

Esophageal Pathology: Eosinophils and other Doozies

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- Disclosures:
 - Salary support: C₂ Therapeutics

Objectives

- Discuss a practical approach to tricky issues/pitfalls encountered in esophageal biopsies.
- Discuss a newer, less known entity commonly seen in esophageal specimens

Topics

- Eosinophilic esophagitis
- Lymphocytic esophagitis
- Lichenoid esophagitis pattern
- Epidermoid metaplasia
- Infectious agents, tricks and pitfalls
 - Candida
 - HSV
 - CMV
- Multinucleated giant cell change
- Esophagitis dissecans superficialis
- Esophageal sebaceous glands
- Esophageal melanocytosis


Eosinophilic esophagitis

EoE

- As defined by the 2018 consensus recommendations:
“...a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation, defined as more than or equal to 15 eos/hpf (approx 60 eos/mm²) in the vast majority of cases.”

Dellon et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. [Gastroenterology](#). 2018 Oct;155(4):1022-1033.e10. doi: 10.1053/j.gastro.2018.07.009. Epub 2018 Sep 6.

EoE

- Main cause of dysphagia and food impaction in children, adolescents, and young adults
- Requires treatment
 - Chronic course
 - Subepithelial fibrosis  strictures and narrow-caliber esophagus

EoE: Diagnosis requires clinicopathologic correlation

Table 2.EoE Diagnostic Criteria

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- Symptoms of esophageal dysfunction
 - Concomitant atopic conditions should increase suspicion for EoE.
 - Endoscopic findings of rings, furrows, exudates, edema, stricture, narrowing, and crepe paper mucosa should increase suspicion for EoE.
 - ≥ 15 eos/hpf (~ 60 eos/mm²) on esophageal biopsy
 - Eosinophilic infiltration should be isolated to the esophagus.
 - Assessment of non-EoE disorders that cause or potentially contribute to esophageal eosinophilia
-

Dellon et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. [Gastroenterology](#). 2018 Oct;155(4):1022-1033.e10. doi: 10.1053/j.gastro.2018.07.009. Epub 2018 Sep 6.

Table 3. Conditions Associated With Esophageal Eosinophilia

- Eosinophilic esophagitis
- Eosinophilic gastritis, gastroenteritis, or colitis with esophageal involvement
- GERD
- Achalasia and other disorders of esophageal dysmotility
- Hypereosinophilic syndrome
- Crohn's disease with esophageal involvement
- Infections (fungal, viral)
- Connective tissue disorders
- Hypermobility syndromes
- Autoimmune disorders and vasculitides
- Dermatologic conditions with esophageal involvement (ie, pemphigus)
- Drug hypersensitivity reactions
- Pill esophagitis
- Graft vs host disease
- Mendelian disorders (Marfan syndrome type II, hyper-IgE syndrome, *PTEN* hamartoma tumor syndrome, Netherton syndrome, severe atopy metabolic wasting syndrome)

Dellon et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. *Gastroenterology*. 2018 Oct;155(4):1022-1033.e10. doi: 10.1053/j.gastro.2018.07.009. Epub 2018 Sep 6.

PPI's no longer used as part of the diagnostic algorithm

Table 1. Rationale for Changing the EoE Diagnostic Criteria and Removing the PPI Trial

Rationale	Comment
Similarities between EoE and PPI-REE	EoE and PPI-REE share similar clinical, endoscopic, histologic, immunologic, and molecular features before PPI treatment, suggesting that distinguishing these entities with a medication trial is artificial and that PPIs are better positioned as a treatment for EoE.
EoE and GERD are not necessarily mutually exclusive	An initial rationale for the PPI trial was to distinguish EoE from GERD, but it is now known that these conditions have a complex relationship and are not necessarily mutually exclusive.
Lack of a criterion standard for GERD diagnosis	Without a definitive method for defining GERD, no single test (including a PPI trial) can exclude the presence of GERD.
Novel mechanisms of action of PPIs to explain response of eosinophilia	Mechanisms that support PPIs as a treatment for EoE and esophageal eosinophilia include acid-independent anti-inflammatory/anti-eosinophil activity and reversal of epithelial permeability.
Observation that PPI-REE could also respond to classic EoE treatments	Patients with PPI-REE can also have a response to dietary elimination or topical steroid therapy, further blurring the line between EoE and PPI-REE.
Concern about using a treatment response to define a disease	Few diseases are primarily defined by response to treatment, and doing so limits potential treatment options for patients with EoE and esophageal eosinophilia.

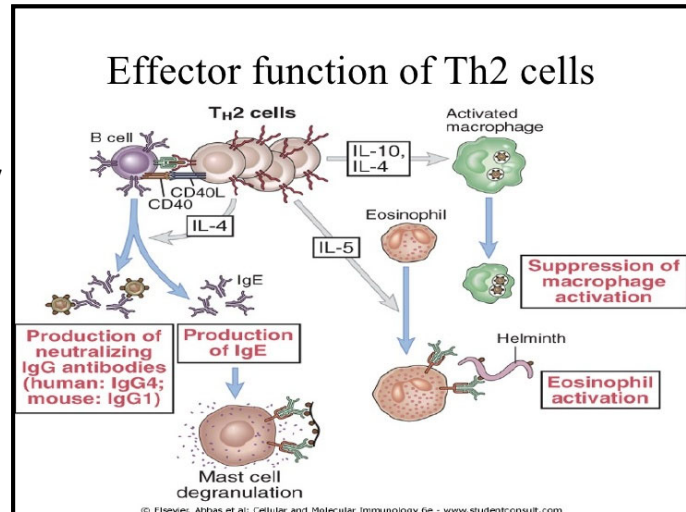
Dellon et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. [Gastroenterology](#). 2018 Oct;155(4):1022-1033.e10. doi: 10.1053/j.gastro.2018.07.009. Epub 2018 Sep 6.

“...These criteria will also allow new research and clinical trials to be conducted that will move the field forward. For example, patients who were previously diagnosed with PPI-REE might be reclassified as having EoE and could be enrolled into clinical trials...Now, the evidence suggests that in many cases PPI-REE is indistinguishable from EoE and that PPIs are better classified as a treatment for esophageal eosinophilia that may be due to EoE than as a diagnostic criterion.”

Dellon et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. [Gastroenterology](#). 2018 Oct;155(4):1022-1033.e10. doi: 10.1053/j.gastro.2018.07.009. Epub 2018 Sep 6.

What's the immunologic mechanism?

- Unknown
- Considered an allergic T_H2 -mediated response in genetically predisposed individuals



<https://www.slideshare.net/AllergyChula/cellmediated-immune-responses>

What's the immunologic mechanism?

- Prevalence of atopic disorders is approximately 50% higher in adult and pediatric patients with EoE than the general population
 - Allergic rhinitis
 - Asthma
 - Eczema
- Over 80% of patients with EoE have serum IgE specific for at least one food- or multiple environmental allergens*.

*Roy-Ghanta et al. Atopic characteristics of adult patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2008;6(5):531-535.

What's the immunologic mechanism?

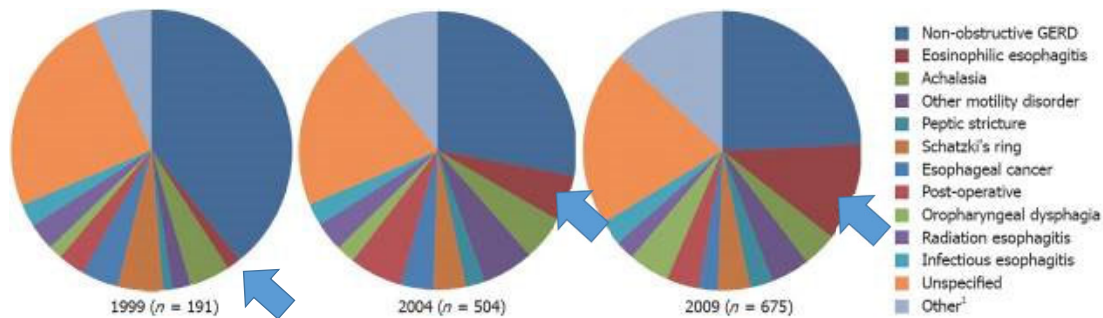
- Others argue that it is a non-IgE mediated food sensitivity
 - Anti IgE tx not effective
 - Some have recently proposed a role for IgG4*
- Multiple genes identified that are likely disease contributing:
 - *TSLP*
 - *CAPN14*
 - *EMSY*
 - *LRRC32*
 - *STAT6*
 - *ANKRD27*
 - *CCL26*

Clayton et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. *Gastroenterology*. 2014 Sep;147(3):602-9. doi: 10.1053/j.gastro.2014.05.036. Epub 2014 Jun 4.

What's the immunologic mechanism?

- Barrier dysfunction
 - Integrity of the basal layer compromised
 - Could facilitate passage of allergenic molecules

Relative Prevalence Increased from 1999-2009



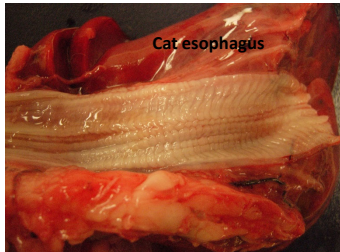
Kidambi et al. Temporal trends in the relative prevalence of dysphagia etiologies from 1999-2009. World J Gastroenterol. 2012 Aug 28;18(32):4335-41

Presentation

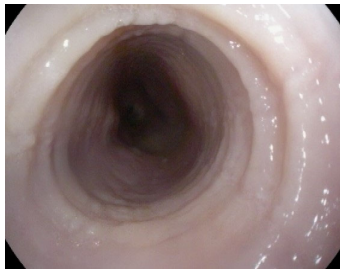
- Dysphagia
 - Food impaction
 - Chest pain
 - Heartburn
 - Dyspepsia
 - Nausea
 - Vomiting
 - Odynophagia
 - Abdominal pain
 - Weight loss
- Most common
- ♂
- ♀

Straumann et al. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years Gastroenterology. 2003 Dec;125(6):1660-9.
 Lynch et al. Gender is a determinative factor in the initial clinical presentation of eosinophilic esophagitis. Dis Esophagus. 2016 Feb-Mar;29(2):174-8. doi: 10.1111/dote.12307. Epub 2015 Jan 27

Concentric Rings (Felinization)



Photograph courtesy of
Melissa D. Sanchez, VMD, PhD, DACVP.



Photograph courtesy of M. Aamir Ali, M.D.

- Loss of normal vascular pattern
- Transient concentric rings
 - Smooth muscle contraction
- Fixed concentric rings
 - Fibrotic stenoses

Linear Furrows

- Linear furrows
 - Mucosal and submucosal thickening
 - Loss of normal vascular pattern



Photograph courtesy of M. Aamir Ali, M.D.

White Exudates

- White exudates
 - Eosinophilic microabscesses
 - Loss of normal vascular pattern

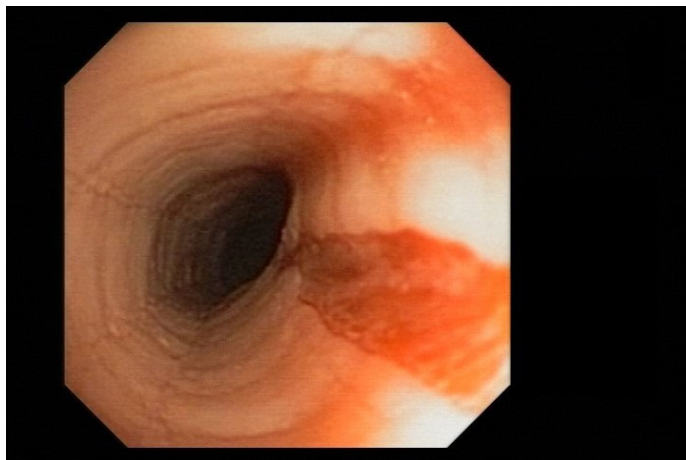


Photograph courtesy of M. Aamir Ali, M.D.

Mucosal Lacerations



- Crepe-paper appearance with mucosal lacerations
 - Endoscope injury
 - Loss of normal vascular pattern



Photograph courtesy of Matthew Chandler, M.D.

Histologic Findings

But first, let's do the numbers.

Is there truly a magic number for diagnosis?

