Non-Neoplastic Esophageal Pathology

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Disclosure Statement

Dr. Montgomery reports no relevant financial relationships with commercial interests.

Basics

When scanning squamous mucosa from esophageal biopsies at low magnification, there are a few features to note:

1. Is there parakeratosis? – Foci of parakeratosis are likely to harbor Candida sp and should be examined for this.
2. Is the mucosa hyperplastic? – If it is hyperplastic with clear cell features, it is worth considering glycogenic acanthosis. If it is hyperplastic and reparative-appearing, the lamina propria might occasionally harbor a granular cell tumor.
3. Is there an ulcer? – Ulcers are, of course, where infectious agents should be sought.
Submucosal glands are very purple on PAS/AB staining.
Oncocytic change in esophageal submucosal glands
Inlet patch

Gastric mucosa in the proximal esophagus
(about 18 cm from the teeth)
About 1% of patients
Usually about 3-5 mm
Usually oxyntic mucosa (with parietal cells)
Associated cancers RARE
Pancreatic Metaplasia/Heterotopia
Common incidental findings
Found in adults and children alike
No need to report this but it can result in false positive Alcian blue staining
Respiratory metaplasia/heterotopia of gastroesophageal junction; rare, probably incidental.
Sebaceous Heterotopia

Found in about 2% of autopsies
Endoscopic small nodular, yellowing
Incidental finding
Sebaceous heterotopia – looks like skin but no granular layer!
Glycogenic acanthosis
Incidental finding in most cases
The endoscopist sees a slightly raised plaque
Some association with Cowden’s disease
Only a layer (or 2) of basal cells and then very thick heavily glycogenated epithelium
Esophageal melanosis/melanocytosis

Rare condition of middle aged adults
Gender ratio of about 2:1, M:F
May be more common in individuals with pigmented skin than in those with pale skin since the largest series is from India
Only on the order of 50 reported cases
Blue/black macules on endoscopy
Found in 8% of esophagi in one autopsy study; relation to esophageal melanoma is unclear
**Esophageal melanosis/melanocytosis**

Melanocytes are pigment-laden dendritic cells on H&E. Like skin counterparts, basal melanocytes of the esophagus lack desmosomes and tonofilaments but possess long dendritic cytoplasmic processes that extend between the keratinocytes, often passing through several layers of cells. Nuclei smaller and slightly more hyperchromatic than those of adjacent keratinocytes.

**Esophageal melanosis/melanocytosis**

Cells have uniform chromatin and indented nuclear contour. Nucleoli are inconspicuous. Positive for melanocytic markers, such as S100 protein, Melan-A, and HMB-45. Underlying lamina propria contains melanophages. No nuclear or cellular atypia. Overlying squamous epithelium may exhibit reactive basal hyperplasia, acanthosis, and hyperkeratosis but appears mature.
Esophagitis - Review

Medications/Drugs
- Older patients, multiple meds, stricture

Injury due to:
- Direct mechanical effect of pill
- Toxicity of medication itself
Iron pill esophagitis with reactive changes
Iron Medication Injury

In our patient population, mucosal iron (ferrous sulfate) is found in about 1% of patients undergoing upper tract endoscopic biopsies.

Iron can cause corrosive injury in the esophagus or can potentiate injury in a pre-existing ulcer or erosion.
Iron pill esophagitis with reactive changes
**Medications/Drugs:**

- Kayexalate
- Ischemic injury
- Seen in Esophagus, stomach, colon

Esophagitis: Infectious

Bacterial:
Primary: RARE
- Mycobacterial (MAI, TB)
- Actinomyces (“sulfur granules”)
- Treponema pallidum (2° or 3° syphilis)
2°: more common, usually mixed
CMV Esophagitis
- note the monocyte-rich background that can result in confusion with lymphoma
Herpes esophagitis: Gross appearances

Early

Late

Herpes esophagitis: biopsy

Herpes esophagitis
Herpes esophagitis, Esophagus brushing

Squamous cell carcinoma

Pseudoepitheliomatous hyperplasia and granular cell tumor
Atypical Stromal Cells in Ulcers

Case. Esophageal biopsies from a 10 year old boy with dysphagia.
Diagnosis – Eosinophilic Esophagitis
### Eosinophils in the Normal G.I. Tract

<table>
<thead>
<tr>
<th>Region</th>
<th>Lamina Propria</th>
<th>Epithelium</th>
<th>Muscularis Mucosae</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESOPHAGUS</strong></td>
<td>Very Few</td>
<td>None (?)</td>
<td>None</td>
</tr>
<tr>
<td><strong>STOMACH</strong></td>
<td>Very Few</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>SMALL BOWEL</strong></td>
<td>Scattered</td>
<td>Rare</td>
<td>None</td>
</tr>
<tr>
<td><strong>COLON</strong></td>
<td>Many*</td>
<td>Scattered</td>
<td>None</td>
</tr>
</tbody>
</table>

