpheniramine** is considered one of the **safest antihistamines for pregnancy**
- Second-generation H_1 antihistamines are also histamine receptor—binding antagonists
  - These include fexofenadine, loratadine, and cetirizine. Fexofenadine has few or no sedative or anticholinergic effects. Loratadine is a long-acting, minimally sedating antihistamine. Cetirizine is a low-sedation metabolite of hydroxyzine
  - **Second-generation H_1 antihistamines are first line for chronic urticaria**
- **H_2 antagonists**
  - Cimetidine and ranitidine (H_2 antihistamines) are used in dermatology. Cimetidine has suppressor T Cell-inhibitory activity by competitively blocking T Cell H_2 receptors
  - H_2 antihistamines have been reported in the treatment of mucocutaneous candidiasis, verrucae vulgaris, and condyloma acuminate (off-label use)
  - **Cimetidine also competitively inhibits dihydrotestosterone at the androgen receptor site.** Side effects include gynecomastia, impotence, and loss of libido
  - **Doxepin is a tricyclic antidepressant with H_1 and H_2 antihistamine activity.** Topical doxepin cream is used for pruritic disorders, neurotic excoriations, and factitial dermatitis; oral doxepin can cause anticholinergic side effects as well as cardiotoxic effects
  - **Cromolyn sodium blocks mast cell degranulation** and is used for controlling diarrhea in mastocytosis

6.11 Antimalarials

- The most commonly used antimalarials are hydroxychloroquine, chloroquine, and quinacrine
- Mechanism of action not well understood. They may work by intercalating into DNA, thereby blocking further transcription
- Chloroquine has immunosuppressive and antiinflammatory activity because it impairs chemotaxis of leukocytes and eosinophils, inhibits lysosomal function, and inhibits antigen-antibody complex formation

- Effective in all forms of cutaneous lupus erythematosus, dermatomyositis, other photosensitive dermatoses like porphyria cutanea tarda and polymorphous light eruption, granulomatous dermatoses, and lymphocytic infiltrates
- **High affinity for melanin-containing tissue, with a tendency to accumulate in ocular tissues such as the choroids and ciliary body**
- Most severe adverse effect is ocular toxicity with retinopathy, which is potentially irreversible
- Premaculopathy associated with changes in visual field is reversible if the antimalarial is discontinued before visual field loss
- True retinopathy is associated with "bull's eye" pigment deposition, central scotoma, and diminished visual acuity
- Only the 4-aminoquinolones, hydroxychloroquine and chloroquine, are associated with ocular toxicity
- Risk of retinopathy is greatest with chloroquine and does not exist for quinacrine
- Chloroquine and hydroxychloroquine should not be given together because of an additive effect on retinotoxicity
- Other adverse effects are hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, GI distress, and infrequent CNS effects with confusion, seizures, and restlessness
- Cutaneous adverse reactions are a **bluish-gray hyperpigmentation over the shins, face, and palate** and in the nailbeds as transverse bands caused by both hemosiderin and melanin
- Quinacrine frequently produces a yellow discoloration in the sclerae and skin, especially over the dorsal hands and feet

6.12 Cytotoxic Agents

The cytotoxic agents include alkylating agents such as cyclophosphamide, chlorambucil, and the anti-tumor antibiotics (doxorubicin and dactinomycin); and the antimetabolites, such as methotrexate, azathioprine, thioguanine, mycophenolate mofetil, and hydroxyurea. Other cytotoxic agents include 5-fluorouracil and bleomycin.

CYCLOPHOSPHAMIDE

- Nitrogen mustard derivative. Cell-cycle nonspecific producing DNA cross-linkages at any point in the cell cycle
- Treatment of choice in granulomatosis with polyangiitis
- Increased incidence of lymphoma, leukemia, bladder carcinoma, squamous cell carcinoma, and leukopenia from bone marrow suppression
- Hemorrhagic cystitis is associated with the increased risk of transitional cell carcinoma of the bladder and can occur in up to 40% of treated patients
- **Azoospermia: Rare but reported adverse reaction**

TIP

Bladder toxicity is due to the acrolein metabolite of cyclophosphamide; mesna (sodium 2-mercaptoethanesulfonate) has been used to reduce this toxic effect

CHLORAMBUCIL

- Like cyclophosphamide, it is an alkylating agent derived from nitrogen mustard
- Interferes with DNA replication and RNA transcription
- Steroid-sparing agent in the off-label treatment of vasculitis, Behçet's disease, dermatomyositis, histiocytosis X, and sarcoidosis
- Bone marrow suppression with leukopenia, oral ulcers, and infertility are notable adverse effects
- In children with nephritic syndrome or adults with a seizure history it can cause generalized tonic-clonic seizures

METHOTREXATE

- S-phase-specific antimetabolite, which competitively and irreversibly blocks dihydrofolate reductase from catalyzing the formation of tetrahydrofolate, an important cofactor in thymidylate and purine synthesis
- Used in the treatment of psoriasis and immunobullous diseases
- Most common significant adverse effect of methotrexate use is hepatotoxicity
- Excessive alcohol intake, renal insufficiency, diabetes, obesity, and higher cumulative doses of methotrexate increase the risk of toxicity
- Cumulative doses at or above 4.0 grams can risk inducing liver fibrosis and cirrhosis. Liver biopsy is the gold standard diagnostic test for methotrexate-induced hepatic toxicity but is performed only when blood evidence of hepatotoxicity is found

- Uncommonly causes acute pneumonitis and pulmonary fibrosis
- Approximately 80% is cleared renally
- Teratogenic effects on both egg and sperm production. Discontinuation of methotrexate for 3 months prior to pursuing pregnancy is recommended for men
- Trimethoprim, the sulfonamides, and dapsone, which inhibit the folic acid metabolic pathway, can lead to hematologic toxicity when combined with methotrexate
- Tetracyclines, phenytoin, phenothiazines, chloramphenicol, nonsteroidal antiinflammatory drugs (NSAIDs), salicylates, and sulfonamides can all increase methotrexate levels by displacement of plasma proteins

TIP

Methotrexate

Patients with renal disease, those using NSAIDs or trimethoprim/sulfamethoxazole (TMP/SMX), and those with no folate supplementation are at greater risk of pancytopenia; leucovorin (folinic acid), with its ability to bypass dihydrofolate reductase in the cell division pathway, is given under conditions of methotrexate-induced myelosuppression

Causes radiation recall, in which the administration of the drug causes either previous sunburn to reappear or previously irradiated skin to develop a toxic cutaneous reaction

AZATHIOPRINE

- Antimetabolite. It is a purine analog that **acts only during the S phase of the cell cycle** to prevent the formation of adenine and guanine nucleotides. Azathioprine is converted into 6-mercaptopurine, which is then converted into the active metabolite 6-thioguanine via the hypoxanthine-guanine phosphoribosyltransferase (HGPRT) pathway
- Azathioprine is also converted into several inactive metabolites via xanthine oxidase and thiopurine methyltransferase (TPMT) activity. TPMT enzyme activity should be tested prior to initiation of treatment
- Used as a corticosteroid-sparing agent in the treatment of autoimmune bullous diseases, vasculitis, and other cutaneous inflammatory diseases
- Renal transplant patients have an increased risk of lymphoproliferative malignancies and cutaneous squamous cell carcinomas because risk corresponds to the level of immunosuppression
- Hypersensitivity syndrome (fever/shock) can occur at 14 days

TIP

When either xanthine oxidase or TPMT activity is diminished, the HGPRT pathway becomes the primary pathway and excess active metabolites, toxic purine analogs, can lead to bone marrow suppression; can occur either in the setting of concomitant allopurinol use, which inhibits xanthine oxidase, or in patients with genetically low TPMT allele activity

MYCOPHENOLATE MOFETIL (MMF)

- Inhibits de novo purine synthesis
- Noncompetitively inhibits inosine monophosphate dehydrogenase (IMPDH)
- Cells dependent on the de novo pathway of purine synthesis rather than the salvage pathway are most affected by inhibition of this enzyme
- T and B cells are particularly affected by the antiproliferative activity of MMF because these cells lack a purine salvage pathway
- Mycophenolate mofetil is cleaved to mycophenolic acid after ingestion
- Liver inactivates mycophenolic acid
- GI tract and epidermis can "reactivate" the inactive form via β-glucuronidase
- Gastrointestinal side effects: Nausea, diarrhea, anorexia, abdominal cramps, vomiting, anal tenderness (more common with higher doses)
- Genitourinary side effects: Urgency, frequency, dysuria
- Reversible bone marrow toxicity (rare)
- Mycophenolate embryopathy includes eye, ear, and lip/palate abnormalities

HYDROXYUREA

- S-phase-specific cytotoxic agent, inhibits ribonucleotide reductase, an enzyme responsible for converting ribonucleotides to deoxyribonucleotides in DNA synthesis
- Side effects include anemia, hepatitis, and renal
- Poikiloderma of the dorsal hands with a band-like distribution over the fingers and toes, diffuse hyperpigmentation, and leg ulcers on withdrawal of the medication have been described

TIP

Other rare cutaneous reactions of hydroxyurea are radiation recall, acral erythema, and dermatomyositis-like reactions

FLUOROURACIL (5-FU)

- Cell-cycle-specific pyrimidine antagonist, preventing the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP) in DNA synthesis
- Has the ability to incorporate into RNA, where it has a higher affinity for rapidly proliferating tumor tissue rather than healthy tissue
- Effective as a topical therapy for actinic keratosis
- Supravenous hyperpigmentation after intravenous infusion has been reported

BLEOMYCIN

- Damages DNA by direct binding during M and G_2 phases
- Effective for dermatologic use as an intralesional therapy for cutaneous HPV infection (off-label use)
- Associated with **Raynaud's phenomenon** occurring in digits treated with intralesional therapy for periungual and plantar warts

KAPOSI'S SARCOMA TREATMENT

Several cytotoxic agents such as doxorubicin, dactinomycin, the vinca alkaloids (vincristine and vinblastine) play an important role in dermatology in the treatment of Kaposi's sarcoma.

- Doxorubicin (Adriamycin)
  - Blocks nucleic acid transcription by intercalation with DNA residues
  - Cardiac toxicity is the major side effect
- Dactinomycin (actinomycin-D)
  - Forms complexes with DNA, inhibiting DNA, RNA, and protein synthesis
- Vinblastine
  - Extract from the periwinkle plant. It is a cell-cycle-specific cytotoxic agent that arrests mitosis in metaphase by microtubule linkage
  - Vincristine is an analog of vinblastine

KLISYRI (TIRBANIBULIN)

- A novel microtubule inhibitor for the treatment of actinic keratoses
- It is applied once a day for 5 days

6.13 Immunosuppressants

CYCLOSPORIN A

- T Cell-specific immunosuppressant because it inhibits calcineurin, a cyclophilin-dependent phosphatase activated in the presence of calmodulin and calcium
- NFAT-1 travels into the nucleus of cells following phosphorylation and initiates IL-2 production, which is important for helper T Cell ($CD4^+$) and cytotoxic T Cell ($CD8^+$) proliferation
- Cyclosporin forms a complex with cyclophilin, blocking its ability to activate calcineurin, and thus preventing calcineurin from phosphorylating the transcription factor NFAT-1
- Metabolized by the hepatic cytochrome **P-450 3A4** enzyme system. Concomitant use of other drugs that inhibit or induce this P-450 isoform can lead to inappropriate circulating levels of cyclosporine
- Used to treat psoriasis, autoimmune bullous disorders, lichen planus, severe atopic dermatitis, and pyoderma gangrenosum
- Most common electrolyte abnormalities are hyperkalemia, hyperuricemia, and hypomagnesemia
- Renal toxicity risk rises with increased dosage and duration of use. Medications such as aminoglycosides, NSAIDs, amphotericin B, and vancomycin can potentiate renal toxicity when combined with cyclosporine

TIP

Adverse Effects

- Nephrotoxicity
- Reversible hypertension
- Paresthesias and dysesthesias
- Hypertrichosis
- Gingival hyperplasia
- Hyperlipidemia
- Electrolyte imbalances

6.14 Dapsone and Sulfapyridine

- Antiinflammatory activity is most effective against polymorphonuclear leukocytes. Works by **inhibiting myeloperoxidase activity and chemotactic abilities of cells**
- Dapsone and sulfapyridine treat leprosy, dermatitis herpetiformis, bullous disease of childhood, bullous systemic lupus, erythema elevatum diutinum, subcorneal pustular dermatosis, Sweet's syndrome, and pyoderma gangrenosum

TIP

Hemolytic anemia and methemoglobinemia are well-known dose-related side effects of dapsone and occur with varying degrees in all individuals

