Bone Tumors: A Practical Approach Based on Clinical and Radiographic Correlation

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The Clinical Team

General practitioner/ER physician etc.

Orthopedic surgeon

Radiologist

Pathologist/Pathology Assistant

Patient

Role of the clinical team in bone tumor diagnosis

- Orthopedic surgeon: provide clinical information, explain the type of surgical procedure; orient the specimen
- Radiologist: describe the exact location and tumor extent and narrow the differential
- PA/pathology resident: correctly describe, dissect and sample
- Histotechnologist: provide good histology
- Pathologist: render final diagnosis
Type of Surgical Procedures

- Incisional biopsy
- Excisional biopsy
  - Intralesional excision: curettage, piecemeal debulking
  - Marginal excision: tumor removed in one piece, cut through pseudocapsule or reactive rind ("shelled out")
  - Wide excision; "en bloc", cut beyond reactive tissue
  - Radical: entire bone or compartment plus adjacent joint and part of adjacent bone

Importance of clinico-pathological correlation in bone tumors

- Clinical history is essential!
  - Age
  - Location
  - Symptoms
  - Duration
- X-ray appearance: always review films
  - Patterns of bone destruction
  - Periosteal reactions
  - Matrix mineralization

Role of imaging

- Detect and localize lesion
- Characterize lesion
- Aid in diagnosis
- Staging – local/distant
- Guide management – biopsy/surgical
- Evaluate treatment response
- Follow-up
Handling bone specimens: Technical aspects

- Frozen section
- Grossing
  - Description
  - Dissection
  - Use of bone saw
  - Fixation and decalcification
  - Sampling for microscopic examination
Has diagnostic tissue been obtained?
- Is the tumor benign of malignant?
- Allocation of tissue for ancillary studies
  - Snap freeze tissue whenever possible!
  - Cytogenetics
  - Molecular diagnostics
  - Flow cytometry (r/o lymphoma)
  - (EM)
  - **Touch imprints (for possible FISH):**
    - Important: do **NOT** use alcohol to fix slide; instead air dry (needs to be taken to lab within 24 hours) or fix in formalin

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### Bone saws

- **Handsaw ("striker" saw):** need vise or clamp
- Oscillating hand held saw
- Butcher type band saw: needed for large specimens
- Safety!!
- **Circular diamond saw:**
  - Cuts through metal
  - Suitable for small specimens
  - Expensive blades

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### Decalcification process

- Necessary for any specimen containing mineralized bone
- Ideal decalcification method/solution
  - Speed
  - Optimal histology
  - Antigen preservation for immunohistochemistry
  - Preservation of DNA/RNA for molecular analysis
Decalcifyers
- Acid based:
  - Most commonly used
  - Rapid
  - Harsh (risk of overdecalcification)
  - Possible loss of antigen reactivity
  - Hampers DNA/RNA based procedure
- Chelating agents (EDTA):
  - Gentle but slow
  - Less effect on DNA/RNA

Commonly used decalcifiers
- RDO rapid decalifier
- RBD Rapid Bone Decalcifyer
- Versenate (EDTA)...

Decalcification solutions
- Acid:
  - Commercial preparation
  - Self prepared: diluted hydrochloric or nitric acid
  - Neutralizing agent used to stop decalcification
- EDTA (ethylene-diamine-tetra-acetate):
  - Solution must be changed frequently
Biological Behavior of Bone Tumors (WHO classification)

- Benign
- Intermediate
  - Locally aggressive
  - Rarely metastasizing
- Malignant

WHO classification of bone tumours (2013)

WHO Classification of bone tumors by presumed histogenesis

- Cartilage forming (chondrogenic) tumors
- Bone forming (osteogenic) tumors
- Fibrogenic/fibrohistiocytic tumors
- Hematopoietic tumors
- Osteoclastic giant cell rich tumors
- Notochordal tumors
- Vascular tumors
- Myogenic tumors
- Lipogenic tumors
- Tumors of undefined neoplastic nature
- Miscellaneous tumors
Case