*35 fold difference between New Orleans and Boston


### Eosinophilic Esophagitis

- **Chronic immune/antigen-mediated disease limited to the esophagus with esophageal dysfunction associated with eosinophil inflammation**
- **Patient population:** children & adult; M > F
- **Presentation:** dysphagia to solid foods; food impaction
- **Diagnosis:** by correlation of clinical history with endoscopic findings and histologic features
- **Endoscopic findings:**
  - Feline appearance: wrinkled, corrugated, furrowed mucosa
  - Ulcerations blisters, webs/rings, strictures
- **Histology:**
  - > 15 eosinophils/hpf in any single field (with few exceptions)
  - Clusters of eosinophils near the surface; eosinophil microabscesses
  - Marked basal cell hyperplasia, elongation of rete pegs, spongiosis
  - Subepithelial (lamina propria) fibrosis/sclerosis
  - Changes as prominent in mid-esophagus as seen distally

### Evaluation of site-specific and seasonal variation in colonic mucosal eosinophils

<table>
<thead>
<tr>
<th>Month</th>
<th>April</th>
<th>May</th>
<th>June</th>
<th>July</th>
<th>August</th>
<th>September</th>
<th>October</th>
<th>November</th>
<th>December</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophils</td>
<td>35 x 15</td>
<td>35 x 10</td>
<td>35 x 10</td>
<td>35 x 10</td>
<td>35 x 10</td>
<td>35 x 10</td>
<td>35 x 10</td>
<td>35 x 10</td>
<td>35 x 10</td>
</tr>
</tbody>
</table>
Eosinophilic Esophagitis

• Incidence estimated at 1 person in 10,000 per year (many repeats because patients are often biopsied on follow-up), similar to incidence of IBD.
• Baltimore population is about 620,000 but greater metropolitan area is about 2,700,000 by 2010 census so that means over 270 new patients per year in our area.
• This is higher than the incidence reported for eosinophilic gastroenteritis and colitis (est 5.1/100,000 and 2.1/100,000); Clinical Gastroenterology and Hepatology 2017; 15: 1753-1741.
• Nice review in – Clinical gastroenterology and Hepatology 2017;15 (1655-1664) – November 2017 issue

“Feline” esophagus in eosinophilic esophagitis

Esophagus from a housecat
Eosinophilic esophagitis has a patchy distribution; these samples are from the same patient.

**Pediatric Eosinophilic Esophagitis**

**Presenting Symptoms**

<table>
<thead>
<tr>
<th>Feeding Disorder</th>
<th>Fraction of Pop.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>13%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>26%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>27%</td>
</tr>
<tr>
<td>Food Impaction</td>
<td>7%</td>
</tr>
</tbody>
</table>

![Graph showing fraction of patients with feeding disorders by age (Years)](image)
Do dietary changes actually work?

- The diets offered are:
  - The elemental diet (unpalatable)
    Elemental formulas contain proteins that have been completely broken down into their simplest form, amino acids. The formulas are designed to meet the full nutritional needs of the growing child without triggering the child’s EoE symptoms. Neocate Infant, Neocate Junior (unflavored, vanilla, chocolate and tropical), EO28 Splash, Neocate Nutra (semi-solid), Elecare and Elecare Jr (unflavored and vanilla).
  - The 6 food elimination diet (horrendous but some can do it)
  - The 4 food elimination diet (unpleasant but do-able)

6 food elimination diet: milk products, eggs, wheat, soy, peanut/tree nuts, and fish/shellfish

4 food elimination diet: milk products, eggs, wheat, soy

Apparently the 4 food elimination is just as good as the 6 and works in about two thirds of people and cow milk is the worst of the “trigger foods”.


Medical Treatment of Active Eosinophilic Esophagitis.

<table>
<thead>
<tr>
<th>Table 1. Medical Treatment of Active Eosinophilic Esophagitis Method</th>
<th>Specific Recommendation or Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elemental diet therapy</td>
<td>—</td>
</tr>
<tr>
<td>Six-food elimination</td>
<td>Elimination of milk, wheat, eggs, soy, seafood, and nuts</td>
</tr>
<tr>
<td>Four-food elimination</td>
<td>Elimination of milk, wheat, eggs, and soy</td>
</tr>
<tr>
<td>Allergy testing-based</td>
<td>Elimination of foods on the basis of results of food challenge testing, skin prick tests, and other diagnostic tests</td>
</tr>
<tr>
<td>Proton-pump inhibitor†</td>
<td>Children: 1 mg twice a day (Children with body weights 10 to 20 kg: 1 mg once a day). Adults: 20 mg to 40 mg a day.</td>
</tr>
</tbody>
</table>
Skin Disease Affecting the Esophagus