- **Hematologic toxicity is related to G6PD function**. G6PD-deficient individuals are more sensitive to the oxidative stress of dapsone metabolites
- Methemoglobinemia is not a major problem for most patients. Cyanosis is seen after levels greater than 10% with symptoms of methemoglobinemia including weakness, tachycardia, nausea, headache, and abdominal pain
- **Cimetidine and vitamin E have both been shown to provide some protection against methemoglobin formation**
- Oral methylene blue is used in emergency situations to lower methemoglobin levels

TIP

Agranulocytosis is an idiosyncratic drug reaction

- Neurologic effects are also idiosyncratic and include a predominantly motor peripheral neuropathy and acute psychosis
- **Dapsone hypersensitivity syndrome: Severe mononucleosis-like reaction, including fever, erythroderma, hepatitis, eosinophilia, and even death**
- Sulfapyridine has a similar but often less severe side effect profile
- Sulfapyridine can cause renal toxicity by crystallization in the urine

6.15 Hormone-Related Drugs

SPIRONOLACTONE

- Aldosterone antagonist that works as an antiandrogen by blocking the androgen receptor and by inhibiting testosterone and dihydrotestosterone (DHT) production
- Steroid molecule with structure closely resembling mineralocorticoids
- The primary metabolite canrenone is the active aldosterone antagonist
- Treats hirsutism, acne, and androgenic alopecia (off-label use)
- Most common and serious side effect is hyperkalemia, most likely to occur when taken with a thiazide diuretic, potassium supplements, or angiotensin-converting enzyme inhibitors or in individuals with severe renal insufficiency
- Routine potassium monitoring is unnecessary for healthy women taking spironolactone for acne
- Other adverse effect is gynecomastia
- **Spironolactone should be avoided in the first trimester of pregnancy for its antiandrogenic effects and potential for feminization of male genitalia**

FINASTERIDE

- Specifically inhibits type II 5α-reductase, which converts testosterone to DHT. This enzyme is localized predominantly in frontal to vertex scalp hair follicles and in sebaceous gland ducts
- Most common dermatologic use is androgenic alopecia in men
- Off-label use for hirsutism in women with polycystic ovary syndrome. In women, adequate contraception is required

- Infrequent reported side effects include decreased libido, erectile dysfunction and decreased ejaculate volume (type II 5α-reductase also largely found in the prostate)
- **Use is contraindicated in women of childbearing potential; pregnant women should avoid contact with tablets**

STANOZOLOL AND DANAZOL

- Synthetic derivatives of testosterone with marked anabolic properties and diminished androgenic properties
- Known to increase concentrations of select hepatic-derived plasma glycoproteins, including the inhibitor of the first component of complement
- Prophylactic treatment for hereditary angioedema
- Potent fibrinolytic activity used in treatment of cryofibrinogenemia, lipodermatosclerosis, and livedoid vasculitis
- Adverse effects include mild alopecia, hirsutism, acne, and menstrual irregularities in female patients
- Other side effects are hypertension, insulin resistance, interference with liver function, and muscle cramps

CLASCOTERONE 1% CREAM (WINLEVI)

- An androgen receptor inhibitor indicated for the topical treatment of acne vulgaris in patients aged 12 and older
- The cream is applied to the affected area twice a day

6.16 Miscellaneous Drugs

Miscellaneous drugs, including colchicine, potassium iodide, and thalidomide, are important dermatologic agents to review.

BEREMAGENE GEPERPAVEC (B-VEC)

- A topical gene therapy that delivers 2 copies of COL7A1 gene to wounds in dystrophic epidermolysis bullosa

COLCHICINE

- Alkaloid used in dermatology for its effects on neutrophils
- Has antimitotic activity
- Binds to tubulin dimers in neutrophils, preventing microtubule assembly critical for neutrophil motility and chemotaxis
- Used in the treatment of gout and familial Mediterranean fever; however, there is some evidence to suggest its usefulness in treating Sweet's syndrome, Behçet's disease, aphthous stomatitis, dermatitis herpetiformis, linear IgA bullous disease, and vasculitis
- Most common side effect is gastrointestinal distress with abdominal cramping and watery diarrhea

POTASSIUM IODIDE

- Mechanism of action not well understood
- May inhibit granuloma formation, which may contribute to its efficacy in treating cutaneous sporotrichosis
- Suppresses hypersensitivity reactions by mediating the release of heparin from mast cells
- Used to treat erythema nodosum, nodular vasculitis, and subacute granulomatosis with polyangiitis, and in some cases, erythema multiforme and Sweet's syndrome
- Can cause iododerma, acneiform or vasculitic eruptions
- Thyroid function should be assessed prior to initiating therapy with potassium iodide and periodically during treatment
- **Wolff-Chaikoff effect:** The inhibition of thyroid hormone synthesis from excess iodides that block organic iodides from binding in the thyroid; in patients with normal thyroid function, autoregulatory mechanisms allow for appropriate escape from the Wolff-Chaikoff effect; in patients with impaired autoregulatory mechanisms, the Wolff-Chaikoff effect can lead to hypothyroidism

THALIDOMIDE

- Inhibits tumor necrosis factor-α and suppresses monocyte and neutrophil phagocytosis
- Other known uses for thalidomide include HIV-associated mucosal ulceration, aphthous stomatitis, chronic cutaneous lupus erythematosus, and chronic graft-versus-host disease (GVHD)
- Peripheral neuropathy, most commonly presenting as proximal muscle weakness and symmetric painful paresthesias of the distal extremities
- A very common side effect is sedation, which is additive with other sedatives, such as alcohol and barbiturates
- Teratogenicity: Most common birth defect is underdevelopment of arms and legs, known as phocomelia; ear malformation, and gastrointestinal and urogenital defects are also well documented; peak vulnerability to thalidomide occurs between days 21 and 36 of gestation, during which only a single dose will cause the birth defects to occur
- Thalidomide is a specially restricted medication distributed through the THALOMID Risk Evaluation and Mitigation Strategy (REMS) program

TIP

Thalidomide is the drug of choice for erythema nodosum leprosum

6.17 Biologic Therapy

- Biologics refer to proteins synthesized through recombinant DNA techniques. In general, these drugs act as immunomodulating agents. They include recombinant human cytokines, humanized monoclonal antibodies, and specific molecular receptors
- Psoriasis and atopic dermatitis are currently the major target for biologic therapies

PSORIASIS THERAPY

- With regard to psoriasis therapy, there are two classes of biologics: the TNF-inhibiting drugs (etanercept, adalimumab, and infliximab) and those directed against interleukins (IL-12/23, IL-17, IL-23). These medications have a risk of serious infection including tuberculosis reactivation
  - Etanercept (Enbrel) is an immunoglobulin/receptor fusion protein. It is a human dimeric fusion protein of the TNF-α receptor linked with the Fc portion of human IgG1. It binds to TNF-α and blocks receptor binding and subsequent proinflammatory TNF-α activity. Etanercept is injected subcutaneously and is effective in treating both psoriasis and psoriatic arthritis
  - Adalumumab (Humira) is a human monoclonal antibody to TNF-α. It binds to both soluble and transmembrane TNF-α. It is given subcutaneously every other week. Adalimumab is effective for psoriasis and psoriatic arthritis
  - Infliximab (Remicade) is a chimeric monoclonal antibody directed against TNF-α. It binds to TNF-α, blocking the receptor binding and proinflammatory activity of TNF-α. Infliximab is administered intravenously and is effective for psoriasis and psoriatic arthritis. Rare association with demyelinating diseases and exacerbation of CHF
  - Certolizumab (Cimzia), an antigen-binding fragment antibody fragment conjugated with polyethylene gylcol moiety, inhibits TNF-a. Lack of Fc region minimizes placental transfer
  - Ustekinumab (Stelara) is a human monoclonal antibody that binds to the p40 protein subunit on both IL-12 and IL-23 cytokines. It is administered subcutaneously and is approved for the treatment of psoriasis and psoriatic arthritis (under Stelara)
  - Secukinumab (Cosentyx) is a human monoclonal antibody and the first biologic to target IL-17, a principal interleukin in psoriasis pathogenesis. Secukinumab is approved for psoriasis, scalp psoriasis, and psoriatic arthritis. Mucocutaneous candidiasis is a unique side effect
  - Ixekizumab (Taltz): Antibodies to IL-17A, preventing binding to IL-17 receptor
  - Brodalumab, an antibody to IL-17 receptor, is FDA approved for psoriasis
  - Bimekizumab, an antibody to IL-17A and F, is approved for psoriasis
  - The IL-17 inhibitors have superior efficacy with PASI-75 achieved in 80% of patients vs. 50-65% with anti-TNF and anti—IL-12/23 biologics
  - Guselkumab (Tremfya) is an human antibody directed against the p40 subunit of IL-23. It is approved for the treatment of Psoriasis
  - Tildrakizumab (Ilumya) is an human antibody directed against the p19 subunit of IL-23. It is approved for the treatment of Psoriasis
  - Risankizumab (Skyrizi) is an human antibody directed against the p19 subunit of IL-23. It is approved for the treatment of Psoriasis
  - Spesolimab (Spevigo) is an antibody against the IL-36 receptor approved for generalized pustular psoriasis

ATOPIC DERMATITIS THERAPY

- With regard to atopic dermatitis, there are currently two biologics that are FDA approved. Dupilumab (Dupixent) is a human mono-clonal antibody. It is the first biologic approved for atopic dermatitis ages 6 month and older As an IL-4 receptor α antagonist, it inhibits IL-4 and IL-13 signaling. Tralokinumab (sold under the names Adtralza and Adbry) is a IL-13 inhibitor. Approved for patients 18 year old and above
- Tralokinumab is now approved down to age 12
- Dupilumab is also approved for prurigo nodularis

OTHER BIOLOGICS

- Omalizumab is an IgG monoclonal antibody that inhibits binding of IgE to high-affinity IgE receptors. It is used for the treatment of chronic idiopathic urticaria. Delayed-onset anaphylaxis has been reported
- Hidradenitis Suppurativa: Adalimumab (Humira) and Secukinumab (Cosentyx) are approved for moderate to severe hidradenitis suppurativa

TIP

Anakinra (Kineret) is an IL-1 receptor antagonist indicated for the treatment of neonatal-onset multi-system inflammatory disease and rheumatoid arthritis. It is used off-label for familial Mediterranean fever syndromes and arthritis

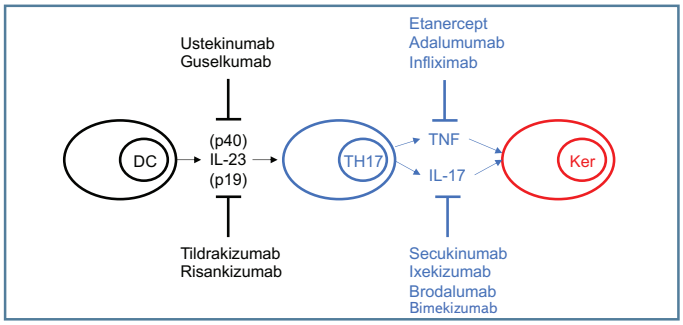

Figure 6.17.1

6.18 Drugs in Pregnancy

In 2015, the FDA replaced pregnancy risk letter categories with a new labeling system with narrative sections addressing pregnancy, lactation, and females and males of childbearing potential.

6.19 Drug Interactions

The most relevant drug interactions in dermatology involve the hepatic biotransformation pathways catalyzed by the cytochrome P-450 isoenzymes from the subfamilies CYP3A3/4. Drugs that induce CYP3A enzymes may decrease levels of drugs that act as substrates for CYP3A. The CYP3A inhibitors may increase levels and cause toxicity of drugs metabolized by cytochrome P-450. See tip box for list of P-450-altering drugs.