- Consensus guidelines magic number is “15”
- 36% of patients with less than 14 eosinophils/hpf who undergo repeat endoscopy may fulfill “criteria” (i.e. 15 eos/hpf) for diagnosis on repeat biopsy*.
- 7-17% of patients with GERD may show more than or equal to 15 eos/hpf**
- One study with a high bias toward pts with GERD showed that 1.1% of biopsies have more than 20 eos/hpf (maximal eosinophil count range in 11 patients with GERD of 20-131/hpf)***

*Ravi, K., et al., Low grade esophageal eosinophilia in adults: an unrecognized part of the spectrum of eosinophilic esophagitis? Dig Dis Sci, 2011. 56(7): p. 1981-6.

**Mueller, S., et al., Comparison of histological parameters for the diagnosis of eosinophilic esophagitis versus gastro-oesophageal reflux disease on oesophageal biopsy material. Histopathology, 2008. 53(6): p. 676-84.

***Ravi, K., et al., Prevalence of esophageal eosinophils in patients with Barrett's esophagus. Am J Gastroenterol, 2011. 106(5): p. 851-7.

***Rodrigo, S., et al., High intraepithelial eosinophil counts in esophageal squamous epithelium are not specific for eosinophilic esophagitis in adults. Am J Gastroenterol, 2008. 103(2): p. 435-42.**

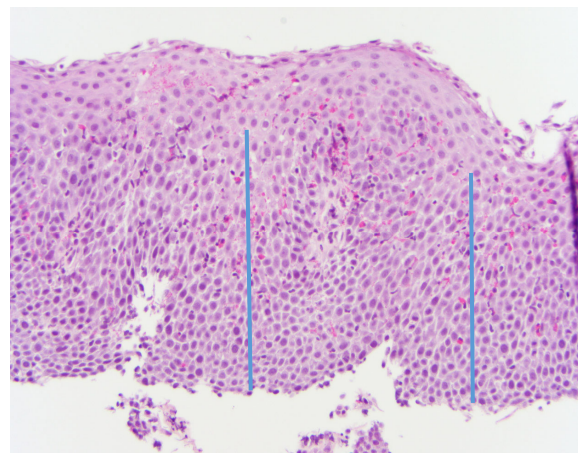
Answer

No

Relying solely on eosinophil count may lead to over or under diagnoses

Ancillary Features: Marked basal cell hyperplasia

- Many times the initial eye-catching feature at low magnification.
- May account for well over 50% of the squamous epithelial thickness
- The degree of hyperplasia tends to be more severe in cases of EoE than GERD*

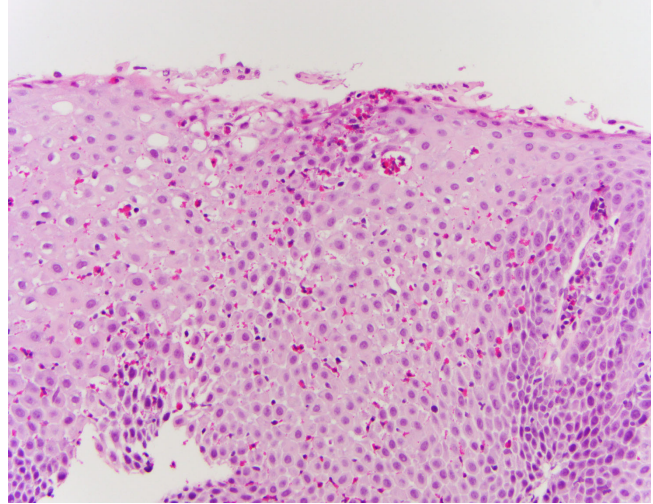


*Li-Kim-Moy, J.P., et al., Esophageal subepithelial fibrosis and hyalinization are features of eosinophilic esophagitis. J Pediatr Gastroenterol Nutr, 2011. 52(2): p. 147-53.

*Parfitt, J.R., et al., Eosinophilic esophagitis in adults: distinguishing features from gastroesophageal reflux disease: a study of 41 patients. Mod Pathol, 2006. 19(1): p. 90-6.

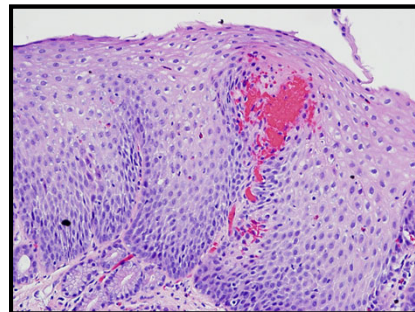
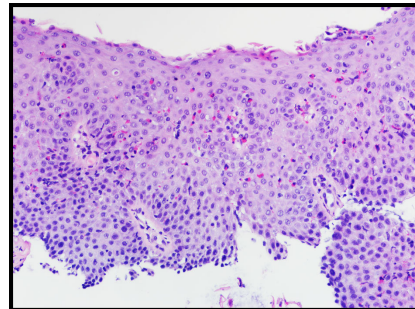
Ancillary Features: Eosinophilic Microabscesses

- Strongly associated with though not entirely specific for EoE



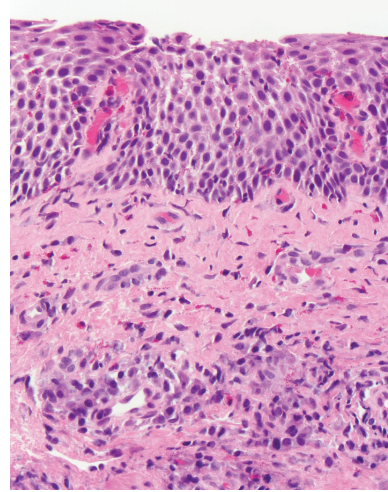
Ancillary features: Full Thickness Epithelial Eosinophil Distribution

- Typically seen distributed diffusely involving both deep and superficial portions of the epithelium
- In GERD: more often predominantly limited to the lower half
- Not cut and dry: superficial eosinophil layering may be seen in a subset of cases of GERD



Ancillary Features: Lamina Propria Fibrosis

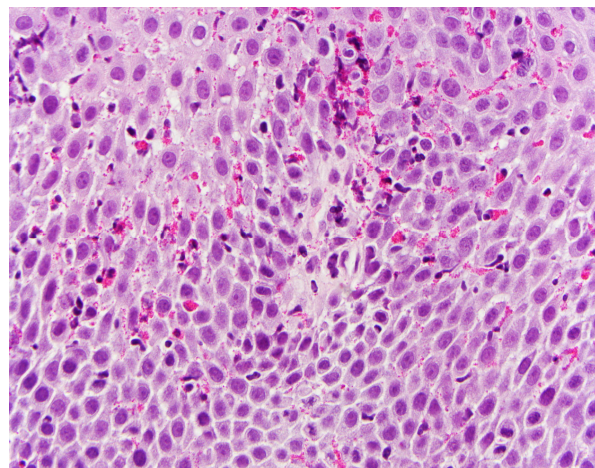
- More commonly associated with EoE than with GERD by some
 - 39% of patients with EoE vs 7% of pts with GERD*
- The majority of biopsies in our material lack this component



*Parfitt, J.R., et al. Eosinophilic esophagitis in adults: distinguishing features from gastroesophageal reflux disease: a study of 41 patients. *Mod Pathol*, 2006. 19(1): p. 90-6.

Ancillary Features: Eosinophil Degranulation

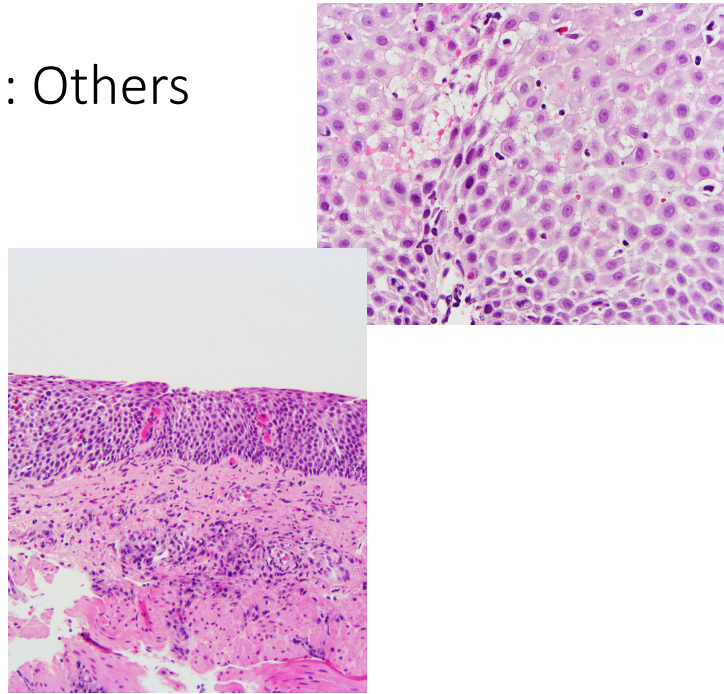
- Some authors have found significantly higher eosinophil degranulation in cases of EoE than in cases of GERD.
- Extracellular eosinophil major basic protein (MBP) has been detected via immunohistochemistry in patients with EoE but not in patients with GERD



Aceves, S.S., et al., Distinguishing eosinophilic esophagitis in pediatric patients: clinical, endoscopic, and histologic features of an emerging disorder. *J Clin Gastroenterol*, 2007. 41(3): p. 252-6.
 Mueller, S., et al., Eosinophil infiltration and degranulation in oesophageal mucosa from adult patients with eosinophilic oesophagitis: a retrospective and comparative study on pathological biopsy. *J Clin Pathol*, 2006. 59(11): p. 1175-80.
 Mueller, S., et al., Comparison of histological parameters for the diagnosis of eosinophilic oesophagitis versus gastro-oesophageal reflux disease on oesophageal biopsy material. *Histopathology*, 2008. 53(6): p. 676-84.

Ancillary Features: Others

- Dilated intercellular spaces
- Intracytoplasmic keratinocyte vacuolation
- Lamina propria papillae elongation
- Lamina propria eosinophils



Comparison of histologic features between eosinophilic esophagitis (EoE) and gastroesophageal reflux disease (GERD)

	EoE	GERD
Degranulated eosinophils	Prominent	Rare
Eosinophilic microabscesses*	Frequent	Uncommon
Diffuse intraepithelial distribution of eosinophils	Prominent	Rare (usually limited to the lower half)
Basal cell hyperplasia ("eye-catching" at low power)***	Prominent (usually $\geq 50\%$ epithelial thickness)	Mild (usually less than $\leq 25\%$ epithelial thickness)
Keratinocyte vacuolation	Possible	Possible
Dilated intercellular spaces*	Possible	Possible
Lamina propria fibrosis	Frequent	Rare
Lamina propria papillae****	May reach upper 1/3 of the squamous epithelium	May reach upper 1/3 of the squamous epithelium
Eosinophil density****	Usually > 24 per 40x field	Usually < 8 per 40x field

* Refers to intraepithelial clusters of 4 or more eosinophils

** In the normal state, the basal layer should constitute $\leq 15\%$ of the thickness of the squamous epithelium.

*** In the normal state, the lamina propria papillae extend into no more than the lower 2/3 of the squamous epithelium.

**** We do not "hang our hats" based on eosinophil number but rather favor or disfavor a diagnosis of EoE based on a combination of all features present (or absent) in the biopsies.

While basal cell hyperplasia, dilated intercellular spaces, and elongated lamina propria papillae may be seen in both conditions, the changes tend to be more severe in cases of EoE.

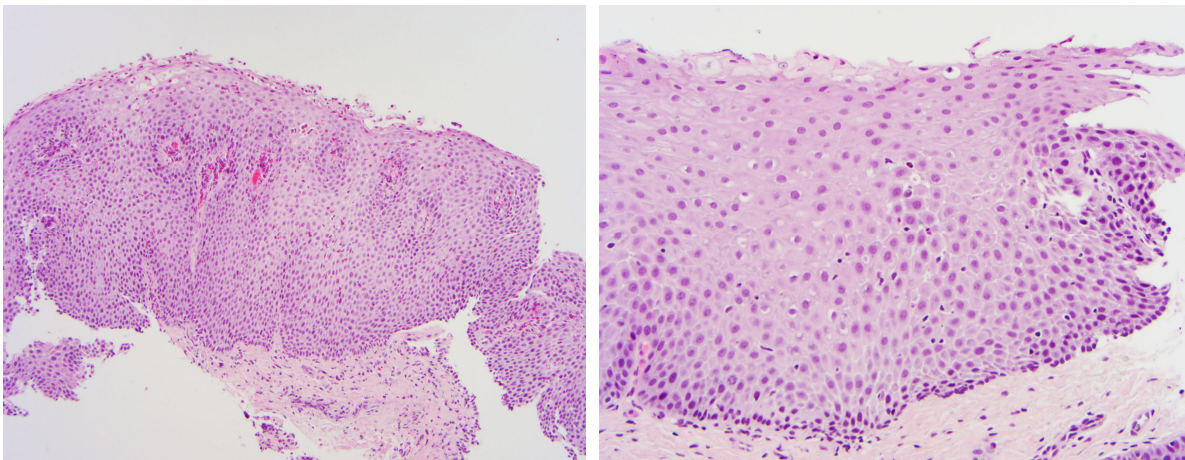
How many biopsies?