Aneurysmal Bone Cyst

13 year old with knee pain after a fall. MR features: fluid-fluid levels
Gross features:

- Usually a curettage (or core bx) specimen
- Small fragments of bone admixed with blood, variable amount of some hemorrhagic or fibrous soft tissue
- Decalcify if bony fragments present
- Submit entirely

ABC: Summary

- All ages, most common <20 (median 13)
- Site: metaphysis of any bone
- Symptoms: Pain/swelling/fracture
- Recurrence: 20-70% following curettage

Case

Unicameral (simple) bone cyst “UBC”
12 yr old male with one month history of right ankle swelling. Recent twisting injury to ankle.

- Obvious fullness of lateral malleolus.
  - No edema, warmth or skin discoloration over fullness.
  - Nontender over fullness.
  - No fevers, weight loss or night pain

Gross features:

- Remarkably small specimen (compared to size of lesion on X-ray)
- Small spicules of bone, scant fibrous tissue, usually not very bloody
- Submit entirely after decal

Scant tissue
Simple bone cyst

- Age: 85% <20
- Site: long bones (proximal humerus, femur, tibia, also pelvis, calcaneus)
- Recurrence: 10-20%

Case

Giant cell tumor of bone

23 yr old female with three month history of wrist pain, worse after a fall one month ago.

- Pain interferes with sleep
- Fullness at distal ulna region with overlying warmth
- Very tender to palpation
- Atrophy of hypothenar muscles
Recurrence

Gross features:
- Usually curettage (rarely en-bloc)
- Often abundant tissue, especially when excisional biopsy
- Brown-red hemorrhagic tissue, mostly soft with minor bony component
- Decalcify only portion that contains bone
- Submit liberally (might be too large to submit entirely)
Giant cell tumor of bone

- Age: 20-45 *(very rare* before skeletal maturity)
- Epiphyseal sites: (distal femur, prox. tibia, distal radius, prox. humerus, also flat and small tubular bones, vertebrae
- Local recurrence 25%, lung metastases 2% (slow growing or regressing)
Bone forming tumors

Osteosarcoma and its variants

General Approach to Handling Bone Tumor Specimens
- Do not freeze the limb (freezing artifact!)
- Ink soft tissue margins (if tumor is close)
- Sample margins, LN's, vessels
- Dissect soft tissue off bone except for soft tissue extension of tumor
- Obtain cross section of the bone margin
- Disarticulate joint if free of tumor
- Section bone longitudinally (avoid smearing ink into bone saw)
cont.: Handling Bone Tumor Specimens

- Clean cut surface (rinse, gently brush)
- Photograph
- Obtain parallel cut (2-3mm)
- Fix in formalin, then decalcify
- Submit entire tumor surface of slab (make drawing, dictate accurately)
- Obtain additional sections as needed

AKA for proximal tibia osteosarcoma

Proximal Margin (bone, soft tissue, skin)
Ink margin (may be omitted if location of tumor is known), and sample soft tissue and vascular (venous!) margin

Limb sparing excision: ink entire margin

Identify neurovascular bundle, sample vascular margin (vein!), soft tissue and bone margin
Remove skin and dissect soft tissue (sample previous biopsy site), look for lymph nodes.

- Inspect joint cavity for tumor involvement
- Disarticulate
- Transect the long bone to a manageable length

Sample synovium
Inspect interosseous soft tissue

Inspect tib/fib joint

After sampling bone margins, obtain longitudinal section (usually coronal)
Obtain additional sections as indicated clinically (X-rays, clinical info)

Cut thin slab (few mm)

Decalcification

- Use relatively thin sections
- Fix in formalin! (never decalcify before the bone is well fixed)
- Decalcify and check for appropriate decalcification, then submit
- Wash decalcifying solution off before definite processing
- Do not overdecalcify
- Decalcify only when necessary!
Handling of Post-chemo Bone tumors

- More sections required to assess % tumor necrosis (may be 30-60)
- Sample sanctuary sites:
  - tumor periphery, soft tissue extension, areas of hemorrhage
- Percent necrosis is assessed microscopically by comparing cellularity to original tumor (critical value is usually 90% necrosis)

Limb sparing resection:
Sections to take from the slab

From: Dorfman and Czerniak's Bone Tumors Mosby 1998

Case

High Grade Osteosarcoma, conventional type
17 yr old female with R knee atraumatic pain/vague swelling x 4-5 months. Acute worsening of night pain x 2-3 weeks.