SPECIFIC DRUG ERUPTIONS

- Acne-inducing drugs
  - Adrenocorticotropic hormone (ACTH)
  - Steroids
  - Halogens
  - Lithium
  - Isoniazid (INH)
  - Dilantin
- Acute generalized exanthematous pustulosis (AGEP)
  - β-Lactam antibiotics
  - Calcium channel blockers
  - Cephalosporins
  - Macrolide antibiotics
  - Mercury
- Fixed drug eruptions (FDEs)
  - Tetracyclines
  - Barbiturates
  - NSAIDs, naproxen
  - Sulfonamides
  - Erythromycin
  - Pseudoephedrine hydrochloride (nonpigmenting FDE)
- Lichenoid eruptions
  - Hydrochlorothiazide
  - Antimalarials
  - NSAIDs
  - Gold
  - D-Penicillamine
  - Captopril
- Linear IgA dermatosis
  - Vancomycin
  - Lithium
  - Amiodarone
  - Captopril
  - Penicillin
- Psoriasis-inducing drugs
  - Lithium
  - Corticosteroid withdrawal
  - Propranolol (β-blockers)
  - Interferons
  - Interleukin-2
- Subacute cutaneous **lupus** erythematosus (SCLE)-like eruption
  - Azathioprine
  - Glyburide
  - Griseofulvin
  - Terbinafine
  - Hydrochlorothiazide
  - Penicillin
  - Penicillamine
  - Piroxicam
- Systemic lupus erythematosus (SLE)-like eruption
  - Anticonvulsants
  - Hydralazine
  - Isoniazid
  - Minocycline
  - Procainamide
  - Penicillin
  - D-Penicillamine
  - TNF inhibitors

TIP

Cytochrome P-450 Inhibitors/Inducers

- Inhibitors
  - Warfarin
  - Azoles
  - Verapamil
  - Erythromycin
  - Sex steroids and methylprednisolone
  - St. John's wort
  - Ciprofloxacin
  - Cimetidine
  - Cyclosporine
  - Clarithromycin
  - Diuretics (furosemide and thiazides)
  - Danazol
  - Diltiazem
  - Grapefruit juice
  - Protease inhibitors

- Inducers
  - Griseofulvin
  - Rifampin
  - INH
  - Propranolol
  - Phenytoin
  - Phenobarbital
  - Carbamazepine
  - Omeprazole
  - Retinoids
  - Tobacco

HYPERSENSITIVITY SYNDROMES

- Seen most often with anticonvulsants and sulfonamides, and less commonly with allopurinol, dapsone, and gold
- Reactions present with fever, rash with facial edema, eosinophilia, lymphadenopathy, hepatitis, and nephritis
- Pathogenesis of anticonvulsant hypersensitivity is related to the individual's inability to detoxify arene oxide metabolites of these medications, due to lack of epoxide hydrolase
- Diphenylhydantoin, phenobarbital, and carbamazepine are known to cross-react, whereas valproic acid generally does not

DRUG-RELATED PIGMENTATION SIDE EFFECTS

- Amiodarone can cause a slate-gray hyperpigmentation in photo-exposed areas. Histologically, periodic acid—Schiff (PAS)—positive yellow-brown granules are seen in macrophages in the dermis; on electron microscopy, membrane-bound structures resembling lysosomes are visualized
- Clofazimine can cause a "drug-induced lipofuscinosis"
  - Skin initially turns pink and then red-brown in lesions of patients with Hansen's disease
  - Granular pigment thought to be lipofuscin is seen in macrophages
- Chlorpromazine, thioridazine, imipramine, and clomipramine cause a sun-exposed purple-gray hyperpigmentation, with corneal and lens opacities
- Gold, silver, and bismuth can induce a slate-gray hyperpigmentation in sun-exposed areas
- Bismuth can cause pigmentation of the gingival margin
- Arsenical melanosis causes truncal hyperpigmentation with depigmented raindrop-like macules

CHEMOTHERAPY-INDUCED CUTANEOUS EFFECTS

- Acral sclerosis
  - Bleomycin
- Bullous pyoderma gangrenosum and Sweet's syndrome
  - Granulocyte colony-stimulating factor (G-CSF)
- Exacerbation of LCV (leukocytoclastic vasculitis)
  - G-CSF
  - Granulocyte-macrophage colony-stimulating factor (GM-CSF)
- Exacerbation of psoriasis
  - Interferon-α
  - Interferon-γ
  - G-CSF
  - IL-2
- Folliculitis
  - Actinomycin D
  - Daunorubicin
  - 5-FU
  - Methotrexate

- Hair loss
  - Methotrexate → flag sign
  - Busulfan
  - Thymidine kinase inhibitors (TKIs)
  - Programmed cell death 1 (PD-1) inhibitors
  - Smoothened (SMO) homolog inhibitors
- Increased growth of eyelashes (trichomegaly)
  - Interferons
- Hand-foot skin reaction (HFSR)
  - TKIs

TIP

Association between development of HFSR and increased tumor response rate / overall survival rate

- Hyperpigmentation: Localized
  - Bleomycin → flagellate or linear
  - 5-Fluorouracil → serpentine hyperpigmentation overlying the veins proximal to the infusion site
- Hyperpigmentation: Diffuse
  - Busulfan
  - Cyclophosphamide
  - Hydroxyurea
  - Methotrexate
- Hyperpigmentation: Under bandages or adhesives
  - Thiotepa
  - Topical carmustine (BCNU)
- Hyperpigmentation: Nails
  - Cyclophosphamide, bleomycin, and 5-FU → transverse bands
  - Doxorubicin causes hyperpigmentation of nails, skin, and tongue
- Interleukin-2 effects
  - Psoriasis exacerbation
  - Diffuse erythema
  - Desquamation
  - Pruritus
  - Mucositis
  - Glossitis
  - Flushing
  - Erythroderma or toxic epidermal necrolysis (TEN)-like reaction
- Neutrophilic eccrine hidradenitis
  - Clinical: Neutropenic patients with fever; erythematous papules, plaques, or nodules
  - Cytarabine (Ara C)
  - Bleomycin
- Oral mucositis
  - PD-1 inhibitors
- Papulopustular acneiform eruption
  - Epidermal growth factor receptor inhibitors (EGFRi) and HER-2 receptor
- Paronychia
  - EGFRi
- Pulmonary fibrosis
  - Bleomycin
  - Methotrexate
- Radiation enhancement and recall
  - Actinomycin D
  - Methotrexate
  - Bleomycin
  - -rubicins (dauno-, doxo-, ida-)
  - BRAF inhibitors
- Raynaud's phenomenon
  - Bleomycin with vinblastine
- Squamous cell carcinoma/keratoacanthoma
  - BRAF inhibitors
  - TKIs
- Toxic erythema of chemotherapy
  - Capecitabine
  - Cytarabine
  - Doxorubicin
  - 5-Fluorouracil (pyridoxine reduces the pain)
  - Methotrexate
- Ulceration over pressure areas
  - Bleomycin
  - Methotrexate
- Urticaria
  - L-Asparaginase
- Vitiligo
  - Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)

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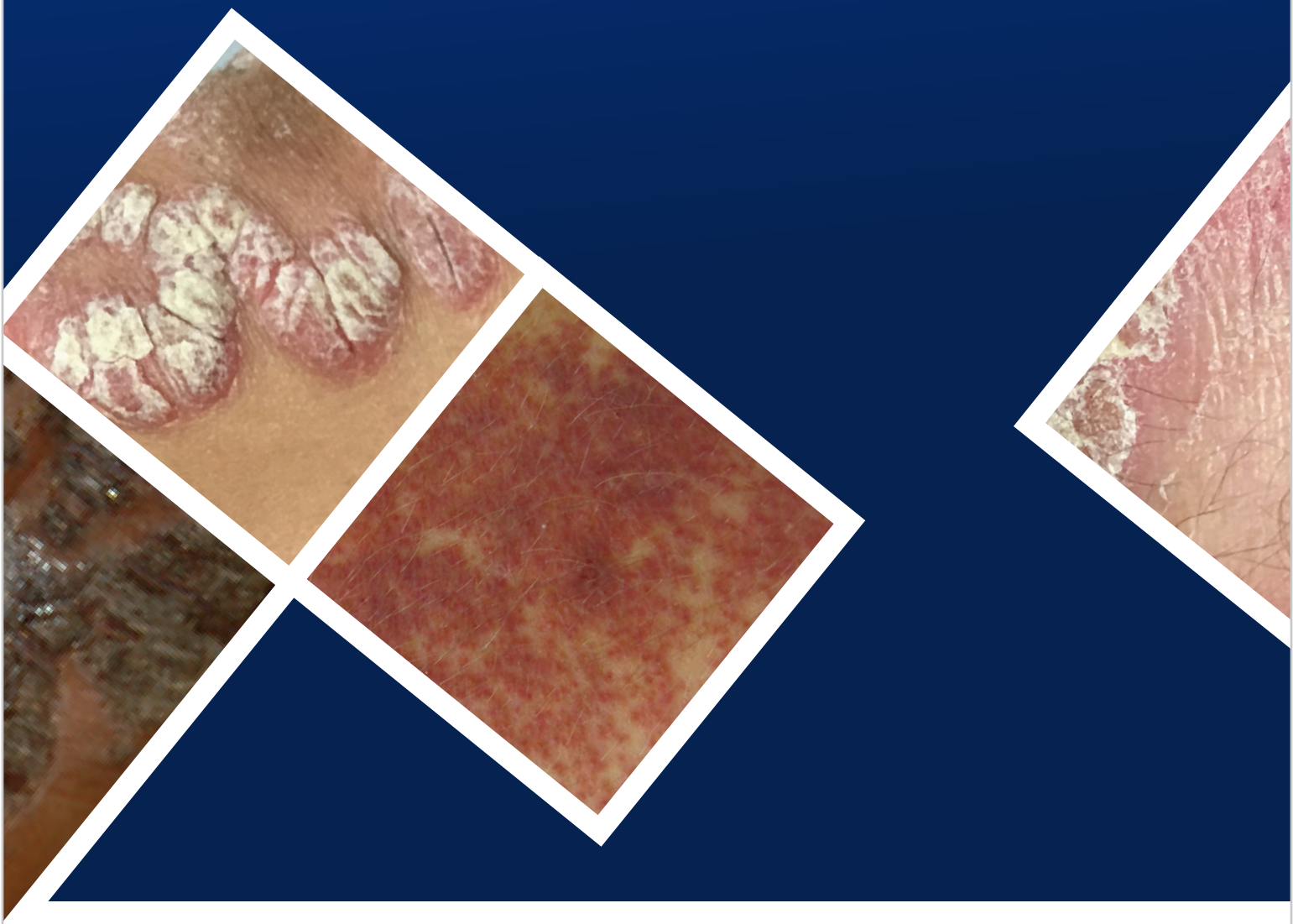

Derm In-Review

DermInReview.com

The basic, core, and applied exams will test you.....r fund of knowledge acquired during the best 3 years of your life and beyond. And here is for the beyond. We tore through a commonly sourced well, a derm pearl treasure chest of sorts, that can be used to generate test questions, the Journal of the American Academy of Dermatology CME section. Enjoy this condensed review designed to prepare you for the winter ahead

— **Adam Friedman, MD**

December 2022

Variations in genetics, biology, and phenotype of cutaneous disorders in skin of color

Variations in Skin Physiology

- Social determinants of health often play a larger role in health care outcomes than biologic or genetic factors attributed to "race"
- As of 2021, SOC makes up 39% of the US population
- Melanosome size: Black>Asian (Indian)>Latinx>Asian (Chinese)>White
- No consistent differences in transepidermal water loss, pH, lipid content, sebaceous glands with race/ethnicity
- Apocrine glands may be larger and more numerous in Black vs White cohort, which may increase risk of hidradenitis suppurativa
- Hair: Asian: fastest growth, larger diameter. Black: lower density, slower growth, ellipsoid shape, fewer cuticular layers, less elastic anchoring fibers, less strength/more breakage: prone to breakage & traction alopecia
- Dermoepidermal Junction thicker with more papillae in Black skin
- Fibroblasts: larger with more MCP-1 in Black skin, possibly related to keloid prevalence

Atopic Dermatitis:

- Filaggrin (FLG) mutation in White and Asian patients; less common among Black patients, where Filaggrin-2 (FLG2) mutation more common
- Asian patients: lichenified & hyperkeratotic phenotype, likely due to upregulated Th17 & Th22
- Black patients: Decreased Th1 & Th17, Increased IL-36: lichenified lesions

Psoriasis:

- HLA-Cw6: increased susceptibility in Asian & Middle Eastern but not Black populations
- HLA-Cw1: increased severity & generalized pustular PsO in Asian & Middle Eastern

Melanoma:

- Acral lentiginous more common in skin of color, fewer BRAF mutations
- 5-year survival: 67% Black patients vs 92% White patients

Cutaneous T-Cell Lymphoma:

- Black individuals: higher incidence, poorer prognosis

Racial Differences in Clinical Presentation		
	Morphology	Location
Atopic Dermatitis	**Black** • Papular/perifollicular • More xerosis, Dennie-Morgan lines, Palmar hyperlinearity • Periorbital hyperpigmentation • Prurigo nodularis • Lichen planus-like • Lichenification **Asian** • Psoriasiform • Lichenification	**Black** • Extensor and Truncal **Hispanic** • Truncal
Psoriasis	**Black** • Thicker plaques, more scaling **Asian** • Small plaque psoriasis variant	None

