Challenging Esophageal Biopsy Cases

Nicole C. Panarelli, MD
Assistant Professor of Pathology
Albert Einstein College of Medicine
Bronx, NY
**Lymphocytes in Esophageal Biopsy Specimens**

**Introduction**

Lymphocyte-rich inflammatory infiltrates in esophageal mucosal biopsy samples may pose diagnostic challenges. Scattered lymphocytes are normally present throughout the esophageal mucosa and tend to be more concentrated in the deeper epithelial layers. Thus, occasional lymphocytes should not be interpreted as pathologic, especially in the absence of other features of mucosal injury. Lymphocytes are a feature of most common esophagitis, including infections, gastroesophageal reflux disease (GERD), and eosinophilic esophagitis, where they are seen admixed with granulocytes. On the other hand, lymphocytes are usually the only inflammatory cells in biopsy specimens from patients with lymphocytic esophagitis.

**Lymphocytic Esophagitis**

Lymphocytic esophagitis is a recently-described pattern of injury with unclear etiology. It typically occurs in women in the seventh decade and presents with dysphagia or odynophagia. Up to one-third of patients have normal endoscopic examinations, whereas others display endoscopic features that overlap with eosinophilic esophagitis, including rings, furrows, and strictures. Finally, endoscopic examination may show a dilated esophagus or hypertonic lower esophageal sphincter, suggesting dysmotility. In fact, lymphocytic esophagitis has been associated with various causes of dysmotility, such as scleroderma, other connective tissue diseases, and achalasia. Some medications are implicated in lymphocytic esophagitis, including anti-malarial drugs, nonsteroidal anti-inflammatory drugs, and thiazide diuretics. Early studies reported a relationship between Crohn disease and lymphocytic esophagitis, but subsequent reports showed this association to be limited to pediatric patients. Histologically, lymphocytic esophagitis is characterized by variably dense lymphocytic infiltration of the esophageal mucosa, which is enhanced in the peripapillary regions and absent or nearly absent granulocytes. Marked intercellular edema is almost always present. Some authors use a threshold of >20 lymphocytes per high-power field to diagnose lymphocytic esophagitis, but due to the wide reported range of lymphocyte density, counting lymphocytes is not currently recommended.

Some cases of lymphocytic esophagitis may reflect superficial biopsy samples of esophageal lichen planus. The latter is uncommon in the esophagus and is typically found in patients who have oral lichen planus, but lack skin involvement. Esophageal lichen planus presents with dysphagia and strictures. Histologic features include esophageal lymphocytosis in a peripapillary distribution, dyskeratotic cells (Civatte bodies), and a subepithelial band of lymphocytes. Thus, lichen planus may be indistinguishable from
other forms of lymphocytic esophagitis in biopsy samples that lack subepithelial connective tissue. The diagnosis of lichen planus may be confirmed with direct immunofluorescence (DIF) which shows globular IgM and complement deposits. The term “lichenoid esophagitis” may be applied to cases where DIF is not performed or when immunofluorescence fails to support the diagnosis.

A large study of the Swedish adult population revealed the 40% of adults with symptoms of reflux and normal endoscopic examinations had biopsy findings characteristic of lymphocytic esophagitis. Thus, lymphocytic esophagitis may also be an early manifestation of GERD, explaining why some lymphocytic esophagitis patients report symptomatic relief with proton pump inhibitor therapy. In support of this theory, recent research in mouse models and human subjects reveals that cytokines released by the esophageal mucosa in response to acid exposure recruit lymphocytes prior to the appearance of eosinophils or neutrophils.

**Lymphocytes in Other Types of Esophagitis**

Lymphocytes are a common inflammatory component of various other esophagitis; thus the presence of lymphocytes admixed with granulocytes should raises a distinct differential diagnosis, depending on the other components of the infiltrate. For example, common infections among immunosuppressed patients, including *Candida* species, cytomegalovirus, and herpesvirus usually occur in a background of neutrophils. However, increased numbers of lymphocytes may also be present. It is important to keep in mind the granulocytes are scare or absent in lymphocytic esophagitis and the presence of a neutrophil-rich infiltrate should prompt a search for microorganisms, including appropriate ancillary stains. Similarly, biopsy samples from patients with GERD and eosinophilic esophagitis may also reveal increased intraepithelial lymphocytes in addition to eosinophils. Importantly, some authors have noted that lymphocytes tend to aggregate in inter- rather than peripapillary regions in such cases, helping to make the distinction from lymphocytic esophagitis.