- Can be patchy
- Localized
- Mucosa may be spared
- Adults: Sensitivity of 55% with one biopsy → 100% with 5*
- Children: Sensitivity of 73% with one biopsy → 84%, 97%, and 100% with 2, 3, and 6, respectively**

Multiple biopsies may be necessary

*Gonsalves, N., et al., Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. *Gastrointest Endosc*, 2006. 64(3): p. 313-9.
** Shah et al. Histopathologic variability in children with eosinophilic esophagitis. *Am J Gastroenterol*. 2009 Mar;104(3):716-21. doi: 10.1038/ajg.2008.117. Epub 2009 Feb 10

Same patient, same endoscopic exam



So, why 15?

- Figure most commonly used among all studies reviewed and it was the lowest density of eosinophils reported for a diagnosis of EoE
- Peak count was the method most commonly used among studies

Not disease-defining

Should be interpreted along with other ancillary histologic features

Clinical context should be taken into account

Our approach

- Cases with prominent eosinophils and aforementioned ancillary features
 - “*Eosinophilic esophagitis **pattern***”
- Also cases with
 - Convincing ancillary features *even* in cases with less than 15 eos in patients with a history of EoE *or*
 - New cases with adequate endoscopic and clinical correlates

Our approach

- Cases with prominent eosinophils but without ancillary features:

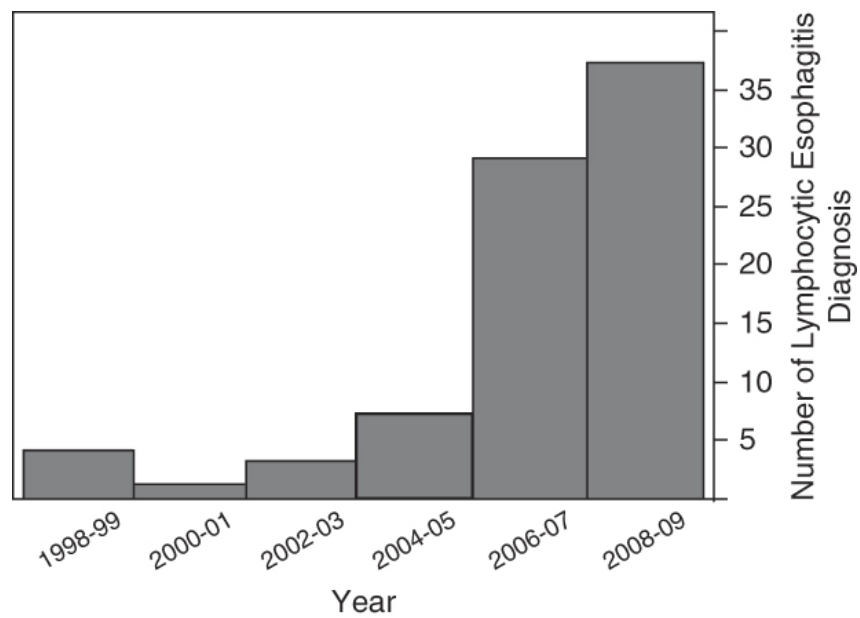
Squamous mucosa with intraepithelial eosinophils (#) and reactive epithelial changes. See note.

Note: The differential diagnosis includes gastroesophageal reflux vs. eosinophilic esophagitis. Clinical and endoscopic correlation are recommended.

Treatment

- Swallowed topical steroid therapy (budesonide and fluticasone propionate)
 - Decrease eosinophils in mucosa
 - Improve symptoms
- Systemic steroids – systemic adverse events
- Food elimination diets
 - Effective but psychosocially challenging

Lymphocytic Esophagitis



Cohen et al. Lymphocytic esophagitis: a diagnosis of increasing frequency. J Clin Gastroenterol. 2012 Nov-Dec;46(10):828-32

Variables	All Patients (n = 81)
Predominant clinical symptoms at diagnosis	
Dysphagia	54 (66.7%)
Heartburn	38 (46.9%)
Abdominal/chest pain	36 (44.4%)
Nausea/vomiting	24 (29.6%)
Odynophagia	10 (12.3%)
Esophageal endoscopic findings	
Normal	24 (29.6%)
Rings	16 (19.8%)
Esophagitis	13 (16.0%)
Stricture	7 (8.6%)
Erythema	4 (4.9%)
Nodularity	3 (3.7%)
Esophageal dilation performed	24 (29.6%)

Cohen et al. Lymphocytic esophagitis: a diagnosis of increasing frequency. J Clin Gastroenterol. 2012 Nov-Dec;46(10):828-32

Lymphocytic Esophagitis: No strong association with a clinical condition or symptom

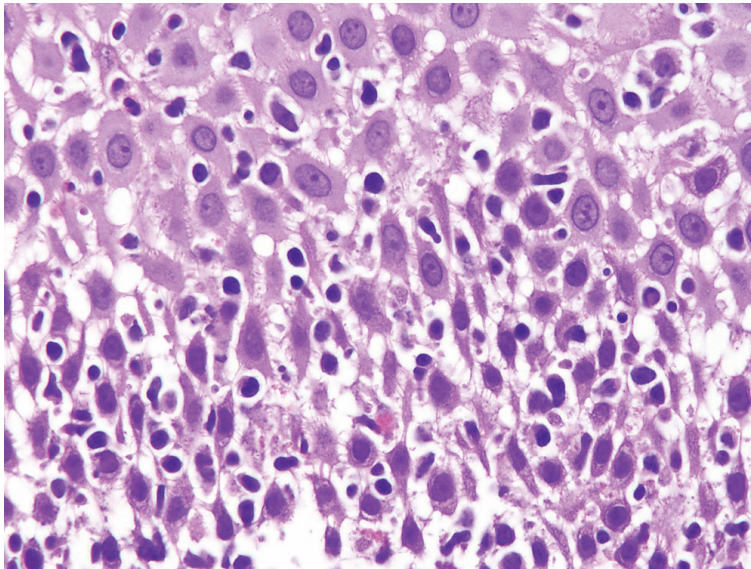
- Crohn disease
- GERD
- Candida esophagitis
- Celiac disease
- Carcinoma
- Allergy
- *H. pylori* gastritis
- Cirrhosis
- Diabetes
- Smoking
- No implicated medications

Rubio et al. Lymphocytic esophagitis: a histologic subset of chronic esophagitis. Am J Clin Pathol. 2006 Mar;125(3):432-7.

Pasricha et al. Lymphocytic Esophagitis: An Emerging Clinicopathologic Disease Associated with Dysphagia. Dig Dis Sci. 2016 Oct;61(10):2935-2941. doi: 10.1007/s10620-016-4230-2. Epub 2016 Jun 24.

Cohen et al. Lymphocytic esophagitis: a diagnosis of increasing frequency. J Clin Gastroenterol. 2012 Nov-Dec;46(10):828-32

Martin et al. Mucosal inflammation in Candida esophagitis has distinctive features that may be helpful diagnostically. Mod Pathol. 2018 Jun 19. doi: 10.1038/s41379-018-0060-4. [Epub ahead of print]



- Peripapillary edema involving the lower 2/3 of epithelium
- 50-58 lymphocytes per 40x field in papillary areas
- No significant neutrophilic or eosinophilic infiltrates

Lymphocytic Esophagitis

- Ringed esophagus similar to EoE reported in some patients*.
- Strictures
- Not a true entity
- Probably an esophageal inflammatory manifestation of other conditions

*Pleet et al. Rings in the esophagus are not always eosinophilic esophagitis: Case series of ring forming lymphocytic esophagitis and review of the literature. Endosc Int Open. 2017 Jun;5(6):E484-E488. doi: 10.1055/s-0043-106579. Epub 2017 May 31.

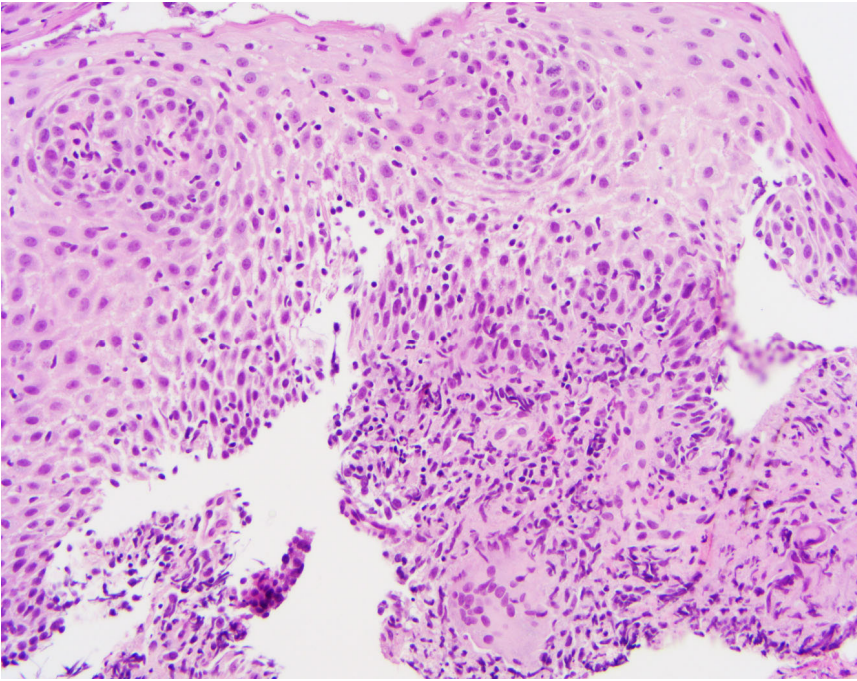
Lymphocytic Esophagitis:

- Typically persists on repeat biopsies
- Management
 - EoE
 - GERD
 - Dilation for strictures

Lymphocytic Esophagitis: Crohn disease

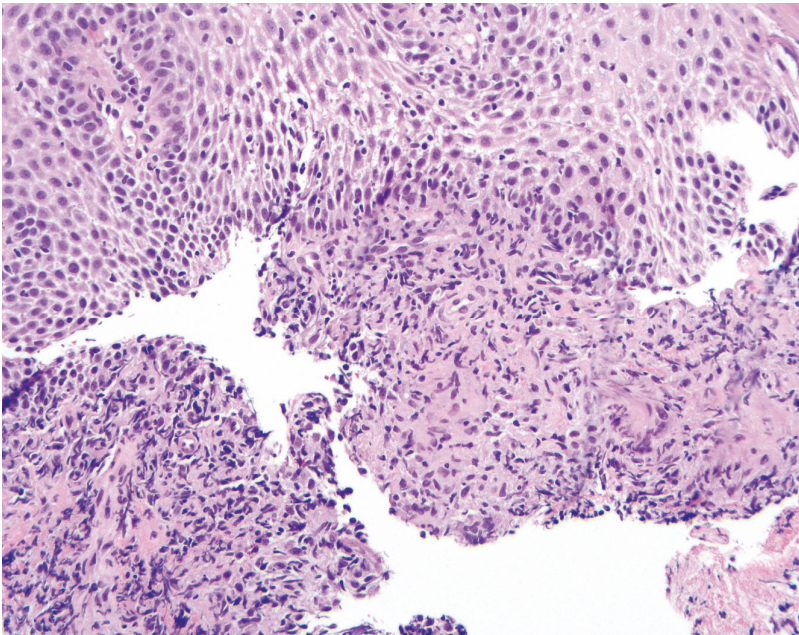
- Crohn disease
 - 5-40% of patients with LE have CD
 - Up to 28% of pediatric patients with CD will show LE
 - Prevalence of esophageal involvement in CD:
 - 5-11% adults
 - 17-42.5% children
 - Associated with advanced ileocolonic disease
 - 88-100% of patients have extraesophageal CD
 - 33% oral ulcers
 - Associated with perianal involvement in children
 - Endoscopy may be normal
 - Erythema, nodules, polypoid lesions, strictures, fistulae
 - Mid or distal esophagus

DeFelice et al. Crohn's Disease of the Esophagus: Clinical Features and Treatment Outcomes in the Biologic Era. *Inflamm Bowel Dis.* 2015 Sep;21(9):2106-13.
 Ammoury and Pfefferkorn. Significance of esophageal Crohn disease in children. *J Pediatr Gastroenterol Nutr.* 2011 Mar;52(3):291-4.