January 2023

Dysplastic Nevus

- Prevalence clinically atypical nevi (CAN): 2-8%; Histologically dysplastic nevi (HDN) up to 53% in Caucasians; highest in young adulthood
- CAN management: serial photography and digital dermoscopy monitoring
- Dyplastic nevi are not melanoma percursors. Patients with multiple atypical nevi- increased general risk of melanoma. Risk of melanoma equal in normal skin, dysplastic nevi, and common nevi.
- Molecular and Genetic Features:
- BRAF V600E mutation in common nevi, dysplastic nevi, and melanoma
- TERT promoter mutation early in melanoma; CDKN2A, PTEN, TP53 in advanced melanoma
- Constitutive MAPK pathway activation necessary for melanoma growth
- Melanoma drivers: CDKN2A, TP53, RAC1, PTEN not seen in nevi

HDN management:

- Mild-Moderate dysplasia with negative biopsy margins: re-excision unnecessary
- Growing evidence that moderately dysplastic nevi with positive biopsy margins but clinically lesion removed doesn't require re-excision
- Severe dysplasia: complete excision with 2-5mm margins

Duke University HistologicGrading System

Architectural Disorder (Mild = 0-1 criteria, moderate = 2-3 criteria, severe = 4-6 criteria)

- Junctional component nested at both edges
- Overall symmetry
- >5% of nests cohesive
- Suprabasal spread prominent or present at edge
- >50% confluence of proliferation
- Single-cell proliferation absent or focal

Cytologic atypia

(Key: Mild = 0-1 criteria, moderate = 2 criteria, severe = 3-4 criteria)

- Nuclei round or oval and euchromatic
- Nuclei larger than basal keratinocytes nuclei
- Nucleoli prominent
- Cell diameter >2x basal keratinocytes

February 2023

Disorders of Hyperpigmentation

Epidermal Hyperpigmentation:

- Ephelides (freckles)
  - Sun-induced
  - Path: normal rete ridges, increased basal layer pigment
- Lentigines
  - Lentigo simplex- early age of onset, sun exposed, elongation of rete ridges with increased basal pigment
  - Solar lentigo- later adulthood, photodamaged skin, curvy elongated rete ridges with increased pigment & more melanocytes at rete tips ("dirty socks")
  - Ink spot lentigo- reticulated pattern, dark brown/black, irregular outline; typically solitary on a background of extensive lentigines; pigment at basal layer with "skip areas" lacking pigment
  - PUVA lentigo- larger and more stellate-appearing with irregular borders; risk related to cumulative PUVA dose
- Café-au-lait Macules
  - 2.7% of infants, 36% children
  - Multiple: consider syndrome: neurofibromatosis type I or II, Legius syndrome, Noonan syndrome, McCune-Albright syndrome
  - Path: increased melanin in both melanocytes and basal keratinocytes
- Pigmentary demarcation lines (Futcher or Voight lines)
  - Develop during puberty, persist into adulthood; Can develop in pregnancy

Dermal Hyperpigmentation:

Acquired Dermal Macular Hyperpigmentation:

Lichen planus pigmentosus:

- Phototypes III-IV
- 3rd to 5th decade
- F>M
- Brown or grey-brown, sun exposed and intertriginous areas

Ashy dermatosis/Erythema dyschromicum perstans:

- Latin America
- Brown or grey-brown on trunk, neck, proximal extremities
- Erythematous border = active stage

Idiopathic eruptive macular pigmentation:

- Brown on trunk, neck, proximal extremities
- Smaller macules than LPP, EDP, AD
- Regresses over months-years

Pigmented contact dermatitis (Riehl melanosis):

- Contact derm with reticulated brown-grey macules on face, neck, upper chest +/- pruritus
- Cosmetics & fragrance

Dermal Melanocytosis:

- Path: dendritic melanocytes dispersed in the dermis

Congenital Dermal Melanocytosis ("Mongolian spot"):

- Present at birth, spontaneously regress in childhood
- Sacrococcygeal, gluteal, or lumbar, sometimes extra-sacral

Nevus of Ota:

- Ophthalmic or maxillary division of trigeminal nerve
- Ocular involvement: 60%; 10% of those have increased intraocular pressure +/- glaucoma
- Nevus of Ito: deltoid or acromioclavicular regions
- Hori's nevus: bilateral malar cheeks
- Sun's nevus: unilateral malar cheek

Mixed Hyperpigmentation:

Post-inflammatory Hyperpigmentation:

- Epidermal: brown; Dermal: blue-gray
- More common & longer lasting in darker skin tones
- Exacerbated by exposure to UV radiation or visible light
- Months to years to resolve

Melasma:

- Light-to-dark-brown macules and patches in sun-exposed areas
- Centrofacial (most common), malar, and mandibular patterns
- Young to middle-aged women with skin types III to VI
- Exacerbated by hormones (pregnancy, oral contraceptives)

Hyperpigmentation from Drugs and Heavy Metals	
Amiodarone	Slate-gray; sun-exposed
Antimalarials	Blue-gray; shins, face, palatal areas, nails Quinacrine: diffuse yellow
Clofazimine	Dark-brown; favors leprosy lesions; may initially have reddish-blue hue
Diltiazem	Reticulated slate blue, gray, brown; sun-exposed
Hydroquinone	Exogenous ochronosis: brown-black macules/papules; usually occurring over bony prominences on the face, neck, back, extensors)
Minocycline	Blue-gray or brown; skin, teeth, sclera Type I: blue-black macules in scars or inflammation on face; iron Type II: blue-gray macules or diffuse on shins & forearms distant from site of inflammation; Iron & melanin Type III: diffuse muddy brown on sun-exposed; Melanin Type IV: blue-gray in scars on back; Melanin & calcium
Zidovudine	Violaceous-to-brown longitudinal or transverse bands or diffuse on nails +/- mucosa

Chemotherapeutic agents	
Bleomycin	Flagellate erythema or hyperpigmentation upper trunk or extremities
Busulfan	Generalized + palmar creases
Cyclophosphamide	Diffuse on skin & mucosa; +/- dark pigmentation of teeth/nails
5-fluorouracil	Various patterns: Sun-exposed or irradiated areas Serpentine supravenous Serpentine on trunk Diffuse on palms Macules of palms/soles Oral mucosa and nails
Daunorubicin	Sun-exposed; transverse melanonychia
Doxorubicin	Diffuse or localized Overlying hand joints, oral mucosa, longitudinal or transverse melanonychia
Hydroxyurea	Blue-gray or brown; skin or oral mucosa; longitudinal or diffuse melanonychia
Imatinib	Diffuse or localized, blue-gray or brown, skin, hard palate, nails; hypopigmentation possible
Mechlorethamine Topical	Generalized hyperpigmentation
Methotrexate	Sun-exposed or areas of eczema

Heavy Metals	
Arsenic	Bronze hyperpigmentation anywhere, favors groin & areola; hypopigmentation within: "rain drops on a dusty road"
Bismuth	Diffuse gray; oral mucosa: accentuation at gingival border, fine granular on hard palate
Gold	Gray, limited to sun-exposed areas, periorbital involvement
Iron	Brown at infusion site due to extravasation
Lead	Gingival brown, or blue line edge of the gingiva ("lead line")
Mercury	Slate gray, predilection for eyelids and skin folds (topical)
Silver	Gray, prominent in sun-exposed

Nail melanoma dermoscopy:

- Pigmented band width [2/3 the nail plate
- Gray or black color
- Irregularly pigmented lines
- Hutchinson's/micro-Hutchinson's signs (periungual spread of pigment)
- Nail dystrophy
- Granular pigmentation

Hyperpigmentation Treatments	
Topical Agents	
Hydroquinone	Inhibits enzymatic oxidation of tyrosinase (normally converts L-DOPA to melanin) Covalently binds histidine & interacts with copper at active site of tyrosinase Destroys melanocytes, degrades melanosomes, inhibits DNA and RNA synthesis
Hydroquinone, retinoid, steroid combo	Retinoids decrease melanosome transfer, inhibit tyrosinase transcription, & interrupt melanin synthesis Corticosteroids: nonselective suppressors of melanogenesis
Azelaic Acid	Interferes with DNA synthesis, inhibits mitochondrial oxidoreductase, competitively inhibits tyrosinase, & decreases free radical formation
Kojic Acid	Inhibits tyrosinase, antioxidant
Ascorbic Acid (Vitamin C)	Protects against UVA-dependent melanogenesis; interacts with copper ions at tyrosinase active site, reduces oxidized dopaquinone
Niacinamide	Inhibits transfer of melanosomes to keratinocytes
Arbutin	Induces reversible tyrosinase activity
Bakuchiol	Modulates retinoic acid receptor genes, upregulates collagen & ECM synthesis enzymes, may block alpha MSH activation & tyrosinase
Thiamidol	Competitive tyrosinase inhibitor; not converted to quinone: no leukoderma
Tranexamic Acid	Prevents plasminogen binding to keratinocytes

Systemic Treatments:

Tranexamic Acid

- Effective but recurrence following cessation
- Induce remission, then topicals for maintenance
- Side effects: GI discomfort, menstrual irregularities
- Absolute contraindications: hypercoagulability (kidney dz, malignancy, pro-coagulant therapy, OCPs, hx of thromboembolic dz)
- Relative: hormonal therapy, recent COVID-19 infection, smoking

Low dose isotretinoin (20 mg daily) for Lichen Planus Pigmentosus

Polypodium leucotomos extract

- improves effect of hydroquinone & sunscreen in melasma

March 2023

Risk of Melanoma and Non-Melanoma Skin Cancer with Immunosuppressants

Immune System Effects on Tumors

- Th1 CD4 T-cells activate CD8 T-cells à tumor destruction
- Th2 CD 4 T-cells activate B-cell abs à down regulate tumor defense à tumor destruction
- Tregs block CD8 activation via CTLA-4 & inhibit NK cellsà tumor growth
- IL23 activates Th17 à proinflammatory cytokines & downregulate CD8 à tumor growth

UV radiation induced immunosuppression

- Disrupts Langerhans antigen presentation à Th2 & Treg upregulation à immunosuppression & tumor growth
- Stimulates IL-10 à tumor growth
- Production of reactive oxygen species à DNA damage à tumor growth

Transplant Recipients

- 65-250x risk of SCC, 10x BCC, 80-200x Kaposi sarcoma, 0-8x melanoma, 70x Merkel cell carcinoma
- Higher dosages, longer duration à higher risk of NMSC

Systemic Calcineurin Inhibitors (CNIs)

- Strongest link to skin cancer
- Examples: Cyclosporine, Tacrolimus
- Dose dependent: No risk with short term use (<1-2 years as in psoriasis)
- Comparable risk to cyclosporine
- Lower doses may also have skin cancer effect and even with just past exposure 4-6x increased risk
- Lifelong recommendation of skin cancer screening with for inflammatory condition > 5 years with azathioprine

Thiopurines

- Antimetabolites that block purine synthesis, ex. Azathioprine

Screening for nontransplant patients	
Drug	**Screening Recommendations**
Calcineurin Inhibitors (Cyclosporine, Tacrolimus)	>12 months continuous exposure >2 years intermittent exposure Cyclosporine >5 mg/kg/d Preexisting risk factors: ex: multiple immunosuppressants
Thiopurines (Azathioprine)	5+ years of therapy
Systemic Corticosteroids	Numerous (10-15) courses Extended course (several months) Additional Immunosuppressant
Methotrexate	1+ year of high cumulative dose (5-8g) Prior skin cancer Risk factors for melanoma
Alkylating Agents (cyclophosphamide)	2+ years of treatment Remote history of cyclophosphamide
TNF Inhibitors	Yearly screen of all patients
Abatacept (CTLA-4 simulator)	Avoid in patients with melanoma risk factors
Natalizumab (Integrin inhibitor)	Assess risk of NMSC (increased risk but insufficient evidence to recommend screening)
Ibrutinib (BTKi)	Screen in lymphoproliferative dz
JAK Inhibitors	Screen all Pso, RA. Screen myeloproliferative dz pts on ruxolitinib

Screening for Transplant Recipients	
No history skin cancer of AK	Yearly
History of AK or 1 low-risk NMSC	Q6 months
Multiple NMSC or high-risk SCC	Q3 months
Pretransplant melanoma	Q6 months
Rapidly developing, aggressive, or metastatic skin cancer	Q4-6 weeks

April 2023

Skin Disorders and Interstitial Lung Disease (ILD)

ILD risk assessment:

- High-risk disease
- Persistent symptoms: cough, dyspnea
- End-respiratory crepitations
- Finger clubbing
- Other: GERD, smoking