References:


Differential Diagnosis of Sloughing Esophagitis (Esophagitis Dissecans Superficialis)

Introduction

Sloughing esophagitis (Esophagitis dissecans superficialis) is a poorly-understood disorder that shows a predilection for elderly women. Most patients are chronically debilitated and take multiple medications. Medications that injure the esophagus, including NSAIDs, bisphosphonates, potassium chloride, and iron, as well as central nervous system depressant that may inhibit the swallow reflex, have been implicated. Patients present with reflux-like symptoms or dysphagia, but many cases are detected on endoscopic examination for unrelated reasons, such as iron deficiency anemia. Endoscopic features are more pronounced in the distal two-thirds of the esophagus and include longitudinal white casts of desquamated epithelium alternating with denuded, erythematous mucosa. Biopsy specimens reveal a “two-toned” appearance that reflects superficial sloughed layers of hypereosinophilic necrotic squamous epithelium and deeper layers of normal-appearing squamous cells. Parakeratosis and orthokeratosis are also seen. Inflammation is not a characteristic feature, but neutrophils and eosinophils may be present in the earlier stages. Treatment is supportive and includes acid suppression and topical analgesics. Several esophageal disorders may simulate the endoscopic and histologic features of sloughing esophagitis, as detailed subsequently; thus, endoscopic and pathologic correlation is essential for appropriate classification of this condition.
Differential Diagnosis

Other conditions that produce casts of desquamated epithelium may simulate sloughing esophagitis endoscopically. The most common are graft-versus-host disease and radiation esophagitis, both of which are easily excluded on clinical grounds and appear histologically distinct from sloughing esophagitis. These disorders are characterized by thinning of the esophageal mucosa and individual apoptotic (dyskeratotic) squamous cells. The epithelium may show marked reactive atypia, but detached fragments of contiguous necrotic squamous epithelial cells are not encountered. Biopsies of radiation esophagitis that contain subepithelial connective tissue may show bizarre fibroblasts. Trauma due to endoscopic procedures may also produce epithelial casts, but biopsy specimens show viable superficial epithelium, allowing distinction from sloughing esophagitis.

Histologic mimics of sloughing esophagitis include other lesions that alter the surface histology of the squamous mucosa. Parakeratosis is a common response to persistent injury, such as may be seen in patients with chronic gastroesophageal reflux. It forms a luminal compact layer of nucleated squamous epithelial cells with hyper eosinophilic cytoplasm. Epidermoid metaplasia is an uncommon histologic correlate of esophageal leukoplakia that involves the mid to lower esophagus of middle-aged females who present with dysphagia. This lesion is associated with tobacco use and excessive alcohol consumption. Concomitant squamous cell dysplasia or carcinoma is often reported in patients with epidermoid metaplasia, raising the possibility that it is a preneoplastic lesion. Epidermoid metaplasia is characterized by a granular cell layer subjacent to dense orthokeratosis that imparts a two-toned appearance to the mucosa. Both parakeratosis and epidermoid metaplasia are distinguished from sloughing esophagitis by the absence of intraepithelial splitting.

References:


Purdy JK, Appelman HD, McKenna BJ. Sloughing esophagitis is associated with chronic debilitation and medications that injure the esophageal mucosa. Mod Pathol. 2012; 25(5): 767-775.
Severe Non-Reflux Esophagitis

Introduction

There are many causes of severe esophagitis unrelated to reflux. Medication-related injury and infections are frequently encountered and most pathologists are familiar with the histologic features of these types of injuries. Some severe esophagitis, such as esophageal involvement in cutaneous bullous disorders, are relatively rare and, thus, pose diagnostic challenges to clinicians and pathologists. Awareness of typical findings in severe non-reflux esophagitis on the part of pathologists is important because appropriate interventions are etiologically specific.