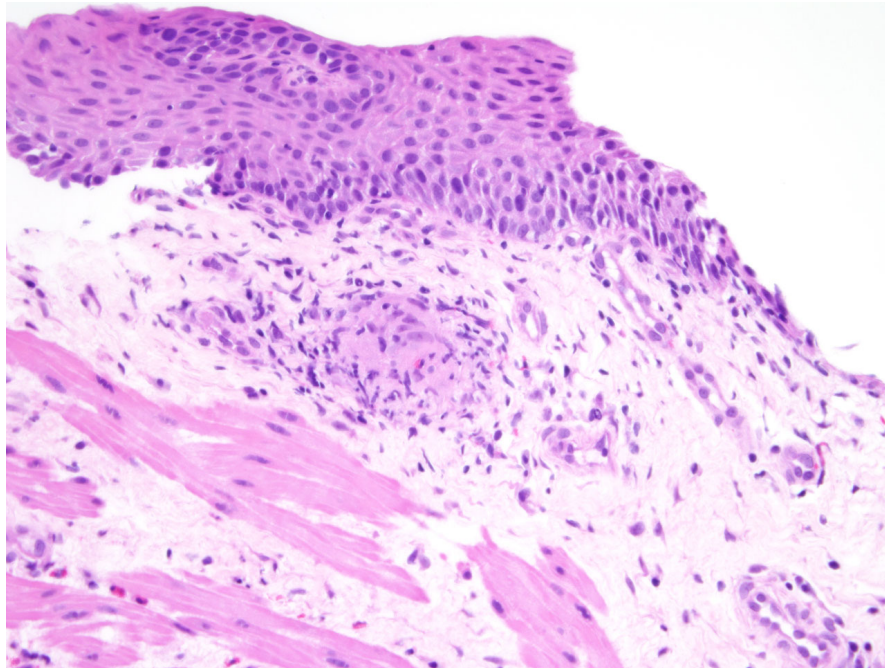
- Lymphocytic esophagitis pattern*

*Rubio et al. Lymphocytic esophagitis: a histologic subset of chronic esophagitis. Am J Clin Pathol. 2006 Mar;125(3):432-7.



- Granulomas present in 25% of pediatric biopsies*
- Mononuclear cells and histiocytes in the lamina propria

*Ramaswamy et al. Esophageal Crohn disease in children: a clinical spectrum. J Pediatr Gastroenterol Nutr. 2003 Apr;36(4):454-8.



Esophageal Crohn Disease

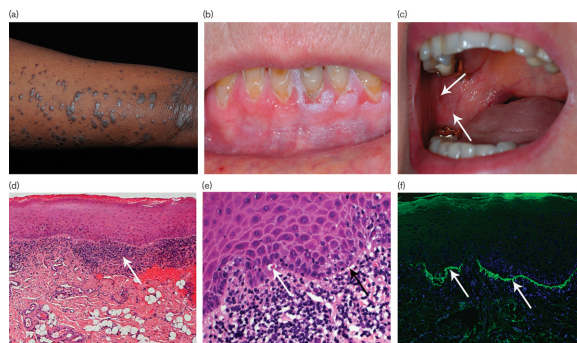
- Prednisone
- Topical budesonide
- Biologics

Lichenoid Esophagitis/Lichen Planus Esophagitis

Lichen Planus

- Subacute to chronic mucocutaneous disorder of unknown etiology
- Skin, nails, and oral and genital mucosa
- Eruptions of violaceous, scaling papules, and plaques

26-63% of patients with LP have esophageal involvement

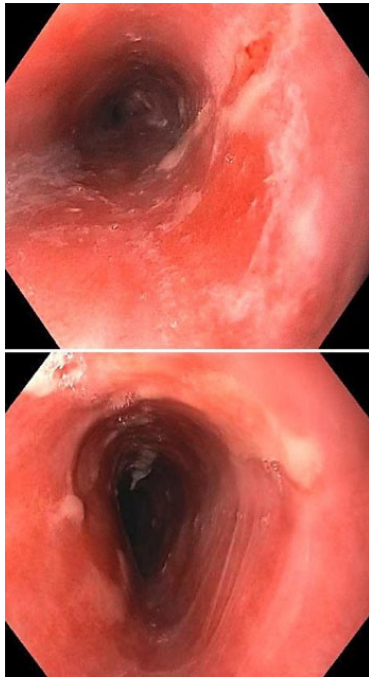


DIF: Fibrinogen deposition along basement membrane

Kern et al. Esophageal involvement is frequent in lichen planus: study in 32 patients with suggestion of clinicopathologic diagnostic criteria and therapeutic implications. Eur J Gastroenterol Hepatol. 2016 Dec;28(12):1374-1382.

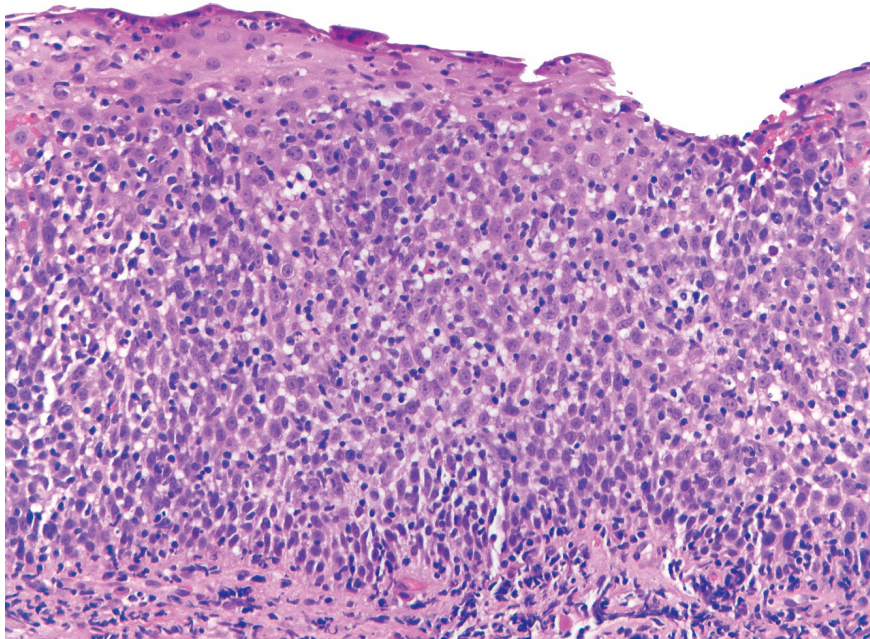
Esophageal Lichen Planus

- Dysphagia
- Food impaction
- Odynophagia
- Oral ulcers

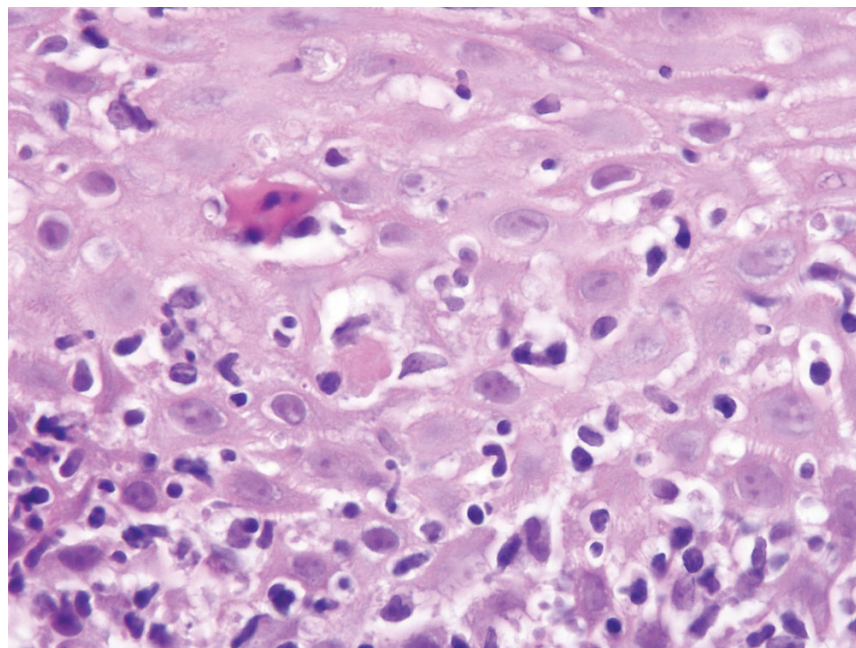


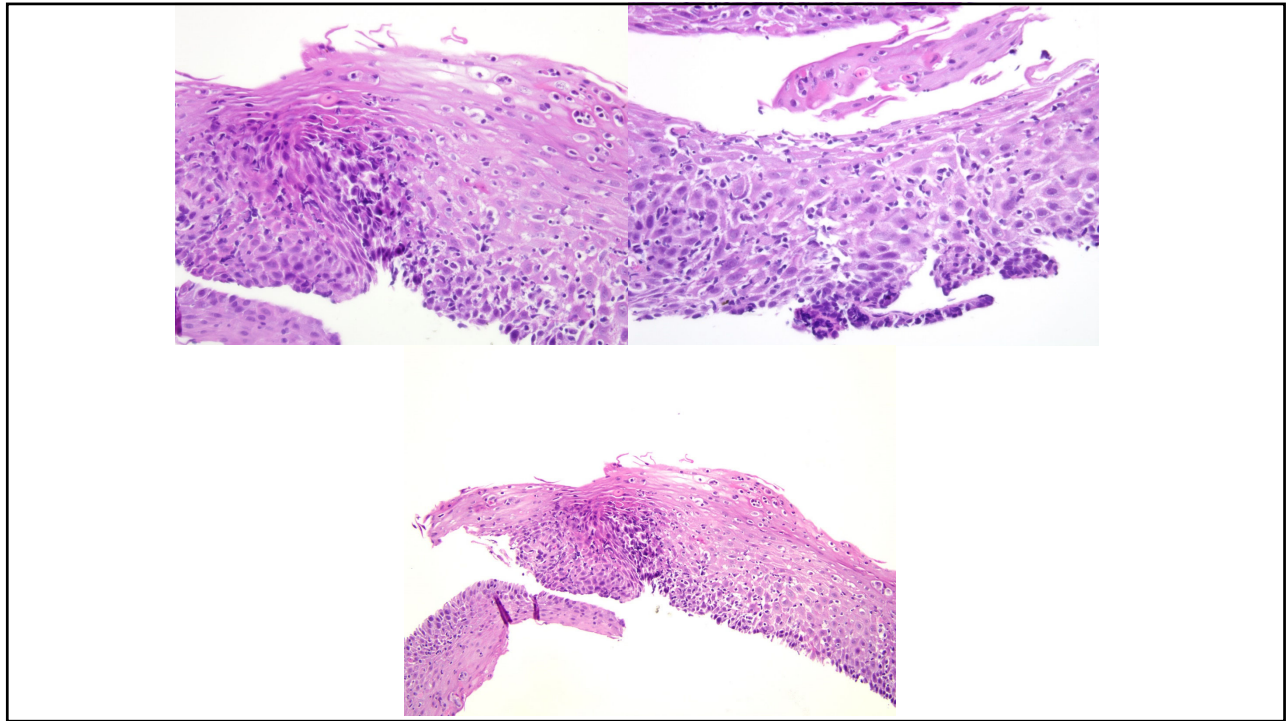
- Mucosal disease mostly women, middle aged
- Strictures (proximal, middle or distal)
- Ringed esophagus
- White exudates
- Hyperemia
- May be normal

Franco et al. Presentation, Diagnosis, and Management of Esophageal Lichen Planus: A Series of Six Cases. Case Rep Gastroenterol. 2015 Jul 22;9(2):253-60.