If present, order High-resolution CT & Pulmonary Function Test

High-Risk Diseases (screen with HRCT & PFTs even if asymptomatic):

- Diffuse Systemic Sclerosis
- Dermatomyositis
- Antisynthetase Syndrome
- Sarcoidosis
- ANCA Vasculitis

Skin Diseases associated with ILD	
Disease	**Notes**
Autoimmune Connective Tissue Diseases	
Systemic Sclerosis	Risk factors: diffuse SSc, African American, older age onset, rapidly progressive skin disease, Abs: Scl-70, RNA-Pol III, Ro52, anti-fibrillarin
Dermatomyositis	Risk factors: Abs: MDA5, Ro52
Antisynthetase Syndrome	Risk factors: African American ethnicity, Abs: EJ, PL12, PL7
Mixed Connective Tissue Disease	Abs: Ro52
Lupus Erythematosus	Higher risk: Long-standing (>10 y), older age, sclerodactyly, Abs: U1RNP
Granulomatous Diseases	
Sarcoidosis	Risk factors: nonresolving inflammation, discontinuation of infliximab
Granulomatous Drug Reactions	Methotrexate, Nitrofurantoin, Pantazocine
Vasculitis	
ANCA vasculitis	Higher risk: microscopic polyangiitis, MPO-ANCA, elevated ESR & CRP
Kawasaki Disease	Risk factors: elevated ESR & CRP, periungual desquamation
Other Autoimmune and Inflammatory Diseases	
Subepidermal Bullous Diseases	Rare in MMP, BP, LABD
Pyoderma Gangrenosum	Higher risk in IBD & smokers Rare, but lung most common extracutaneous site
Neoplastic and Lymphoproliferative	
Langerhans Cell Histiocytosis	Higher risk in smokers
Lymphomatoid Granulomatosis	EBV-driven B-cell disorder: lung, skin, other organs
Rosai-Dorfmann Disease	Rare (<3%)
Kaposi Sarcoma	Up to 45% lung involvement. Risk: HIV with low CD4
Immumoglobulin G4-related Disease	Risk: smokers & SSA ab
Light-Chain Deposition Disease	Secondary to lymphoproliferative disease

High-risk Diseases

Systemic Sclerosis

- ILD and Pulmonary Hypertension (PH) leading causes of mortality
- Risk factors: dcSSc, topoisomerase I ab, severe skin disease (ie, fibrosis, digital ulcers, capillaroscopy abnormalities), male sex, African American ethnicity, older age, longer disease duration
- ILD early complication: first 3 years in half of patients
- Very Early Diagnosis: Raynaud's, puffy fingers, nailfold capillary changes, high-titer ANA and/or SSc-specific abs. Opportunity to detect internal involvement early
- All SSc: baseline HRCT and PFT (with DLCO), serial PFTs every 3-12 months for first 3-5 years
- Treatment: Mycophenolate mofetil first-line

Dermatomyositis

- ILD ~40% of patients, higher in clinically amyopathic, antisynthetase syndrome, and anti-MDA5
- Risk factors ILD-related mortality: older age, higher CRP, anti-MDA5 ab
- High-risk patients: baseline HRCT + PFTs, if negative: monitor symptoms regularly
- Mycophenolate mofetil + systemic glucocorticoids first-line therapy

Systemic Lupus Erythematosus

- Pleural disease most common, ILD and/or PH should not be overlooked
- Higher risk: Older, longer duration, overlap syndrome (sclerodactyly, SSc capillary abnormalities, U1-RNP, Ro52 ab)

Mixed Connective Tissue Disease

- Up to 78% have lung involvement, ILD in >50% and PH in ~25%
- Presence/severity of ILD and/or PH: higher mortality
- Baseline HRCT + PFTs, regular monitoring

Sarcoidosis

- Lung disease (airway obstruction +/- ILD) ~90%
- Screening: CXR, PFTs (including DLCO), ECG
- Risk factors: African American ethnicity, older age (40 years), stages III-IV lung sarcoid, internal organ involvement
- Time-limited disease: e. nodosum, Löfgren's syndrome; Higher risk: lupus pernio
- Systemic glucocorticoids and MTX first-line therapy

ANCA Vasculitis

- Screen all patients
- Eosinophilic granulomatosis with polyangiitis: severe recalcitrant asthma
- Vasculitis stage of EGPA & granulomatosis with polyangiitis (GPA)/microscopic polyangiitis (MPA), lung affected up to 55% of patients
- Risk factors: MPA, myeloperoxidase antibodies, older age (>65), male sex

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May 2023

Update on viral-induced cutaneous lymphoproliferative disorders, Epstein-Barr virus and human T-lymphotropic virus type-1 cutaneous manifestations

Lymphoproliferative Disorders

Hydroa Vacciniforme-like Lymphoproliferative Disorder

- Associated with Epstein-Barr Virus
- Can progress to systemic lymphoma
- Classic HV/early stage: indolent, self-limited photodermatosis in children
  - Erythema, vesicular papules, bullae, and ulcers on sun-exposed areas, varioliform scars
  - Systemic symptoms absent; tends to spontaneously regress
- Aggressive/late stage: aggressive systemic disorder with lymphadenopathy + hepatosplenomegaly
- Progression to advanced disease heralded by:
  - Lack of improvement with photoprotection
  - Worsening of facial and lip swelling
  - Systemic complications

- Histology:
  - Classic: spongiosis, vesiculation, necrosis, diffuse atypical lymphohistiocytic infiltrate with neutrophils
  - Aggressive: atypical T-cell infiltrate + monoclonal rearrangement of the T-cell receptor (TCR) genes and EBV expression
  - Advanced cases: ulceration +/- epidermotropism
- No guidelines for treatment:
  - Early stage- conservative treatment (sun protection, topical steroids)
  - Systemic involvement: antivirals (acyclovir/valacyclovir), immunonodulators (IFN-a, thalidomide, hydroxychloroquine, IVIG, IL-2), steroids, chemotherapy, radiotherapy, allogeneic stem cell transplant

Primary Cutaneous Extranodal Natural Killer/T-cell Lymphoma (ENKTCL):

- Highly aggressive lymphoma prevalent in Asia and Latin America
- Historically "midline lethal granuloma"
- Extranodal lymphoma of NK or T-cell lineage, characterized by angiodestruction, tumor necrosis factor, cytotoxic phenotype, and strong association with EBV
- Clinically: ulcerated mass in the nasopharyngeal mucosa, destroying nasal septum
- Hemophagocytosis in approximately 10% and associated with lethal outcome
- Histology: Diffuse malignant lymphocytic infiltrate with necrosis; Ulceration, epidermotropism, angiocentricity, and angiodestruction often; NK phenotype (CD2, CD56, CD7, CD3); EBER+ in all cases

Adult T-cell Leukemia/Lymphoma:

- Aggressive peripheral T-cell lymphoma subtype associated with HTLV-1 infection with 5 clinical subtypes:
  - **Acute** (50% of patients): significant blood lymphocytosis with flower cells, LA, hypercalcemia, increased LDH, hepatosplenomegaly, eosinophilia, lytic bone lesions, cutaneous manifestations
  - **Chronic** (favorable/unfavorable forms): absolute lymphocytosis, LA, cutaneous lesions without internal organ involvement
  - **Smoldering:** asymptomatic or manifest mild cutaneous plaques. Best outcome overall
  - **Lymphomatous:** LA and no peripheral blood lymphocytosis with/without extranodal lesion
- Skin findings: Polymorphous patches, papules, plaques, nodules, tumors, erythroderma, purpura. Plaques common in smoldering type. Papules, nodules, tumors common in leukemic/lymphomatous. Erythroderma worst prognosis, followed by nodulotumoral.
- Diagnosis: serology (+ for HTLV-1) + classic histology, lymphocytosis with abnormal flow: abnormal CD4 predominance, CD25+
- Treatment: Zidovudine + IFN-a, chemotherapy, allogeneic HSCT

Lymphomatoid Granulomatosis

- EBV-driven B-cell lymphoproliferative disease
- Commonly involves lungs >> CNS, skin, kidney, and liver
- Skin lesions at any stage; ~1/3 skin initial manifestation
- Typically lymphohistiocytic panniculitis: Multiple erythematous, dermal, subcutaneous papules/nodules +/- ulceration on extremities/trunk
- No consensus guidelines for treatment

Epstein-Barr virus-positive mucocutaneous ulcer

- Rare, indolent, assoc. w/ immunosuppression, isolated to skin & mucosa
- Must distinguish from other aggressive lymphomas
- Isolated, shallow, and well-delineated ulcer of oropharyngeal mucosa most commonly (>70% of cases)

Non-Neoplastic/Preneoplastic Conditions associated with EBV and HTLV-1

Epstein-Barr Virus

- Infectious Mononucleosis
- Exudative pharyngitis, cervical lymphadenopathy, rash with β-lactam antibiotics
- Diagnosis: serum heterophile antibodies (Monospot test)
- Acute EBV infection > infectious mononucleosis
  - >70% of exposed adolescents
  - Self-limited, fevers (2-3 weeks), pharyngitis associated with exudate (30% cases), and cervical adenopathy

Severe Mosquito Bite Allergy

- Mosquito bite > CD4+ T-cells react to saliva > reactivation of latent EBV in NK-cells > inflammation > hemorrhagic skin lesions (blister, induration, ulcer, necrosis)
- Systemic symptoms (fever, LAD, elevated LFTs)
- Prolonged symptoms or late onset (>9 years old): risk of hemophagocytic lymphohistiocytosis, severe forms of CAEBV, aggressive NK-cell leukemia, ENKTCL

Chronic Active EBV Disease (CAEBV)

- Systemic lymphoproliferative disorder: polyclonal, oligoclonal, or monoclonal EBV-positive T or NK cells
- Recurrent EBV-related systemic symptoms >3 mo
- Hypersensitivity to mosquito bites & prominent lip or periorbital edema
- Fever, LA, hepatosplenomegaly, anemia, thrombocytopenia, diarrhea, uveitis
- Risk of lymphoma/leukemia. Poor prognosis: age >8 years + thrombocytopenia

Lipschutz Ulcer

- Primary EBV infection, painful ulcers of external genitalia of nonsexually active female adolescents
- Ulcers large (>1 cm), deep, purple-red halo + necrotic base with greyish exudation or grey-black adherent scale, symmetric ("kissing phenomenon")
- +/- preceding flu-like symptoms or mononucleosis, Lip swelling, inguinal LAD
- Severe pain, dysuria almost always
- Single episodes; heal in 2-6 weeks without scar
- Treatment symptomatic: prednisone or topical steroids

Gianotti-Crosti Syndrome (Papular Acrodermatitis of Childhood)

- Self-limited, asymptomatic symmetric monomorphic edematous papules on face and dorsal hands in young children +/- generalized LAD
- Various viral triggers. EBV one of most frequent

June 2023

Immunotherapy for keratinocyte cancers.

Part I: Immune-related epidemiology, risk factors, pathogenesis, and immunotherapy management of keratinocyte cancers

Keratinocyte Carcinoma immune surveillance "3 Es"

- **Elimination phase** - Immune system destroys cancer cells: cytokine production, innate/adaptive immune responses (cytotoxic T cells)
- **Equilibrium phase** - Balance between cancer cells and immune system: some cancer avoid detection- cells reduce MHC-I expression, secrete inhibitory proteins
- **Escape phase** - cancer cells resist immune destruction -->to clinically visible KCs

Immunotherapy management of keratinocyte cancers

- **Topical** - Imiquimod: activates TLR-7 pathway, stimulates innate immune response; superficial BCCs, off-label for SCCis
- **Systemic** - PD-1 inhibitors (cemiplimab, pembrolizumab): increase CD8+ T cells
  - Pembrolizumab: advanced SCC; Cemiplimab: locally advanced/metastatic BCC treated with Hh pathway inhibitor

Special patient populations: *Considerations: compromised immune systems (HIV, hematologic malignancies, autoimmune disease, chronic wounds), treatments affecting immune function (solid organ transplant recipients)*

- *Possible worse outcomes-reduced response rates, transplant rejection. ICI may cause or worsen psoriasis*

June 2023

Immunotherapy for keratinocyte cancers.