Pemphigus vulgaris
Mucous membrane pemphigoid
Epidermolysis bullosa
Lichen sclerosis
Lichen planus
Toxic epidermal necrolysis

Lichen planus of Skin

Subacute to chronic mucocutaneous disorder of unknown etiology
Involves skin, nails, and mucosal surfaces.
Lichen planus of the skin affects both genders with equal frequency at any age, although most patients are middle-aged adults.
Cutaneous lichen planus: eruptions of violaceous, scaling papules and plaques.
Intensely pruritic.
Extensor surfaces of the forearms and legs.
Mucosal Lichen Planus

Mucosal surfaces: perineum, oral mucosa, and pharynx.
Predominantly a disease of middle-aged women. Oral involvement, in particular, coexists with skin lesions in approximately 30% to 50% of patients, but can be the sole disease manifestation.
Esophageal vs Skin Lichen Planus

Parakeratosis, no hypergranulosis [Esophagus lacks orthokeratin or granular layer]
Often atrophic.
Band-like inflammatory infiltrate, T cells, basal layer degeneration, Civatte bodies.

Hypergranulosis, hyperorthokeratosis, acanthosis, and "saw-tooth" elongation of the rete pegs.
Often acanthotic
Band-like inflammatory infiltrate, T cells, basal layer degeneration, Civatte bodies.

Skin vs Mucosal LP
An aside:

A lymphocytic esophagitis pattern has been associated with Crohn’s disease; especially in children.
This was not confirmed in a study by Dr. Barbara McKenna. She did not uncover a definite association with any condition; noted a trend towards association with Crohn’s disease in children; also considered something akin to a contact dermatitis (Am J Clin Pathol, Oct 2005).

Lichenoid Esophagitis Pattern in Patients Without Lichen planus

Both present with dysphagia, with superimposable histologic features
LP is more likely than LEP to arise in women, result in stricture formation, be associated with rheumatologic disorders and use of multiple medications
Identical histology is associated with viral hepatitis and HIV.

Lichenoid Esophagitis Pattern in Patients Without Lichen planus

Either process can be associated with progression to neoplasia in a minority of case.
The risk of stricture formation is higher in true lichen planus esophagitis so it is worth performing pertinent IF studies to confirm
Ps. Be sure to check for Candida

**Pemphigus Vulgaris**

Most common form of pemphigus, M=F, 4th and 5th decades. Skin and the mucous membrane involvement typical. Any mucosal surface can be involved, but oral lesions are hallmark - present in almost every case and are the presenting sign in half of affected patients. Esophageal involvement found in most patients if sought.
Crohn’s Disease Affecting the Esophagus

Found in 5-25% of persons with Crohn’s disease, usually in those with severe ileocolic disease

Somewhat nonspecific histology when there are no granulomas

Lymphocytic esophagitis pattern correlates well with Crohn’s disease in children
Esophageal Crohn's disease – note lymphocytic esophagitis pattern and granuloma in lamina propria.
Precursors to Squamous Cell Carcinoma
Basal cell hyperplasia – fails to retain Lugol's iodine; >15% basal cell thickness – controversial
"Leukoplakia" (orthokeratotic dysplasia/epidermoid metaplasia) – not well-established as a precursor but provocative
Low-grade Intra-epithelial neoplasia/ squamous dysplasia (lower half of epithelium – mild cytologic alteration).
High-grade (over half thickness; more striking cytologic alterations)

Leukoplakia (orthokeratotic dysplasia/epidermoid metaplasia)
Leukoplakia refers to a persistent white patch usually encountered in the buccal mucosa that corresponds histologically to areas of hyperkeratosis. Corresponding esophageal lesions are rarely encountered and are sporadically mentioned in the literature.
Leukoplakia (orthokeratotic dysplasia/epidermoid metaplasia)
Plaques of white, thickened mucosa, or red areas which are typically more prominent toward the distal third of the esophagus. Biopsies show epithelial hyperplasia and hyperkeratosis and a granular layer just like skin.

Leukoplakia (orthokeratotic dysplasia/epidermoid metaplasia)
Significantly greater history of alcohol consumption, head and neck pathology (squamous carcinoma/dysplasia, leukoplakia, and lichen planus), esophageal squamous dysplasia and/or squamous carcinoma when compared to those surveyed due to Barrett esophagus. Our cases were also associated with squamous neoplasia but we had far fewer.


Esophageal epidermoid metaplasia – note granular layer and parakeratosis – presents as a plaque to the endoscopist.
Esophageal epidermoid metaplasia with granular layer and parakeratosis

Epidermoid metaplasia and mass

Epidermoid metaplasia
Epidermoid Metaplasia

The molecular alterations are identical to those in the associated squamous cell carcinomas!