Civatte bodies





Pathologic Features Different from Skin LP

Esophagus

- No hypergranulosis
- No hyperorthokeratosis
 - + parakeratosis
- No acanthosis
 - Often atrophy
 - Variable thinning and thickening
- + Intense band-like infiltrate
- + apoptotic keratinocytes

Skin

- + hypergranulosis
- + hyperorthokeratosis
- + acanthosis
- + Intense band-like infiltrate
- + basal layer degeneration
- + apoptotic keratinocytes

Esophageal Lichen Planus

- A risk of malignancy is not well established
- Cases with associated esophageal squamous cell and verrucous carcinoma are documented
- Recognition important
 - Persistent dysphagia from esophagitis and stricture.
 - Trauma from therapeutic dilation can lead to exacerbation of lichen planus in a Koebner-like phenomenon (lesion development at injury site).

Therapy

- Topical budesonide
- Systemic corticosteroids
- Multiple dilations sometimes needed

Lichenoid Esophagitis Pattern

- We use this term in patients without a history of lichen planus
- Viral hepatitis
- HIV
- May also develop squamous neoplasia

Salariya et al. Lichenoid esophagitis: clinicopathologic overlap with established esophageal lichen planus. Am J Surg Pathol. 2013 Dec;37(12):1889-94.

Epidermoid Metaplasia

(A.K.A. Esophageal Leukoplakia)

Demographics and symptoms

- Slight female predominance
- Mean 61.5 y
- Dysphagia (56%)
- Personal history of smoking or exposure to second-hand smoke (61%)
- Alcohol (39%)

Singhi et al. Esophageal leukoplakia or epidermoid metaplasia: a clinicopathological study of 18 patients. *Mod Pathol*. 2014 Jan;27(38-43).

Endoscopic Findings

- White, tan, or villiform plaque-like areas with cobblestone appearance
- 1-10 cm
- More prominent toward the middle and distal third of the esophagus

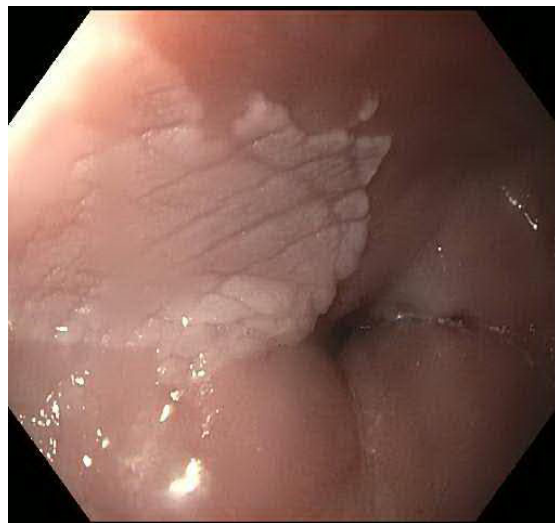
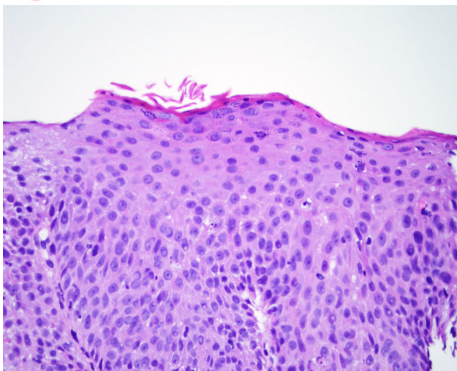
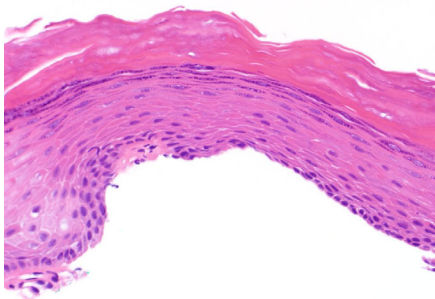
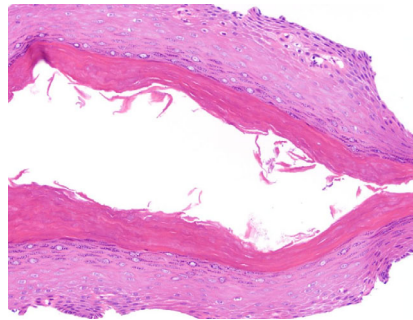
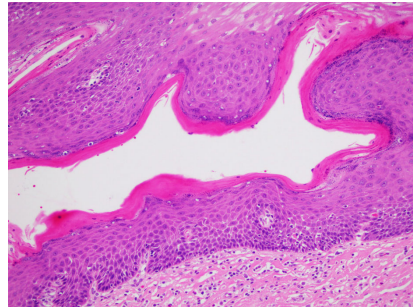


Image provided by Dr. Dora Lam-Himlin, Mayo Clinic, Arizona.

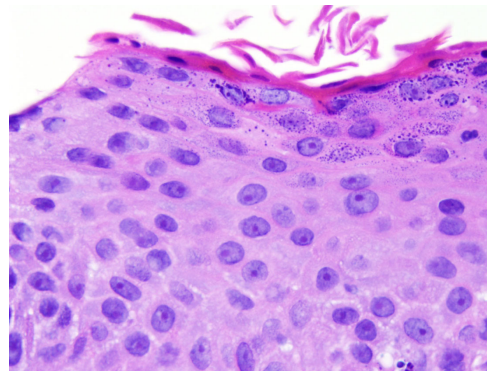
Histologic Findings

- Low magnification: Undulating squamous mucosa with flattened rete pegs and epithelial hyperplasia
- Closer look: Thick basal layer with acanthotic midzone
- Compact orthokeratosis overlying area of parakeratosis and a prominent, one-to-four-cell thick granular layer.



Histologic findings

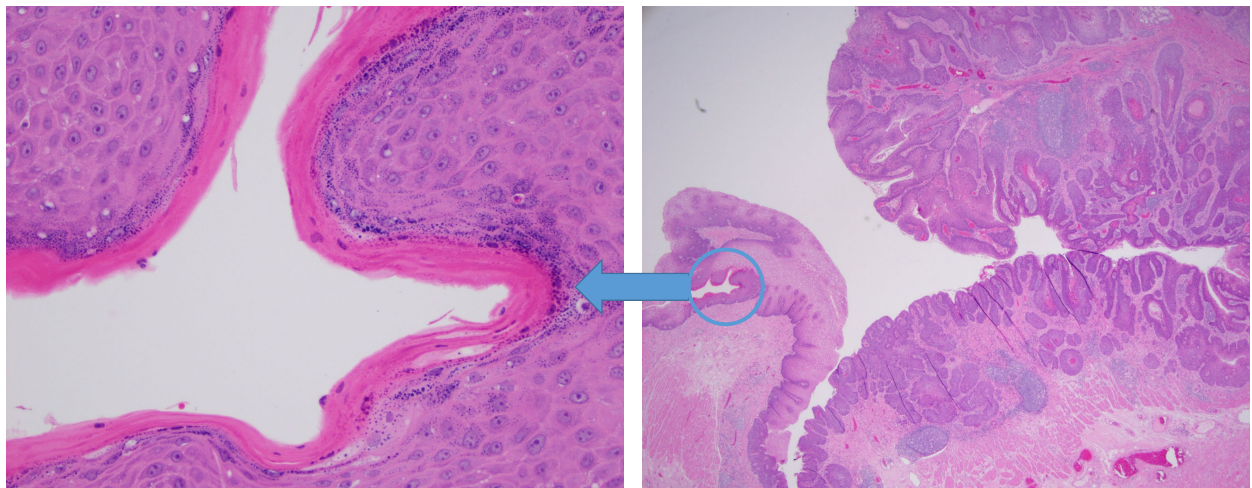
- Adjacent squamous dysplasia and or SCC possible
- Over half of pts have persistent disease



Significance

- Precursor to squamous cell carcinoma
- Supported by a recent study:
 - 67% of esophageal epidermoid metaplasia specimens' harbored alterations in genes often associated with esophageal squamous cell carcinoma
 - TP53, PIK3CA, EGFR, MYCN, HRAS, and the TERT promoter
 - Sequencing of synchronous and metachronous high-grade squamous dysplasia/esophageal squamous cell carcinoma identified shared genetic alterations with corresponding esophageal epidermoid metaplasia specimens
 - TP53 mutations correlated with concurrent or progression to HGSD/SCC.
 - No genetic alterations were detected in uninvolved esophageal squamous mucosa.

Singhi et al. Targeted next-generation sequencing supports epidermoid metaplasia of the esophagus as a precursor to esophageal squamous neoplasia. *Mod Pathol.* Nov;30(11):1613-1621



Sample Diagnosis

- Squamous mucosa with epidermoid metaplasia. See note.

Note: Epidermoid metaplasia may be associated with esophageal squamous dysplasia/neoplasia. Patient follow-up may be prudent.

References:

1. Singhi et al. Esophageal leukoplakia or epidermoid metaplasia: a clinicopathological study of 18 patients. *Mod Pathol.* 2014 Jan;27(1):38
2. Singhi et al. Targeted next-generation sequencing supports epidermoid metaplasia of the esophagus as a precursor to esophageal squamous neoplasia. *Mod Pathol.* Nov;30(11):1613-1621

Clues from the Inflammatory Backdrop in Infectious Esophagitis

Candida Esophagitis

Candida Esophagitis

- Incidence, 5.2%
- Clinically unsuspected in 54% of the cases.
- Dysphagia and odynophagia are predictive in non-HIV patients

Takahashi et al. Upper Gastrointestinal Symptoms Predictive of Candida Esophagitis and Erosive Esophagitis in HIV and Non-HIV Patients: An Endoscopy-Based Cross-Sectional Study of 6011 Patients. *Medicine (Baltimore)*. 2015 Nov;94(47):e2138

Clinical Features: Significant Associations

- Diabetes
- Malignancy
- End stage renal disease
- HIV
- Advanced age
- Medications for:
 - Asthma
 - Autoimmune disease
 - Transplant

Clinical Features

- Seen in 0.4% of healthy individuals
- Self limited

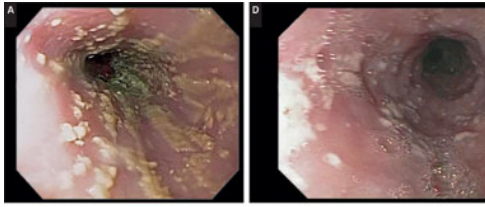
Lee et al. The clinical course of asymptomatic esophageal candidiasis incidentally diagnosed in general health inspection. Scand J Gastroenterol. 2015;50(12):1444-50.