Part II: Identification and management of cutaneous side effects of immunotherapy treatments

Cutaneous adverse effects (CAEs):

Topical or Intralesional Immunotherapy:

- **Imiquimod:** pruritus, inflammation, eruptive pustular dermatosis, psoriasis, lupus erythematosus-like reaction, eruptive keratoacanthoma
- **Talimogene laherparepvec (T-VEC)**: oncolytic herpes virus, intralesional for metastatic CSCC (off-label); no reported CAEs; risk of herpes transmission (contact precautions, treat with acyclovir)

Systemic Immune Checkpoint Inhibitors:

- 6%-32% of patients
- Onset: <1 month to >6 months
- Mild to moderate, rarely severe
- Majority eczematous, lichenoid; others- psoriasis, bullous pemphigoid
- Eruptive KAs may mimic primary KC; biopsy to avoid misdiagnosis
- All immune-related AEs associated with survival benefit

Treatment:

- **Eczematous** - systemic steroids, dupilumab. Avoid UVB (risk of carcinogenesis)
- **Lichenoid** - acitretin, systemic steroids, cyclosporine (impact on antitumor effect uncertain), infliximab
- **Bullous** - doxycycline (controversial- gut microbiome alteration), rituximab recommended (NCCN, Society for Immunotherapy of Cancer), dupilumab effective (particularly in melanoma)
- **Psoriasiform** - Moderate: apremilast. Severe: methotrexate, cyclosporine, biologics (secukinumab, guselkumab, risankizumab), acitretin
  - Avoid Ustekinumab, UVB (risk of CSCC)
  - Data IL12A, IL17A inhibitors do not affect survival for some malignancies (KCC needs study)
- **Eruptive squamous atypia** - Acitretin, topical/intralesional steroids

July 2023

Dermatology workforce in the United States.

Part I: Overview, transformations, and implications

- Overall shortage, especially rural areas
- Higher density in urban; disparities rural
- Uneven distribution: pediatric dermatologists, Mohs surgeons
- Increasing female presence, underrepresented in Mohs surgery and senior academic positions
- Limited racial/ethnic diversity; underrepresentation of Hispanic and Black dermatologists in academic and non-academic settings and Mohs surgeons
- Low LGBT representation to address needs of LGBT patients

Demographics and Diversity of Leadership in Dermatology

- **Female Dermatologists:** Well-represented as junior faculty, residency directors. Underrepresented in advanced roles: department chairs, fellowship leaders, academic speakers, professional organizations. Fewer publications, citations vs male counterparts
- **Black and Hispanic Dermatologists:** Underrepresented in academia, lacking leadership roles in Mohs Surgery. Limited senior roles, hindering mentorship, advocacy, care for vulnerable groups

Insurance Acceptance by Dermatologists

- Low Medicaid acceptance worsens access for underserved minorities.
- Male dermatologists bill more Medicare services, particularly procedural
- Female dermatologists conduct extended visits, limiting volume.
- Pattern less pronounced in academics and pediatric dermatologists

Trends in Dermatology Practice Models

- Dermatologists mostly in single, multispecialty private practices
- Mohs surgeons, pediatric dermatologists more in academic centers (vs general dermatologists). New graduates less likely to go solo, prefer academic settings
- Rising consolidation through private equity (PE) acquisitions- enhances efficiency, provides capital, raises concerns about prioritizing profits (focus on elective procedures, NPC employment, retaining highly reimbursed services- Mohs surgery).

July 2023

Dermatology workforce in the United States

Part II: Patient outcomes, challenges, and potential solutions

Availability: Dynamic Interaction Between Supply and Demand for Dermatologic Care

- Better outcomes with higher dermatologist density: lower melanoma mortality. Rural: later stage melanoma diagnoses, fewer biopsies, poorer outcomes. Merkel cell carcinoma lower survival
- Potential Solutions for Rural, Underserved Areas: Financial incentives, recruitment, telehealth, Nonphysician clinicians: (NPCs), primary care physicians to fill gaps in care- requires careful oversight/ training to maintain care quality

Accommodation: Delivery of Care Serving All Patients in Their Community

- Barriers for Underserved Populations: Racial minorities, Medicaid patients, inmates face significant barriers, delayed treatment, poorer outcomes. Underrepresented racial minorities (URMs) use dermatology services less, have worse outcomes, lower melanoma survival rates
- Insurance and Access Issues: Declining Medicare, Medicaid reimbursements challenge optimal care. Low Medicaid acceptance->disparities
- Solutions for Improving Access: Academic institutions with higher Medicaid acceptance crucial for socioeconomically disadvantaged populations.
- Increase number of academic dermatologists- shortage of academic dermatologists due to bureaucracy, lower salaries, lack of mentorship

Appropriateness: Dermatologic Care Adequacy, Quality, and Effectiveness

- Non-physician clinicians (NPCs) increase access often perform more biopsies than needed, reducing cost-effectiveness. Higher number needed to biopsy to diagnose skin cancers, raising healthcare costs, delays

August 2023

Part I: Cutaneous manifestations of cardiovascular disease
General dermatological signs of cardiac disease

- **Edema:** associated with right-sided heart disease, pulmonary hypertension, ischemic cardiomyopathy, congenital heart disease
- **Cyanosis:** linked to right-to-left shunt in congenital heart disease, arteriovenous malformation, reduced cardiac output
- **Clubbing:** a/w cyanotic congenital heart disease, cor pulmonale, secondary polycythemia, chronic congestive heart failure, pulmonary disorders
- **Diagonal earlobe crease:** associated with coronary artery disease, peripheral vascular disease
- **Quincke pulse:** Visible pulsation of capillaries in nail beds/lips; indicates severe aortic valve insufficiency
- **Xanthoma and corneal arcus:** corneal arcus=lipid deposits in cornea; both related to hyperlipidemias

Cholesterol Embolization Syndrome (CES):

- Aka blue toe syndrome
- dislodged atherosclerotic plaque--> ischemia, infarction, necrosis.
- High mortality (60-80%).
- Common in men, older individuals, post-invasive procedures, spontaneous plaque eruption, anticoagulation therapy
- Cyanosis, ulcerations, gangrene, necrosis, blue toe syndrome (tender, cool, blue or purple toes- normal pulses), livedo racemosa, erythematous nodules
- Systemic involvement: kidneys, heart, other organs
- **Management:** supportive care, treat cardiovascular risk factors, anticoagulation/thrombolysis controversial

Lipid disorders:

- **Tendinous Xanthomas:** Firm nodules on tendons, associated with familial hypercholesterolemia (FH), dysbetalipoproteinemia
- **Tuberous Xanthomas:** Red-yellow nodules on pressure areas (elbows, buttocks) linked with FH, familial dysbetalipoproteinemia (FD)
- **Eruptive Xanthomas:** Small, yellow papules with erythematous borders, seen in types I, IV, V hyperlipoproteinemia
- **Planar Xanthomas:** Yellow/orange macules/plaques on neck, palms, chest. Palmar xanthoma hallmark of FD

Cardiac Amyloidosis

- Causes: primary AL amyloidosis (most common type, a/w plasma cell dyscrasia, worst prognosis, often fatal within six months post-heart failure onset), secondary amyloidosis, familial amyloidosis, senile systemic amyloidosis
- Nontraumatic ecchymoses, periorbital pinch purpura, petechial eyelid lesions
- Waxy papules, nodules, macroglossia, nail dystrophy, cutis laxa
- Heart Failure: restrictive cardiomyopathy (bilateral lower-extremity edema, abdominal bloating, shortness of breath, possible arrhythmias)
- **Diagnosis:** Endomyocardial biopsy or non-cardiac tissue biopsy (Abdominal fat pad biopsy highly sensitive for AL amyloidosis) plus supportive echocardiographic findings. Skin biopsies of purpuric lesions may show dermal, subcutis amyloid deposition

Cardiac Myxomas

- Rare cardiac tumors in adults
- 75% arise from left atrium, more common in women
- 80% sporadic; 20% genetic; 5% associated with Carney complex
- Generally benign. Complications- valvular obstructions or pulmonary hypertension
- Weight loss, fever, fatigue, anemia, finger clubbing, valvular obstruction, pulmonary edema, chest pain, symptom relief upon position change- differentiates from conditions like infective endocarditis. Cutaneous symptoms due to embolic fragments- splinter hemorrhages, petechiae, livedo reticularis
- Diagnosis: transesophageal echocardiography (TEE-superior), transthoracic echocardiography (TTE)
- **Treatment:** surgical removal

Other cardiac conditions with mucocutaneous findings

- **Infective Endocarditis:** Bacterial/fungal infection (Staphylococcal aureus, Streptococcal species); splinter hemorrhages, Osler nodes, Janeway lesions; diagnosis based on Duke criteria.
- **Acute Rheumatic Fever:** Post-streptococcal infection in children; subcutaneous nodules, erythema marginatum; diagnosis using Jones criteria
- **Kawasaki Disease:** Unknown etiology, suspected infectious cause; common in Japanese children; diffuse rash, conjunctivitis, strawberry tongue; diagnosis requires fever >5 days with additional symptoms

August 2023

Part II: Cutaneous manifestations of peripheral vascular disease

Common cutaneous findings in peripheral vascular disease:

- Edema, dilated veins, corona phlebectatica (fan-shaped confluence of blue telangiectasias), cyanosis, ulcers, gangrene, hemosiderin pigmentation, lipodermatosclerosis, stasis dermatitis, acroangiodermatitis (reactive angiodysplasia; violaceous macules, indurated plaques/nodules; cool, shiny, brittle, skin lacking hair +/- nail changes)

Chronic Venous Disease

- **Etiology:** Idiopathic, secondary (trauma, prolonged standing, hormonal changes, venous thrombosis), or congenital
- **Symptoms:** leg pain, edema, cramps, limb heaviness
- **Stages:** Early (telangiectatic, reticular, varicose veins); advanced (nonpitting edema, stasis dermatitis, hyperpigmentation, lipodermatosclerosis, venous ulcers)

Venous Thromboembolism

- **Risk Factors:** surgery, oral contraceptives, trauma, immobility, obesity, or cancer
- **Clinical Signs:** pitting edema (unilateral or bilateral), tenderness, warmth, skin discoloration (violaceous or cyanotic), palpable tender cord, superficial non-varicose venous dilation
- **Virchow's triad:** venous stasis, vascular injury, hypercoagulability

Peripheral artery disease

- **Symptoms** vary from no symptoms to intermittent claudication, critical limb ischemia
- **Clinical signs:** Atrophic, cool, shiny skin; reduced hair growth; discolored, brittle nails; cyanotic toes; ischemic ulcers (pale, painful, punched out); wet/dry gangrene
- **Diagnosis:** decreased/absent pulses; Ankle-brachial index (ABI) ≤0.90 suggests PAD (can be >1.4 in PAD with non-distensible arteries); advanced imaging (duplex US, CTA, MRA) to locate stenoses

Lymphedema

- Primary: congenital, Milroy disease, lymphedema praecox (lymphatic malformation, females age 9-25), lymphedema tarda (35+ years)
- Secondary: trauma, surgery, recurrent infection, tumor
- Stemmer sign: dorsum of 2nd toe cannot be pinched

Raynaud's Phenomenon

- Primary: onset 15-30 years; no specific cause; symmetric, episodic
- Secondary: connective tissue disorders (ie. scleroderma, antiphospholipid syndrome, systemic lupus erythematosus, Sjogren syndrome); asymmetric, more frequent, severe attacks->digital ulceration, hair loss, necrosis, gangrene, autoamputation

Acrocyanosis

- Painless blue discoloration of hands, feet, face; worsened by cold.
- Symmetric, longer duration, lacks pallor, usually painless vs Raynaud's.
- Primary or secondary (connective tissue diseases, Buerger's disease, myocardial infarction, drug exposure)
- Severe cases may lead to ulceration or gangrene

Pernio (chilblains)

- Itching/burning purple discoloration of toes, fingers
- Symmetric purplish discoloration, typically within 1 day of cold exposure, lasts up to 1 week. Temporal worsening in cooler months. Response to conservative warming
- Vs Raynaud's: longer duration, lacks digital pallor and cyanosis
- COVID-19 toes: similar appearance, differentiated by clinical suspicion, viral and serologic testing
- Chilblain lupus: histologic or DIF confirmation, response to antilupus therapy, negative cryoglobulin & cold agglutinin, + SSA, RF, hypergammaglobulinemia

Erythromelalgia

- Episodic blood vessel occlusion in hands/feet; triggered by heat, exercise, dependency; relieved by cold, rest, elevation
- Primary: AD mutations in voltage-gated sodium channels-->hyperexcitable channels, painful responses
- Secondary: myeloproliferative disorders, infections, autoimmune disorders, gout, diabetes; often lower limbs
- Burning, warmth, pain, erythema, numbness during attacks; mild edema, acrocyanosis, anhidrosis/hypohidrosis, potential ulcers with myeloproliferative disorders

Livedo Reticularis

- Benign, reversible vasospasm, commonly idiopathic, healthy women 20-50 years
- Asymptomatic or mild pain/numbness, symmetric net-like mottling (red-blue to purple), triggered by cold, improved with heat