Xray AP view

Xray lateral view

Bone scan

CT without and with contrast

Coronal slab

Sagittal slab
Histology

Treatment of Osteosarcoma
- Pre-operative Chemotherapy
- Surgical Excision
- (Radiation)
- Post Operative Chemotherapy

Treated osteosarcoma
Epidemiology of Osteosarcoma

- Most common primary malignancy of the skeleton
- 20% of primary sarcoma of bone
- Incidence is 4-5 per million
- 1000-1500 newly diagnosed cases in US

Osteosarcoma

Classification of Osteosarcoma

**Intramedullary**
- Conventional: osteoblastic, chondroblastic, fibroblastic
- Telangiectatic
- Small cell
- Giant cell
- Well differentiated

**Juxtacortical**
- Well-differentiated (Parosteal)
- Chondroblastic, low to intermediate (periosteal)
- Osteoblastic, high grade surface
Parosteal OS

Periosteal OS

Courtesy of Dr. Gunnlaugur P. Nielsen
Telangiectatic OS

Cartilage tumors

Chondrosarcoma and its DD
- Osteochondroma
- Enchondroma
- Conventional chondrosarcoma
- Dedifferentiated chondrosarcoma
- Chondroblastic osteosarcoma
Gross features:
- May be intact or fragmented
- Orientation:
  - Recognize margin of resection (base of exophytic lesion) and cartilage cap
  - Describe thickness of cap and sample
  - Decalcification required

Osteochondroma
- Mushroom shaped with stalk (or sessile)
- Peripheral portion consists of cartilage cap
- Enchondral ossification beneath (inner portion of the lesion and stalk consist of bone) similar to growth plate
- Cortex of the stalk merges with cortex of the bone it arose from (medullary cavity of the osteochondroma and bone are connected)
Large osteochondroma removed in fragments

Enchondroma

- small bones of the hand > feet (60%) > long tubular bones
- asymptomatic
- ? pain

Enchondroma

7:1
Gross features:

- Usually curettage
- Sample liberally if clinical suspicious for malignancy

CT enchondroma

Enchondroma
Enchondroma

- Gray-blue and translucent (like normal cartilage)
- Well-circumscribed nodules of benign cartilage (low cellularity)
- Periphery of nodules with ossification
- No cortical erosion or soft tissue extension

Case

Osteochondroma

...Later revised to low grade chondrosarcoma

14 yo girl with left arm mass since infancy now interfering with her sleep
Family h/o multiple osteochondromatosis
Fragmented exophytic lesion, thick irregular cartilage cap

Conventional Chondrosarcoma
- 2nd most common primary bone sarcoma
- 1/4 of all primary bone sarcomas
- ilium > femur > humerus
- 6th-7th decade of life

Intramedullary Chondrosarcoma
Proximal Femur
Example of grade 2 CS

- Consistency softer (more gelatinous = myxoid)

Gross features:

- Often large
- Low grade tumors resemble hyaline cartilage (glistening grey-white, often lobulated)
- Focal gritty calcifications
- Higher grade tumors often myxoid with hemorrhage and necrosis

CS grade 1-2/3

- Permeative growth with destruction of bony trabeculae
- Residual trabecula
- Soft tissue extension
Case

Dedifferentiated Chondrosarcoma

44 yr old female presents with left shoulder pain for 10 years, recently enlarging, painful left shoulder mass and night pain

Scapula Tumor
Dedifferentiated CHSA

- transformation of a low grade CHSA into a high grade sarcoma (OSA, MFH)
- 10% of all CHSA
- Femur > pelvis > humerus
- 6th - 7th decade
- 90% die within the first year