Other Clinical Associations

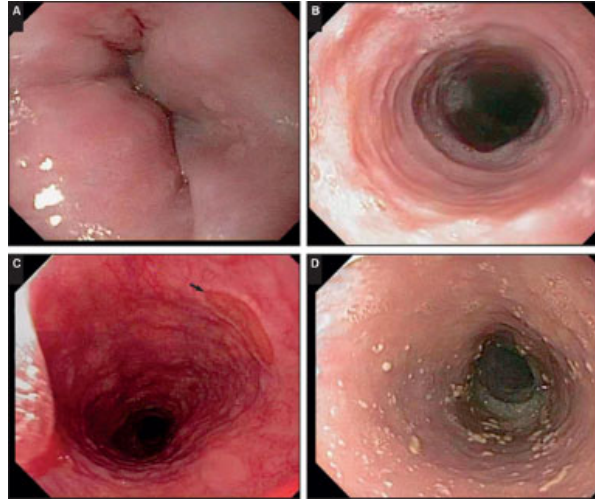
- Smoking
- Alcohol use seems protective

Endoscopic appearance

- White plaques
- White exudates
- Mucosal breaks



Alsomali, M. et al. Challenges to “Classic” Esophageal Candidiasis: Looks Are Usually Deceiving. American Journal of Clinical Pathology, Volume 147, Issue 1, 1 January 2017, Pages 33–42



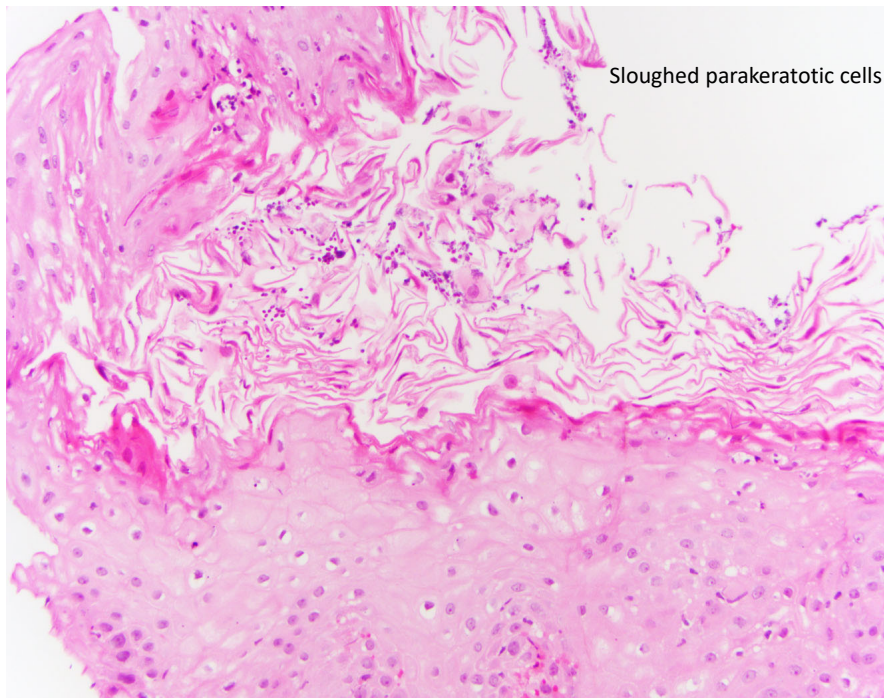
Candida Esophagitis: Histology

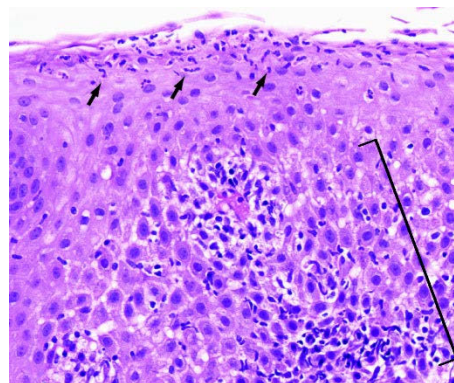
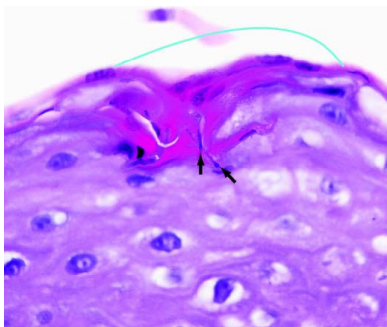
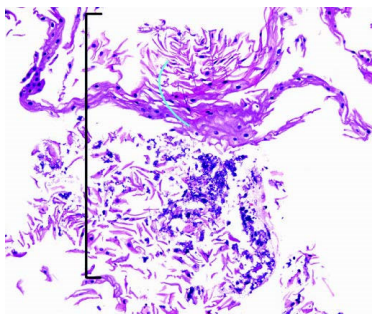
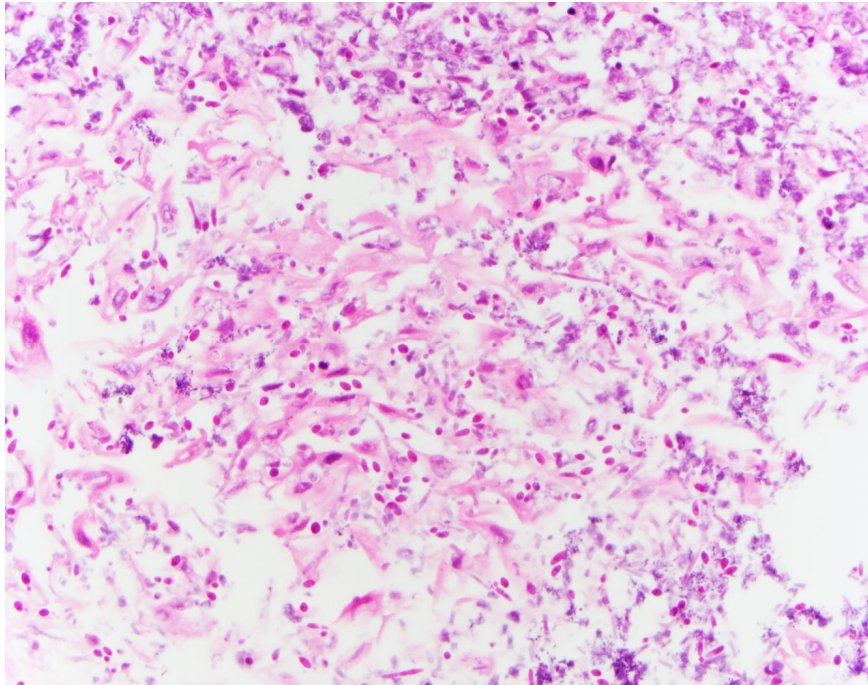
- 92.5% of cases display pseudohyphae on H&E
- Rare cases require use of ancillary stains

Candida Esophagitis: Histology

- Sloughed parakeratotic cells (pseudohyphae here 80%)
- With or without neutrophils
 - 30% have no neutrophilic infiltrate
 - When present typically superficially clustered
- With or without intraepithelial lymphocytosis
- Desquamated, hyper-pink parakeratosis (pseudohyphae here 62% time)
- Dead keratinocytes
- Bacterial overgrowth
- Increased intraepithelial lymphocytes

Alsomali, M. et al. Challenges to "Classic" Esophageal Candidiasis: Looks Are Usually Deceiving. American Journal of Clinical Pathology, Volume 147, Issue 1, 1 January 2017, Pages 33–42
Martin et al. Mucosal inflammation in Candida esophagitis has distinctive features that may be helpful diagnostically. Mod Pathol. 2018 Jun 19. doi: 10.1038/s41379-018-0060-4. [Epub ahead of print]





Alsomali, M. et al. Challenges to "Classic" Esophageal Candidiasis: Looks Are Usually Deceiving. American Journal of Clinical Pathology, Volume 147, Issue 1, 1 January 2017, Pages 33–42

When to order PAS or GMS?

- Ulcer
- Desquamated or hyper-pink parakeratosis
- Superficial neutrophils
- Intraepithelial lymphocytosis
- Clinical suspicion

Herpes simplex and Cytomegalovirus infection

HSV

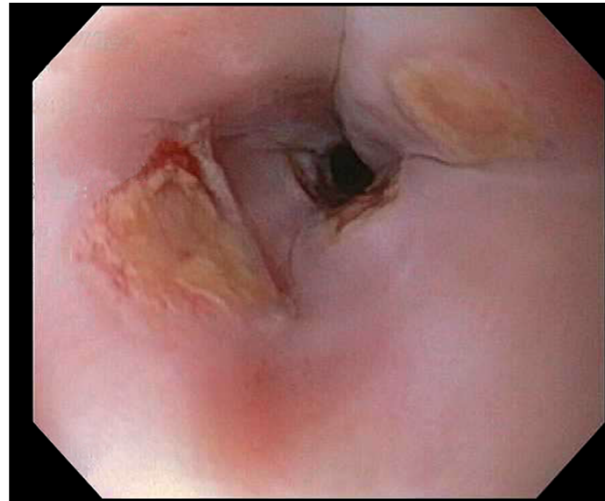
- Debilitation and immunosuppression
- Reported in immunocompetent kids with EoE
 - As a harbinger
 - In patients with an established history

Fritz et al. Herpes Simplex Virus Esophagitis in Immunocompetent Children: A Harbinger of Eosinophilic Esophagitis? J Pediatr Gastroenterol Nutr. 2017 Sep 20.

Zimmermann et al. Acute Herpes Simplex Viral Esophagitis Occurring in 5 Immunocompetent Individuals With Eosinophilic Esophagitis. ACG Case Rep J. 2016 Apr 15;3(3):165-8.

CMV

- Debilitation and immunosuppression
- 25%-50% of those with GI tract infection are immunocompetent
- Fever common
- 83% may be asymptomatic
- Odynophagia and dysphagia
- Mucosal ulcerations that may be large and deep
- May have tumoral appearance
- May rarely lead to strictures



Marques et al. Cytomegalovirus Disease of the Upper Gastrointestinal Tract: A 10-Year Retrospective Study. GE Port J Gastroenterol. 2017 Nov;24(6):262-268

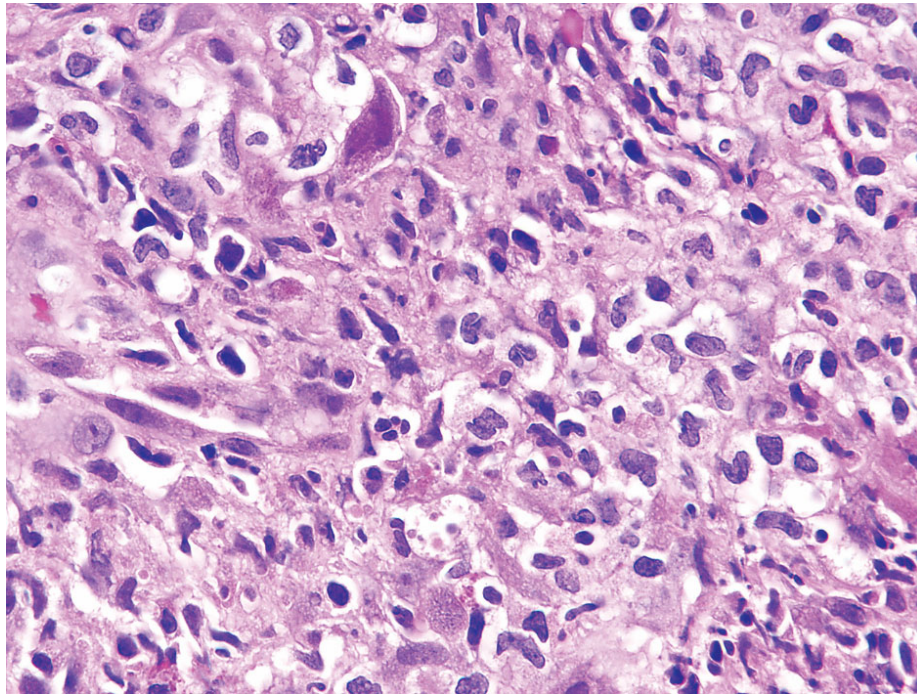
Lin et al. Clinical and endoscopic features for alimentary tract cytomegalovirus disease: report of 20 cases with gastrointestinal cytomegalovirus disease. Chang Gung Med J. 2005 Jul;28(7):476-84.

Laguna et al. Pseudotumoral appearance of cytomegalovirus esophagitis and gastritis in AIDS patients. Am J Gastroenterol. 1993 Jul;88(7):1108-11.