Livedo Racemosa

- Pathologic, persistent vasospasm, thrombosis, hyperviscosity, secondary to autoimmune disorders, medications, hematologic disease, anorexia nervosa, livedoid vasculopathy
- Persistent asymmetric, irregular broken circles, more generalized, associated with purpura, nodules, macules, ulcerations, atrophie blanche
- Antiphospholipid syndrome
- Secondary may show vasculitis, calciphylaxis, intravascular eosinophilic plugging, intraluminal thrombosis, cholesterol clefting

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September 2023

Melanoma in skin of color

Part I: Epidemiology and clinical presentation

Incidence and Mortality Trends in the United States

- Incidence increased by 1.4% annually, currently 22.8 per 100,000 people.
- Highest- non-Hispanic white (NHW) men: 34.7 per 100,000
- Lowest- Black women 0.9 per 100,000
- Skin of Color (SOC): diagnosed at later stages-thicker, ulcerated melanomas. Mortality higher in NHW
- 5-year survival: Localized disease: 99.4%; Distant metastatic disease: 29.6%
- Largest survival difference between Black and White patients across all cancers is melanoma (25%)

Most common sites of primary melanoma

- **Skin of Color (SOC)**: Hips, lower limbs. Exception: American Indian/Alaska Native (AI/AN) descent, trunk more common

- **Asian American:** Lower extremities; fewer on trunk, head, neck vs NHW
- **Non-Hispanic White (NHW):** Trunk
- **Hispanic:** Women: lower limbs/hips; Men: trunk; Low SES Hispanic women: head, neck

Melanoma Subtype

- Most common overall- superficial spreading, except Black patients=acral lentiginous
- Mucosal melanoma more common in SOC; Asian/Pacific Islander highest proportion; genitourinary highest across all racial groups; anorectal most common among women. Hispanic patients highest proportion head/neck mucosal melanoma. Significant female predominance for mucosal
- Volar/subungual acral: fewer BRAF mutations vs acral nevi= rarely arising from nevi (<11%)
- Nevus-associated melanoma (~1/3) linked to green/blue eyes, high nevus count, truncal location, not skin phototype (SPT)

Clinical diagnosis of melanoma in SOC

- Often non-sun-exposed areas with less pigmentation. Often thicker, ulcerated at diagnosis. Tendency for acral lentiginous/mucosal vs NHW
- Feet/anils: CUBED: colored, uncertain, bleeding, enlarged, delay
- Acral lentiginous: blue-black, irregular patches on palms/soles or reddish-pink (amelanotic), often mechanical stress points.
- Subungual: brown-gray nail lines-->exophytic nodule, nail matrix most common, thumb, hallux>other fingers, mistaken for trauma or physiologic pigment; Hutchinson sign + nail plate ulcer/destruction = pathognomonic
- Mucosal: nasal cavity: sinus pressure, epistaxis; oral cavity: asymptomatic or ulcer, pain, bleeding; vulvovaginal: irregular brown-black macule, bleeding, pruritus; anorectal: amelanotic, bowel habit changes, rectal bleeding, pain, pruritus; Early stage genital usually asymptomatic. Changing, irregular mucosal pigmentation needs biopsy!

Dermatoscopic Patterns:

- Parallel ridge pattern key diagnostic feature
- BRAAFF checklist high sensitivity/specificity, 6 variables: irregular Blotch, parallel Ridge, Asymmetry colors, Asymmetry structures, Fibrillar pattern, parallel Furrow
- Acral lentingous melanoma in situ: fewer colors (red, blue, white) and patterns (atypical vasculature, blue-white veil, ulcers)

Melanoma Mimics

- **Nevi in SOC:** Darkly pigmented, less prevalent vs NHW, more common on acral areas.
- Acral nevi dermoscopy:
  - Common: parallel furrow, lattice-like, fibrillar. Parallel ridge pattern may be seen in benign acral nevi in SOC
  - Most prevalent minor patternin SOC: homogeneous pattern of diffuse mottled hyperpigmentation without other features
  - Congenital acral nevi: “peas in a pod”
  - Acquired: Fitz I, II- pink- or brown uniform distribution, multifocal hyperpigmentation, hypopigmentation; Fitz V, VI- gray, black, reticular pattern, central hyperpigmentation. Fitz VI- blue, black, or gray with structureless pattern
- **Mucosal Pigmentation:** Common in SOC. Physiologic (melanocyte activation), medications, smoking, systemic disorders. Gingiva, lips (labial melanotic macules), palate; light tan to black. Non- gingival: less defined borders.
- **Longitudinal Melanonychia:** Common in SOC, single or multiple evenly spaced parallel brown-to-black bands, usually >1 nail, pseudo-Hutchinson sign; dermatoscopy distinguishes benign LM from nail melanoma:
  - Melanonychia: gray background, thin, uniform, gray lines
  - Melanocytic hyperplasia: brownish color with melanin inclusions
  - Matrix nevi: Parallel and regularly spaced pigmented bands
  - If irregular: biopsy

September JAAD CME

Melanoma in skin of color

Part II: Racial disparities, role of UV, and interventions for earlier detection

Racial Disparities in Melanoma specific survival

- Thicker, ulcerated melanomas, more advanced stage.
- Lower SES: more advanced at diagnosis, worse survival.
- Higher SES: earlier diagnosis, higher likelihood of receiving immunotherapy, longer survival
- Uninsured/Medicaid: advanced-stage vs private insurance. Uninsured rates: Hispanic (18.3%)> Black (10.4%)> Asian (5.9%)> NHW individuals (5.4%)
- Diagnosis by dermatologists: thinner, improved survival. Lower SES, rural residence, uninsured: decreased dermatologist access
- SOC: longer delay diagnosis to surgery and immunotherapy vs NHW. Medicaid: longest wait times vs privately insured.
- Black, Medicaid, low-income: less likely to receive immunotherapy.
- Acral and mucosal melanoma: sun-protected areas, lower mutational burden- less response to immunotherapy

Role of Ultraviolet Radiation (UV)

- High, intermittent UV exposure during childhood: melanoma risk factor in fair skin, limited evidence for darker skin
- SOC: more likely sun-protected areas, fewer UV signature mutations
- Darker skin: increased melanin density; larger, less-clustered melanosomes, UV protection- reduced melanoma risk

Disparities in Melanoma Risk Perception

- SOC: lower awareness, decreased risk perception; less likely to receive skin cancer education; Lack of public education on melanoma arising in non-sun exposed areas

October 2023 JAAD CME

Implementing patient safety and quality improvement in dermatology

Part 1: Patient safety science

General Principles of QI and Patient Safety

Term	Definition
Patient Safety	Freedom from accidental/preventable injuries from medical care; Activities to avoid, prevent or correct adverse outcomes
Quality improvement	Systematic evaluation/modification of practices to correct deficiencies and improve system.
Safety culture	Individual and group values, attitudes, perceptions, competencies, and behaviors that determine the commitment to, style, and proficiency of organization's health and safety management
Nonpunitive response to error	Mistakes and errors will not be held against the reporter.
Psychological safety	A reporter's comfort level to challenge a person or system deemed more powerful than themselves without any negative action.
Root cause	A factor that caused a nonconformance and should be addressed with corrective action (should be specific and identifiable causes).
Root cause analysis	Method of identifying the cause of a problem, solving it, and preventing it from occurring again. Uncovering the correct and accurate reason(s) why something is happening or has occurred (should generate effective recommendations).
Active errors	Almost always involve frontline personnel and occur at the point of contact between a human and some aspect of larger system (ie, a human—machine interface).
Latent errors	Accidents waiting to happen—failures of organization or design that allow the inevitable active errors to cause harm.
Failure modes effect analysis	Prospectively identify error-prone situations, or failure modes, within a specific process of care.

General Principles of QI and Patient Safety (Cont.)

Term	Definition
Common-cause variation	Natural or expected variation in a process (eg, measurement errors).
Special-cause variation	Unexpected variation from unusual occurrences. It is important to identify and try to eliminate.
Proximate cause, or active failures	Obvious reasons an error happened/adverse event occurred. Usually, proximate cause identified in investigations and often reflects a superficial analysis, focusing on human error.
Latent conditions	Aspects of a process than can allow an error to occur

6 Dimensions of Health Care Quality

Health care dimension	Definition	Examples in dermatology practice
Safety	Avoiding injuries to patients from care	Availability of hyaluronidase during filler injections Standardization of biopsy site photography to avoid wrong-site surgery Protocol for logging dermatopath specimens Labeling of medications with date opened
Timeliness	Reducing waits and delays to receive and give care	Pathology result reporting time Reduction of wait times for dermatology appointments with modified scheduling temples Telederm or group visits to increase access
Effectiveness	Services based on scientific knowledge	Evidence-based medicine to inform treatment decisions Consideration of the accuracy and precision of tests, including positive and negative predictive values
Efficiency	Avoiding waste (equipment, supplies, ideas, energy)	No unnecessary labs for isotretinoin or spironolactone Avoid duplicative lab, imaging, or med orders Reflectance confocal microscopy or dermatoscopy to reduce the number needed to biopsy
Equity	Care does not vary in quality because of personal characteristics (gender, race, ethnicity, disability, education, sexual orientation, geographic location, SES)	Include Medicaid patients Skin of color curriculum in residency programs Satellite clinics in underserved areas or telederm Training in unconscious bias Readability of patient handouts
Patient-centeredness	Compassion, empathy, responsiveness to the needs, values, and preferences of individual patient	Patient-centered outcome measures in research and clinic Behaviors to improve patient experience Buffer, smaller gauge needles, warming to minimize discomfort of lidocaine injection Layman's terms and language patients can understand Understandable patient handouts

- Near Miss - potential for harm, prevented by chance, prevention, or mitigation. Identification can prevent errors
- Sentinel Event - results in death, permanent harm, or severe short-term harm.

Root Cause Analysis: systematic, retrospective, problem-solving to identify/ eliminate root causes through process improvement. 7 key categories: institutional context, organizational/management factors, work environment, team factors, individual staff, task factors, patient characteristics.

Identifying Root Causes

- Process mapping: visualizes workflows leading to event; clarifies team responsibilities, resource needs; document current process vs ideal
- Failure mode and effects analysis: Systematic evaluation of process, potential failures, impact. Prioritizes changes based on risk assessment (occurrence, detection, severity)
- Fishbone diagram: cause-and-effect diagram to brainstorm, identify deeper root causes

October 2023 JAAD CME

Implementing patient safety and quality improvement in dermatology.

Part II: Quality improvement science

Frameworks of Quality Improvement (QI):

- LEAN- focus on waste reduction. Improve efficiency, decrease costs. Identify, reduce sources of waste (supply overuse, inefficient processes)
- Six Sigma- reduce process variability, improve quality, reduce costs. Used to decrease patient wait times, increase patient satisfaction, other healthcare QI efforts
- IHI-QI: 3-question framework and Plan-Do-Study-Act (PDSA) cycles
  - 3 core questions: what needs to be accomplished, metrics for change significance, systemic change post-implementation
  - PDSA cycles: planning, testing, analyzing, refining changes in small, iterative steps
    - PLAN: Change that will lead to improvement
    - DO: Implement change on small scale
    - STUDY: Analyze results and reflect
    - ACT: Adopt or abandon change, decide next cycle

QI Metrics in Dermatology:

- Aim statements- Specific, Measurable, Achievable, Relevant, Time-bound (SMART)

Measure	Definition	Dermatology example
Outcome	Assesses impact on patient	Percentage of surgical site infections
Process	Assesses the actions that may influence outcomes	Percentage of melanoma patients with annual skin exam
Balancing	Assesses change in 1 area to evaluate possible unintended changes in others	Number of adverse reactions to preoperative antibiotic

November 2023

Gaps in medical education curricula on skin of color in medical school, residency, and beyond: Part 1

Skin of color (SOC):

- Cultural competency:
  - Improved patient rapport and outcomes
  - Includes providing services respectful of diverse health beliefs
  - Example: considering patient's hair type and styling practices when formulating a treatment plan

Racial and ethnic disparities in clinical research and the dermatology workforce: Part 2

- Lack of racial and ethnic diversity in research leads to decreased generalizability
- Ways to increase the diversity:
  - Holistic review of applicants
  - Create a pipeline program within the local community
  - Introduces underrepresented-in-medicine high school students to medicine
  - Pair them with mentors

December 2023

Cutaneous tuberculosis.