Small round cell tumors
Bone lesions with a permeative pattern by X-ray

- Osteomyelitis
- Ewing’s sarcoma
- Lymphoma (Non-Hodgkin’s)
- Myeloma
- Langerhans histiocytosis
- Bone metastases

Osteomyelitis: Radiographic mimicker of malignancy

Small round cell tumors of bone

- Lymphoma/Leukemia
- Ewings/PNET
- Mesenchymal Chondrosarcoma
- Osteosarcoma (small cell variant)
- (Metastatic small round cell tumors, i.e. rhabdomyosarcoma, neuroblastoma, Wilms tumor, melanoma, small cell carcinoma..)
### Allocation of tissue for ancillary studies important in round cell tumors DD

- Snap freeze tissue whenever possible
- Cytogenetics (fresh tissue in cell culture medium)
- Molecular diagnostics (snap frozen or paraffin block)
- Flow cytometry (r/o lymphoma), fresh tissue
- Electron microscopy, in glutaraldehyde fixative
- Touch imprints (for possible FISH):
  - important: do NOT use alcohol to fix slide; instead air dry (needs to be taken to lab within 24 hours) or fix in formalin

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### Case

**Ewing sarcoma**

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18 yr old female with several month history of left thigh pain

![X-rays](image1.png)

![Bone scan](image2.png)
Small round cell tumor

- Additional studies required
Immunohistochemistry results

- CD99
- LCA
- S-100
- Keratin

Ewing sarcoma: Ancillary Tests

- Immunohistochemistry: CD99 etc.
- Molecular: Tumor specific translocation
  - t(11;22) in 85% → gene fusion gene EWS/Fli-1 (oncogene)
- Diagnostic tests used to identify fusion gene:
  - conventional cytogenetics (requires live cells)
  - RT-PCR
  - FISH

Ewing's Sarcoma/PNET

Round cell sarcoma with varying degree of neuroectodermal differentiation
Ewing Sarcoma/PNET:

- Primary bone sarcoma (majority)
  - 2nd most common primary malignant bone tumor in children
- Extraskeletal Ewing’s:
  - 2nd most common soft tissue sarcoma in children
- Age: 10-30 (80% <20)
- Symptoms: pain, mass, fever, ↑ESR, anemia, leukocytosis, large soft tissue mass common

Resection post-chemotherapy

Case

Diffuse Large Cell (B-cell) Lymphoma
69 yr old male with a 6 month history of right elbow pain and swelling. The pain is present at all times and interferes with sleep. Originally treated for tennis elbow with PT.

Case #2
Incisional Biopsy
Lymphoma

- Allocate tissue for lymphoma work-up whenever lymphoma is suspected (clinically or at the time of frozen section)

Bone Metastases

- Most common bone malignancy overall
- 3rd most common metastatic site
- Rare in children (may be seen in neuroblastoma, RMS, clear cell sarcoma of kidney)
- Sites: bones rich in red marrow (vertebrae, proximal femur, ribs, skull, pelvis, sternum, shoulder)
- Symptoms: pain, swelling, fracture, neural symptoms, hypercalcemia
Metastatic carcinoma: Radiographic features

- Periosteal reaction is uncommon
- Lytic
- Pure lysis and blow out: renal cell
- Mixed lytic and blastic: breast, lung, GI
- Pure blastic: prostate, medulloblastoma
- Intracortical: lung
- Hands and feet (acral metastasis): lung

Bone Metastases: Pathology

- Osteoblastic (dense on Xray): prostate, some breast, lung
- Osteolytic (hypodense on Xray): renal cell, most metastases in general
- Micro: recapitulates the original tumor
- Immunohistochemistry often required to confirm the tumor origin
- Fresh tissue may be required for special studies (chemosensitivity, molecular analysis)

Case

Metastatic breast cancer
Distorted femur head
Ill-defined hemorrhagic lesion

Metastatic carcinoma: touch prep during frozen section
Metastasis (left) and previous breast biopsy (right). Notice that the histology is very similar.

Thank you!