HSV and CMV

- Same features as elsewhere
- Background may offer clues when viropathic cells are not easily identified
- **Aggregates of macrophages** adjacent to the infected epithelium in HSV
- **Aggregates of macrophages in CMV ulcers**
 - Granulation tissue and or exudate location
 - Perivascular, diffuse or patchy distribution

Greenon et al. Prominent mononuclear cell infiltrate is characteristic of herpes esophagitis. Hum Pathol. 1991 Jun;22(6):541-9
Greenon. Macrophage aggregates in cytomegalovirus esophagitis. Hum Pathol. 1997 Mar;28(3):375-8



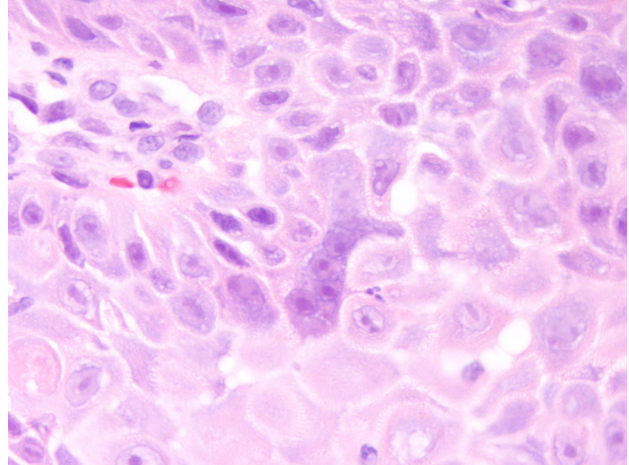
Multinucleated Giant Cell Change

Multinucleated Giant Cell Change

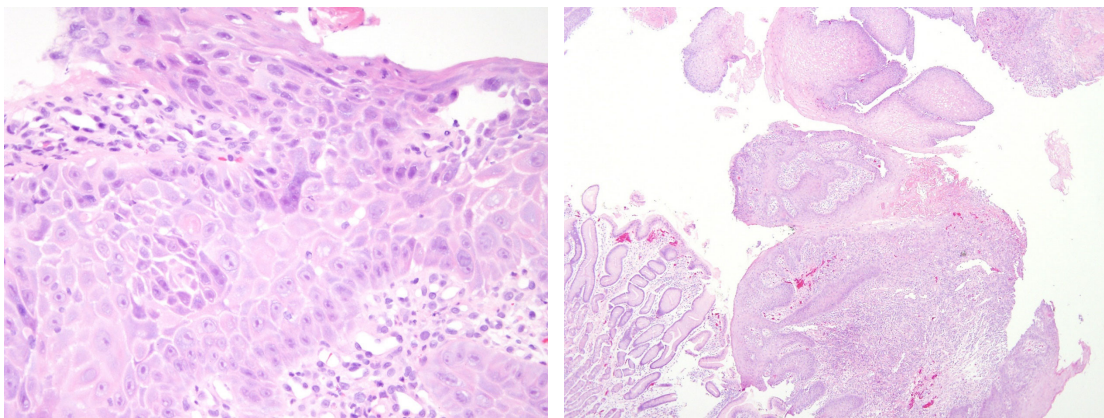
- Reparative change associated with
 - Reflux
 - Radiation
 - Drugs
 - Infection

Histologic findings

- Multiple multinucleated squamous epithelial cells, usually confined to the basal zone
- Nuclei with a single or multiple eosinophilic nucleoli
- No inclusions
- No hyperchromasia
- No atypical mitoses
- May see ulcers or active inflammation, basal cell hyperplasia, and elongation of the lamina propria papillae



Histologic findings

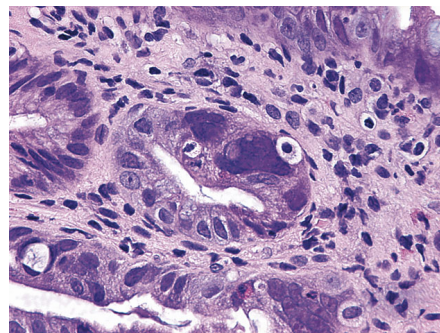
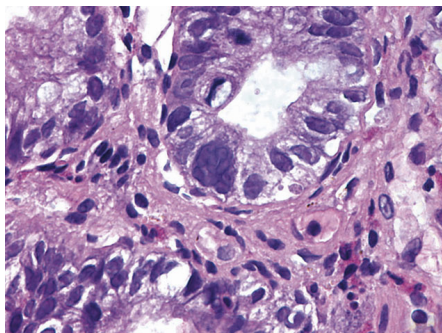


Immunostains

- AE1/3 pos
- S100, HSV, CMV, HPV-ISH neg

Multinucleated Giant Cell Change

- Similar findings reported in colon polyps

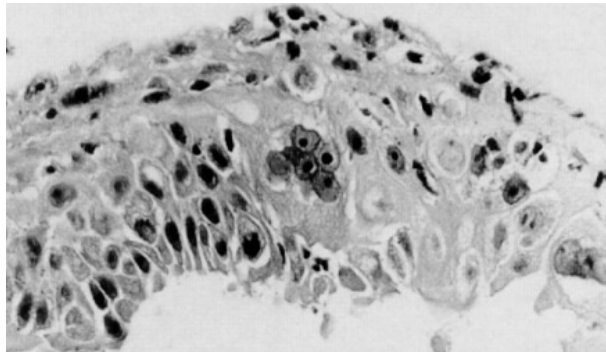


Kambham et al. Multinucleated epithelial giant cells in colorectal polyps: a potential mimic of viropathic and/or dysplastic changes. *Am J Surg Pathol.* 2005 Jul;29(7):912-9.

Lambie and Brown. Multinucleate epithelial change in colorectal hyperplastic polyps: a review of 27 cases. *J Clin Pathol.* 2008 May;61(5):611-4

Significance

- Distinguish from viral cytopathic changes and neoplasia



Surendra and Odze. Multinucleated Epithelial Giant Cell Changes in Esophagitis: A Clinicopathologic Study of 14 Cases. Am J Surg Pathol. 1998 Jan;22(1):93-9.

Esophagitis Dissecans Superficialis

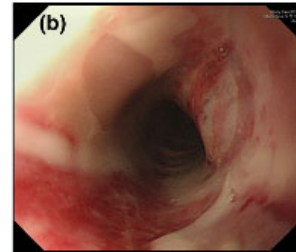
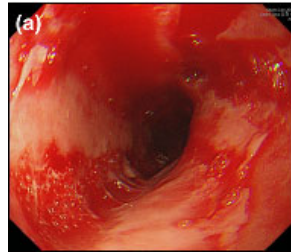
Esophagitis Dissecans Superficialis, A.K.A. Thermal Injury and Sloughing Esophagitis

- Patient presentation:
 - Most patients White, females
 - Typically asymptomatic, incidental finding
 - Some patients report dysphagia and may have strictures
 - Rarely patients may vomit large esophageal cast with a tubular configuration
- Endoscopy:
 - Whitish strips or streaks of peeling esophageal mucosa (mid to distal esophagus)
 - The mucosa is seen sloughing on endoscopy, blister-like appearance

Coppola et al. Chronic esophagitis dissecans presenting with esophageal strictures: a case report. *Hum Pathol.* 2000 Oct;31(10):1313-7.

Associations

- Debilitation/impaired mobility
- Polypharmacy
- Pemphigus vulgaris and bullous pemphigoid)
- Heavy smoking
- Physical trauma
- Immunosuppression
- Drugs (biphosphonates, psychoactive)



Joon Oh S. et al. Esophagitis dissecans superficialis associated with pemphigus vulgaris. *The Journal of Dermatology.* 2016. Feb;43:215-216.



Moawad and Appleman. Sloughing esophagitis: a spectacular histologic and endoscopic disease without a uniform clinical correlation. *Annals of the New York Academy of Sciences.* (2016) 178–182

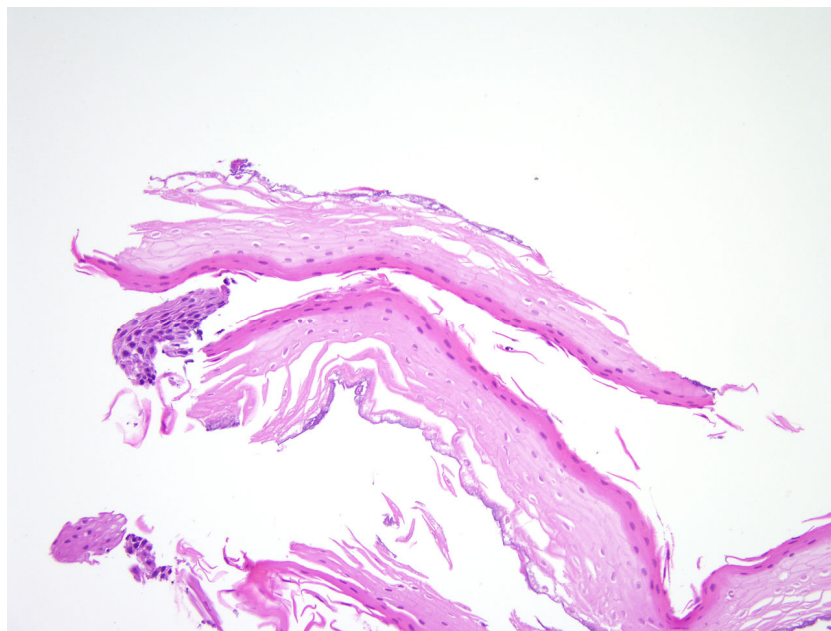
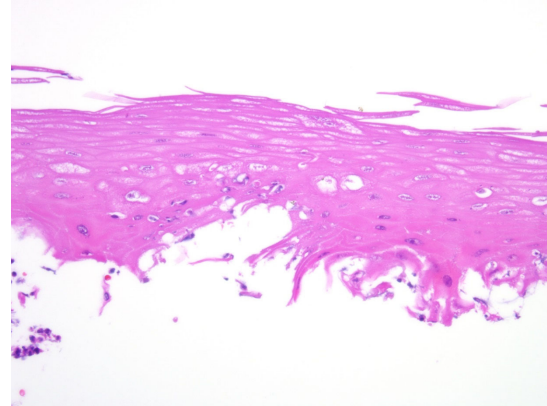
Hart et al. Esophagitis Dissecans Superficialis: Clinical, Endoscopic, and Histologic Features. *Dig Dis Sci.* 2015 Jul;60(7):2049-57.

Purdy et al. Sloughing esophagitis is associated with chronic debilitation and medications that injure the esophageal mucosa. *Mod Pathol.* 2012 May;25(5):767-75

Carmack et al. Esophagitis dissecans superficialis ("sloughing esophagitis"): a clinicopathologic study of 12 cases. *Am J Surg Pathol.* 2009 Dec;33(12):1789-94.

Histology

- Two-tone appearance at low magnification
- Normal basal layer
- Nonviable superficial epithelium with ghost nuclei, which may separate from a normal underlying basal layer.
- Not much inflammation
 - Some pus and bacteria possible between viable and non-viable layers



Management

- ?
- Tx underlying skin condition, if present
- Consider cessation of any known offending medications
- Acid suppressants often prescribed, but benefit uncertain
- Benign condition, patients typically heal in a short period of time

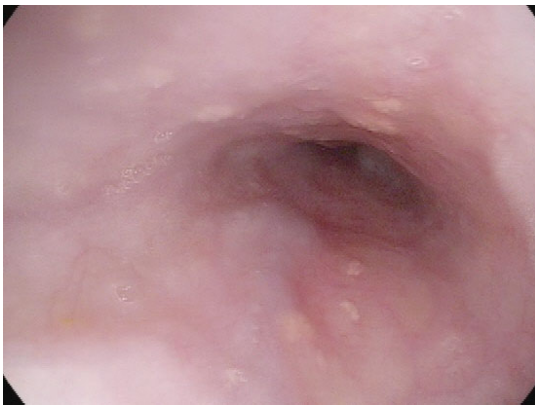
Esophageal Sebaceous Glands

Sebaceous Heterotopia

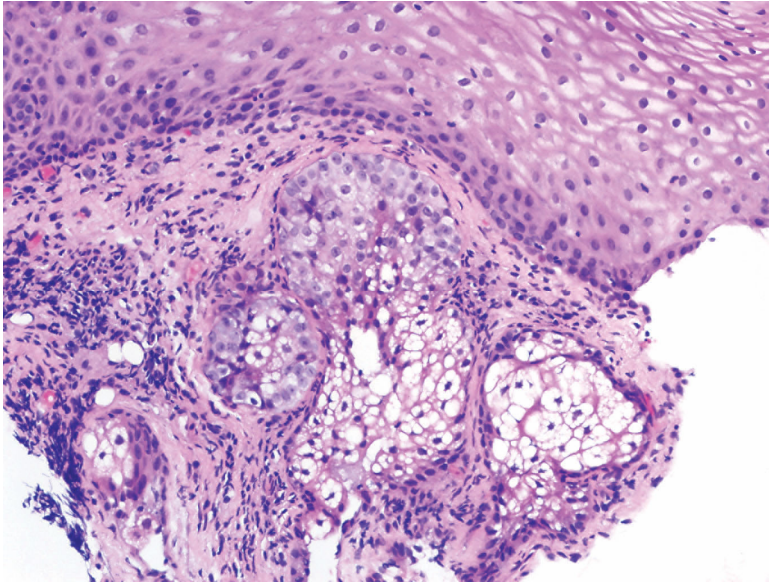
- Initially reported as an incidental finding in 4 out of 200 autopsies in 1962
- Slightly raised, irregular, yellow nodules or plaques
- Solitary or multiple, measuring from a few millimeters up to 2 cm in greatest dimension
- 0.05% of asymptomatic subjects

Park et al. Prevalence rate and clinical characteristics of esophageal ectopic sebaceous glands in asymptomatic health screen examinees. *Dis Esophagus*. 2017 Jan 1;30(1):1-5

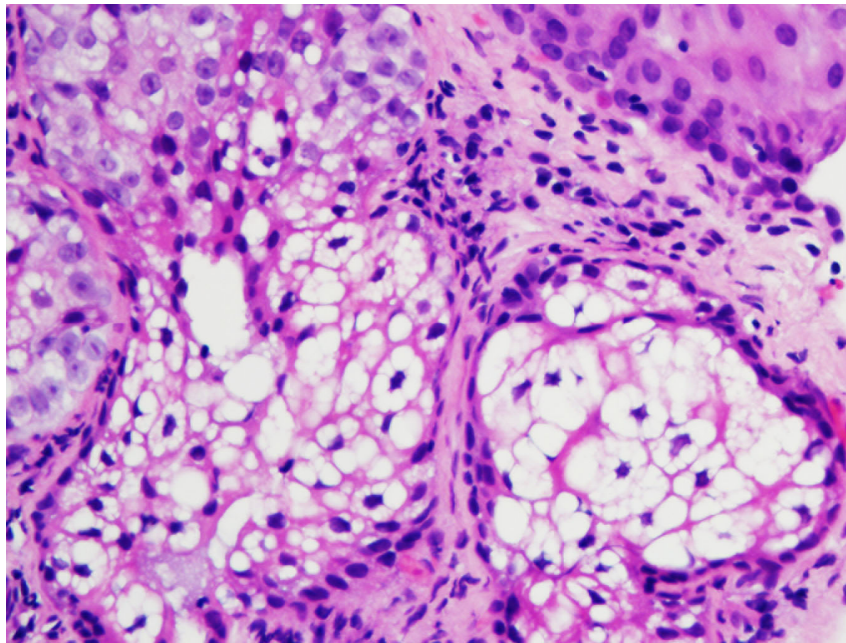
De La Pava, S. and J.W. Pickren, Ectopic sebaceous glands in the esophagus. *Arch Pathol*, 1962. 73: p. 397-9.

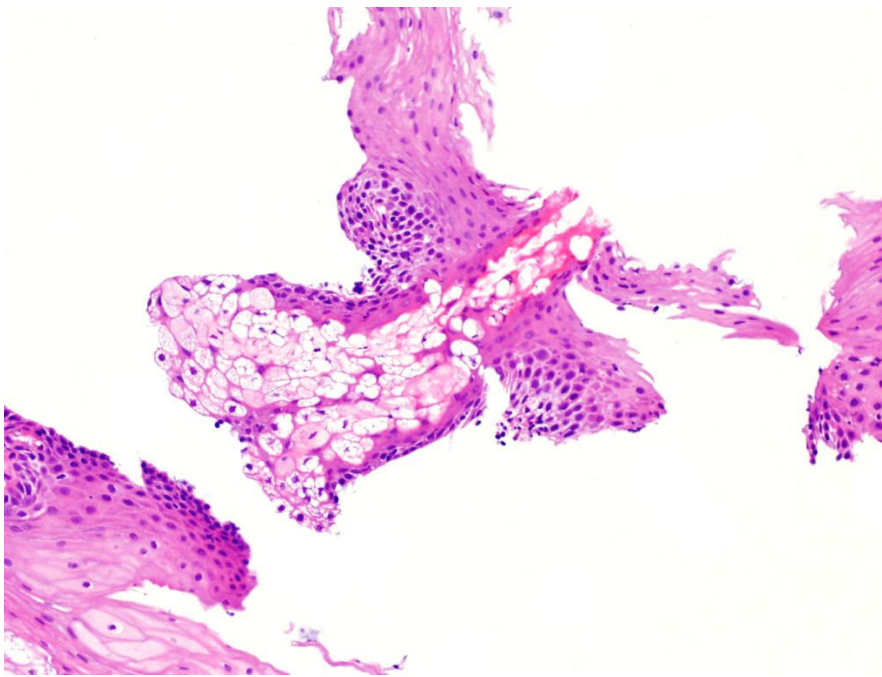
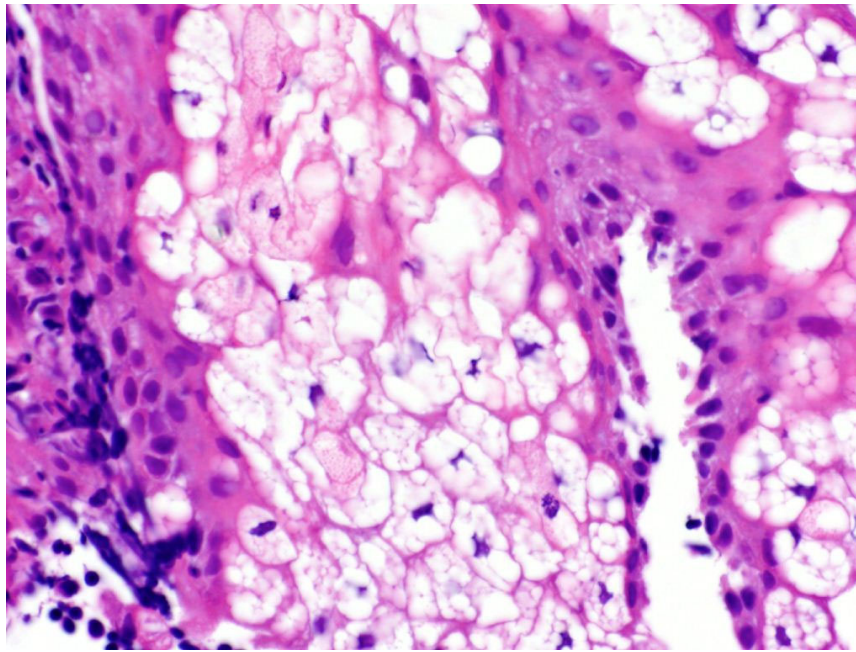


Courtesy of Dr. Vijay P. Singh, Mayo Clinic, Arizona



- Lobules of large, polygonal, clear cells with vacuolated cytoplasm
- Lamina propria
- Chronic inflammatory infiltrate without hair follicles
- Squamous-lined duct with a granular layer that connects the lobule to the luminal surface may or may not be present





Courtesy Dr. Dora
Lam-Himlin, Mayo
Clinic, Arizona

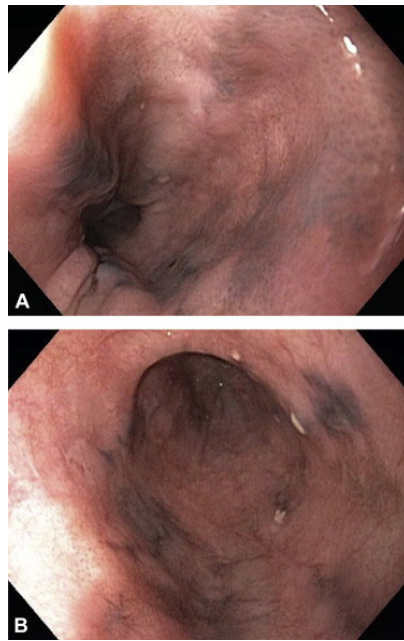
Esophageal Sebaceous Glands

- Some argue congenital anomaly
- Others argue metaplastic
- Completely benign and requires no endoscopic follow up

Esophageal Melanocytosis

Melanocytosis (or melanosis)

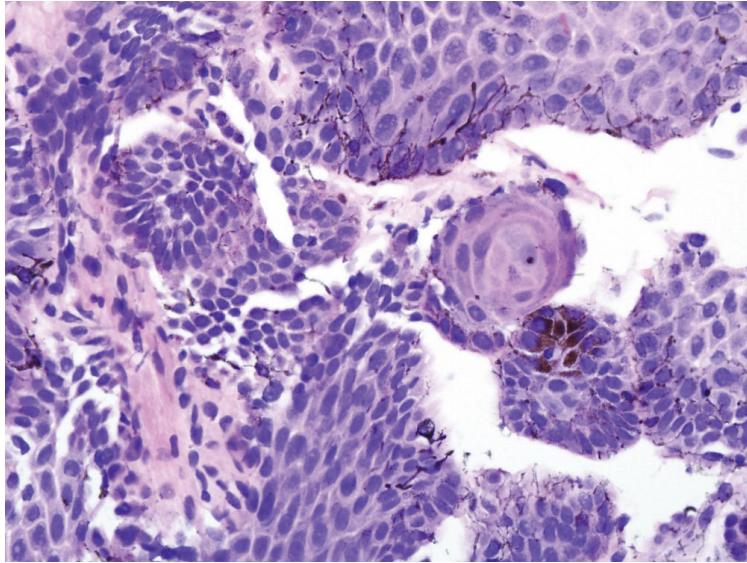
- Rare
- Lower or middle third
- Blue to black mucosal macules
- Detected in about 2-8% of esophagi



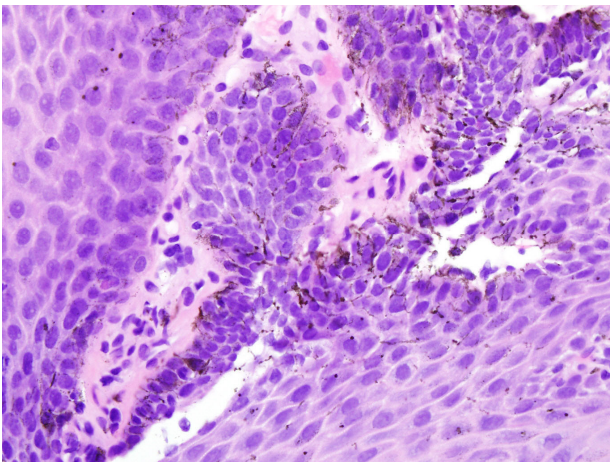
Dinneen, HS. Darkest before dawn: esophageal melanocytosis mimicking primary esophageal melanoma. *Gastrointest Endosc.* 2014 Dec;80(6):1203-5

Melanocytosis (or melanosis)

Increased numbers of melanocytes in the basal layer of esophageal squamous epithelium and an increased quantity of melanin in esophageal mucosa



Melanocytosis (or melanosis)

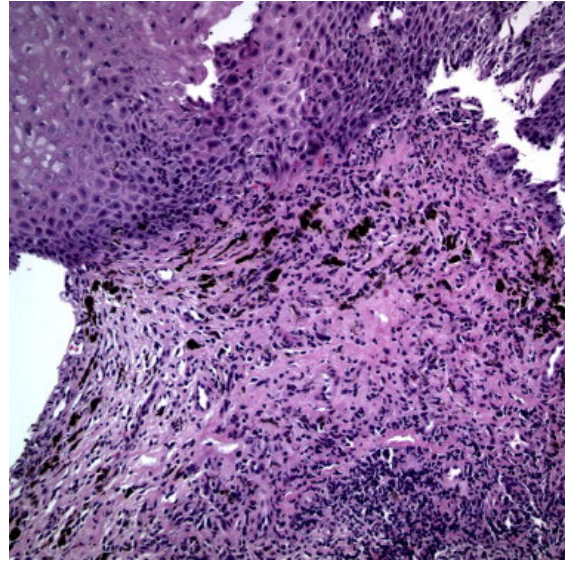


- Basal melanocytes of the esophagus lack desmosomes and tonofilaments but possess long dendritic cytoplasmic processes that extend between the keratinocytes, often passing through several layers of cells.
- Nuclei are smaller and slightly more hyperchromatic than the nuclei of adjacent keratinocytes with uniform chromatin and indented nuclear contour
- S100, melanA, HMB45 pos

Melanocytosis (or melanosis)

- Underlying lamina propria contains macrophages laden with coarse brownish black pigment on H&E-stained slides
- No atypia

Dinneen, HS. Darkest before dawn: esophageal melanocytosis mimicking primary esophageal melanoma. Gastrointest Endosc. 2014 Dec;80(6):1203-5



Melanocytosis (or melanosis)

- Benign but progression to melanoma described in one case

Maroy and Baylac. Primary malignant esophageal melanoma arising from localized benign melanocytosis. Clin Res Hepatol Gastroenterol. 2013 Apr;37(2):e65-7

Thank you