Part I: Pathogenesis, classification, and clinical features

Cutaneous tuberculosis (CTB):

- All cases should be evaluated for regional lymphadenopathy
- Lungs most common systemic focus of TB
- More common in South-East Asia, Indonesia, and China
- More common in children > adults
- HIV coinfection promotes disseminated disease, drug resistance, mortality
- Suspect a tuberculid when:
  - Complete response to antitubercular treatment
  - Past or present history of TB
  - Positive tuberculin test

Classification	Route of infection	Form	Immune status
True cutaneous TB	Inoculation	Tuberculous chancre	No prior TB exposure
	Inoculation	TB verrucosa cutis	Good immunity
	Hematogenous	Lupus vulgaris	Good immunity
	Hematogenous	Acute military TB	Low immunity
	Hematogenous	TB gumma	Low immunity
	Hematogenous	Orificial TB	Low immunity
	Contiguous/autoinoculation	Scrofuloderma	Low immunity
	Contiguous	Lichen scrofulosorum	Low immunity
Tuberculids	Endogenous	Papulonecrotic tuberculid	Strongest immune response (hypersensitivity)
	Endogenous	Erythema induratum of Bazin	Strongest immune response (hypersensitivity)

Clinical Presentation:

Tuberculous Chancre:

- Brown-red, asymptomatic papule->friable painless ulcer with undermined edge; Site of entry, 2-4 weeks after injury/inoculation

Tuberculosis Verrucosa Cutis:

- Verrucous, asymptomatic, slow-growing plaque at inoculation site
- Most commonly: lower extremities or buttocks (barefoot, squatting where someone spit)
- Dermoscopy: papillated surfaces with yellow-red background and dirty, white, thick scales. Dilated papillary vessels with multiple yellow-to-orange, structureless, and globular areas at 40× magnification

Lupus Vulgaris:

- Common form: 4-63% of cutaneous TB
- Slow-growing, asymptomatic red-brown plaque with one advancing border with scale crust, other border scarred, central atrophy
- Sporotrichoid spread possible
- Head, neck, legs most common
- Dermatoscopy: scattered, yellow-white globules; white scales; white structureless areas; pink-red background in all cases, telangiectasias in 84%. Facial: 4-dot clods, white rosettes, patulous follicles

Miliary Tuberculosis:

- Multiple subcentimetric, polymorphic, erythematous papules & pustules, +/- central necrosis or umbilication
- Predominantly limbs and trunk
- Coinfection with HIV/AIDS common

Metastatic/TB Gumma:

- Fluctuating, subcutaneous nodules
- Hematogenous spread & poor prognosis
- Orificial Tuberculosis:
- Painful or painless, nonhealing, punched-out ulcers
- Oral cavity>anogenital

Scrofuloderma:

- Painless, solitary, or multiple subcutaneous swellings, Undermined ulcers with violaceous edges, or Indurated plaques with fistulae with purulent or caseous drainage
- Usually overlying enlarged lymph nodes
- Neck > groin, trunk, mandible, axilla, hands
- In axillae mimics hidradenitis suppurativa

Tuberculids:

- Lichen scrofulosorum: innumerable, grouped, erythematous, perifollicular papules, often scale crust; trunk and proximal extremities. Dermoscopy: pale, monomorphic, perifollicular, round dots with central black plugs and peripheral scaling and hyperpigmentation
- Papulonecrotic tuberculid: Recurring crops of painless, polymorphic, erythematous to violaceous, papules, pustules, nodules; extremities and trunk, with varioliform scarring
- Erythema induratum of Bazin: tender, erythematous nodules that ulcerate; posterior calves. Resembles e. nodosum and nodular vasculitis

Cutaneous tuberculosis. Part II: Complications, diagnostic workup, histopathologic features, and treatment

- Long-standing lupus vulgaris: risk of squamous cell carcinoma
- Mortality depends on underlying disease and host immunity
- Check HIV in scrofuloderma
- To make a diagnosis obtain:
  - Tuberculin skin test
  - Histopathology with mycobacterial stains
  - Cultures
  - PCR
- Path: caseation necrosis, giant cells, tuberculoid epithelioid granulomas
- Acid-Fast Bacilli Stains: Ziehl-Neilsen, Fite-Faraco, and Auramine-rhodamine
- Treatment: rifampicin, isoniazid, ethambutol, pyrazinamide x 2 months, then rifampicin + isoniazid x 4 months

January 2024

Chronic graft-versus-host disease.

Part I: Epidemiology, pathogenesis, and clinical manifestations

Chronic GVHD:

- Leading cause of morbidity and mortality after HCT
- Skin and mucous membranes most frequent site
- Primary predictor: degree of human leukocyte antigen (HLA) match between the donor and recipient
- Conditioning with total body irradiation increases risk of sclerotic chronic GVHD
- Pathophysiology can be conceptualized into 3 phases:
  - (1) tissue injury and early inflammation
  - (2) dysregulated B-cell and T-cell immunity
  - (3) fibrosis
- Diagnostic manifestations of skin cGVHD:
  - poikiloderma
  - lichen planus (LP)-like
  - deep sclerosis
  - morphea-like
  - lichen sclerosus (LS)-like features
- Oral cGVHD: initially resembles mucositis (dry mouth, sensitivity to spicy food), evolves into tissue fibrosis
- Genital cGVHD presentation:
  - Discomfort
  - Dyspareunia
  - Vaginal or penile adhesions
  - LS and LP-like features
  - Adhesions
  - Scarring

January 2024

Chronic graft-versus-host disease.

Part II: Disease activity grading and therapeutic management

Treatment:

- 1st line for nonsclerotic: high-potency topical steroids
- Topical anesthetics for oral pain
- Hypoestrogenic vulvovaginal atrophy or vulvovaginal cGVHD: topical estrogen
- Multisystem cGVHD or moderate-severe skin disease
  - 1st line: systemic corticosteroids
  - < 20% achieve durable response
- FDA-approved for steroid-refractory: Ibrutinib, Ruxolitinib, Belumosudil
- Supportive care:
  - pruritus management
  - photoprotection
  - wound care
  - multimodal rehabilitation (occupational therapy, physical therapy, and home stretching for fasciitis/contractures)

February 2024

Raynaud's Phenomenon

- Exacerbated by nonselective beta blockers, smoking, estrogen replacement therapy, and intense vibratory stimuli
- Treatment for both primary + secondary: calcium channel blockers

Primary Raynaud's:

- Vasospastic response
- Reversible clinical symptoms
- No endovascular remodeling, fibrosis, stenosis, or ischemic tissue injury
- Associated with migraine history

Secondary Raynaud's:

- Seen with ACTD, particularly systemic sclerosis
- Other causes: medications, toxins, infections, anatomic variation, occupation exposures, dysproteinemias
- Impaired angiogenesis and vasoconstriction, increased fibrosis, and microthrombi
- Gold standard for diagnosis: ANA immunofluorescence

Treatment:

- Smoking cessation
- Lifestyle modifications (cold avoidance,"frisbee maneuver")
- Topical nitrates (AE: headache)
- Calcium channel blockers (AE: edema)
- Identify and treat underlying cause in secondary
- Bosentan: pulmonary HTN and digital ulcers
- Anti-coagulants in prothrombotic states (SLE, anti-phospholipid antibody syndrome)
- Botulinum Toxin Injection to interdigital web spaces and/or neurovascular bundles

March 2024

Erythromelalgia (EM)

- Primary, secondary, and idiopathic
- Females more commonly affected
- Primary: mutation in the SCN9A gene: inherited or occur de novo
- Secondary: Polycythemia vera, essential thrombocytosis
- Episodes of burning pain, erythema, and warmth of distal extremities
- Less commonly face and ears
- Crises triggered by exercise, increased temperature, dependency of limb
- Relief with cooling
- CBC to rule out myeloproliferative conditions
- Differential:
  - Paroxysmal extreme pain disorder
  - Complex regional pain syndrome (CRPS)
  - Peripheral neuropathy
  - Fabry's disease
  - Raynaud's phenomenon
- Trigger avoidance
- Safe cooling techniques

- Topical: 1% Amitriptyline/0.5% Ketamine gel, Lidocaine 5% patch, Capsaicin cream/patch; Systemic: mexiletine, carbamazepine, rizatriptan, oxcarbazepine, aspirin, venlafaxine, gabapentin, pregabalin, misoprostol, magnesium sulfate; IV: nitroprusside, lidocaine, prostaglandin E1 analog
- Fabry disease presentation:
  - Episodic burning pain in the hands and feet
  - Skin of affected areas remains normal during attacks
  - Symptoms do not resolve with cooling
  - Patients have numerous angiokeratomas
- Important side effect of mexiletine: cardiac arrhythmias

April 2024

Performance measurement

- Safe, Timely, Effective, Efficient, Equitable, and Patient-centered (STEEEP) helps organize complex measurement of value
- 5 domains of care:
  - Effectiveness
  - Access/availability
  - Utilization
  - Risk adjusted utilization
  - Measures reported using electronic clinical data systems
- Merit-Based Incentive Payment Program (MIPS) Value Pathways: new payment pathway
- Promotion of interoperability: a MIPS universal category supporting exchange of health information and use of certified electronic health record technology
- Other universal performance categories include:
  - Quality
  - Improvement activities
  - Cost
- Receiving accreditation and licensure under the Joint Commission and CMS requires annual reporting of performance measures through a publicly available database known as Care Compare
- Provides hospital and provider's performance measurement data
- Value=outcomes (quality + service) ÷ costs

5 main types of performance measures:

Measure	Description	Dermatology example
Process	Measure of clinical practice	Percentage melanoma patients screened annually with skin exam
Structural	Structural component of healthcare process	Percentage of patients taking high-risk medications for psoriasis with labs tracked on a log
Outcome	Improvement in patient's health based on measurable outcome	Percentage of eczema patients with 2+ point reduction in itch over 1 year
Cost	Monetary value of care or resources during a care period	Net outpatient costs per patient with severe psoriasis over a 6-mo period
Patient-reported	Reported patient or consumer experience within healthcare organization	Percentage of patients with 4+ improvement in DLQI over a 6-mo period

DLQI=Dermatology Life Quality Index

May 2024

Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms

- Typically 2-6 weeks latency. Most common drugs: anticonvulsants, antibiotics, and allopurinol
- Reactivation of Human herpesvirus 6
- Morbilliform eruption + facial edema

Organ	Frequency	Notes	Drugs with increased risk
Hematologic	100%	Fever, lymphadenopathy, leukocytosis (neut, eos), atypical lymphocytosis, abnormal erythrocytes, thrombocytosis, thrombocytopenia, DVT, Hemophagocytic lymphohistiocytosis	
Hepatic	75%	Hepatosplenomegaly, hepatitis, hepatic necrosis	Phenytoin, TB antibiotics, Allopurinol
Renal	37%	Acute nephritis, acute kidney injury, CKD exacerbation, proteinuria, hematuria, vasculitis	Carbamazepine, Dapsone, Vancomycin, Allopurinol
Pulmonary	32%	Interstitial pneumonitis/SIADH, pneumonia, pulmonary nodules, pleural effusion, ARDS	Minocycline
Cardiac	13%	Pericarditis, myocarditis, AV block, acute necrotizing eosinophilic myocarditis	Ampicillin, Minocycline

Initial Evaluation
CBC w/ diff, LFTs, BUN, Cr, UA, Spot urine for protein:creatinine ratio
Treatment Discontinue suspected drug Prednisone 1-2mg/kg/day with gradual taper Steroid sparing: Case-control study: cyclosporine; Case reports/series: IVIG, IL-5 inhibition, JAK inhibitors, methotrexate, azathioprine, infliximab, rituximab
Evaluation for Sequelae TSH + Free T4 at 3 months, 1 year, and 2 years Monitor for PTSD, depression, anxiety for 1 year

June 2024

Acne scars

- Morphologic classification: atrophic, hypertrophic, keloidal, and papular
- Atrophic scars: icepick, boxcar, and rolling
- Treat after complete remission of acne x 6 months

Treatment:

- Topical retinoids
- Microdermabrasion improves skin tone
- Platelet-rich plasma
- Peels: cost-effective; any type of scar depending on strength and method
- TCA-CROSS (Trichloroacetic acid chemical reconstruction of skin scars): ice pick; risk of scar enlargement
- Filler volume replacement: rolling and superficial boxcar
- Radiofrequency: rolling and boxcar scars
- Microneedle radiofrequency safe in all skin types
- Fractional ablative lasers: several days of downtime
- Platelet-rich plasma injections decrease the down-time after fractional CO2 laser
- Nonablative lasers: pulsed dye, Q-switched alexandrite, Er:Glass, and neodymium:yttrium-aluminum-garnet
- Er:YAG laser has more dramatic results compared to Er:Glass laser
- Deep boxcar scars: subscision, punch excision, punch elevation
- Resurfacing procedures typically used after punch procedures to enhance results

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