Pill Esophagitis

A growing list of medications causes injury to the esophagus, usually by direct contact with the esophageal mucosa. Drug-related esophageal injury, also referred to as “pill esophagitis” tends to occur at points of extrinsic esophageal compression, including the junction of the proximal and middle third of the esophagus where it passes over the aortic arch, the gastroesophageal junction, and the segment overlying the left atrium in patients with left atrial enlargement. It is more common among elderly patients, who may spend more time in the recumbent position, and those who take multiple medications. Pill esophagitis is often characterized by sudden onset of severe retrosternal pain. Treatment of pill esophagitis includes removal of the offending agent and supportive care. Most pill-induced contact injury results in ulcers and produces non-specific histologic changes, such as neutrophilic inflammation, erosions, and granulation tissue. Ulcers may contain fragments of refractile cellulose filler material that is used in many medications. Some patterns of injury suggest a specific medication. For example, tetracycline antibiotics, which are used to treat acne cause severe injury characterized by marked intercellular edema in the deep to mid layers of the squamous mucosa and neutrophilic inflammation. Bisphosphonates are osteoclast inhibitors used to treat osteoporosis and other disorders of bone remodeling. They injure the esophagus by producing an alkaline pH upon dissolution. Although most cases of bisphosphonate-associated esophagitis are indistinguishable from other pill-induced injuries, sloughing esophagitis due to bisphosphonates has been reported.

Infectious Esophagitis
Severe esophagitis of infectious etiology is most often seen in immunosuppressed patients. The most commonly encountered viruses are in the herpesviridae family, namely herpes simplex (HSV) and cytomegalovirus (CMV), and timely initiation of antiviral therapy is critical. Both HSV1 and HSV2 can infect the esophagus with HSV1 being more common. The virus has a predilection for the mid and distal esophagus where ruptured vesicles appear as discrete ulcers to the endoscopist. Diagnostic features are present in denuded or intact squamous epithelial cells. Infected cells contain single or multiple enlarged nuclei bearing viral inclusions. Cowdry A type inclusions have an eosinophilic, glassy appearance, whereas Cowdry B inclusions have a powdery, homogeneous, basophilic quality. Cytomegalovirus produces large, discrete ulcers that may be confluent and are more pronounced in the mid to distal esophagus. In contrast, to HSV, CMV does not infect squamous epithelial cells, but shows a tropism for endothelial cells and glandular epithelia; thus esophageal infections are most readily detected when the ulcer bed is sampled. Viral inclusions may be intranuclear or intracytoplasmic. Nuclear inclusions are deeply amphophilic and have a peripheral clearing. They have a lentiform contour in some planes, and thus are referred to as “owl’s eye” inclusions. Cytoplasmic inclusions take the form of multiple brightly eosinophilic granules.

**Esophageal Involvement in Cutaneous Bullous Disorders**

Bullous diseases are primarily dermatologic disorders that disrupt intercellular adhesion. The esophageal squamous mucosa may be affected, resulting in a range of complications including dysphagia, bleeding, and strictures. Therapy includes immunosuppression and supportive measures, such as acid suppression and nutritional supplements. Pemphigus vulgaris is a rare autoimmune disorder in which autoantibodies to intercellular binding proteins, desmoglein 3 and desmoglein 1, cause blisters to form on the skin and mucous membranes. Esophageal involvement is reported in up to 70% of cases. Endoscopic findings include flaccid bullae, superficial erosions, and ulcers. Biopsy samples show suprabasilar clefting of the epithelium with a mild inflammatory infiltrate, including neutrophils and eosinophils. Squamous cells above the split have a rounded appearance, whereas basal epithelial cells clinging to the basement membrane are elongated, resembling tombstones. The diagnosis of pemphigus vulgaris can be confirmed with DIF, which shows intercellular IgG and C3 deposition throughout the mucosa. Bullous pemphigoid is also immune-mediated, primarily affects the skin, and involves the esophagus in ~5% of cases. It is caused by autoantibodies targeting hemidesmosomes that attach epithelial cells to the basement membrane; thus, subepithelial bullae form. Direct immunofluorescence demonstrates linear IgG and C3 deposition along the basement membrane.

Epidermolysis bullosa refers to a group of disorders characterized by trauma-induced blisters and may affect any squamous epithelial-lined surface. The junctional and
dystrophic forms of epidermolysis bullosa result from mutations in genes that encode basement membrane-associated collagens and integrins, allowing formation of subepithelial bullae. Mutations in keratin-encoding genes cause epidermolysis bullosa simplex. Biopsy samples demonstrate suprabasilar epithelial splitting. The esophagus is involved in 30-50% of cases where contact injury results from passage of food boluses. Webs and strictures are reported to form at sites of healed blisters in patients with this disorder. Direct immunofluorescence shows linear IgG deposits on the roof of blisters in the junctional and dystrophic forms, whereas immunoglobulin deposits on the floor of blisters in epidermolysis bullosa simplex. Complement deposits are usually absent.

References:


