

# What to do with the Lymphocytic Esophagitis Pattern

Meredith Pittman, MD

GIPS Forum

February 29, 2020

- 
- No financial disclosures.



# The Problem

---

- “With no formal definition and a variety of clinical presentations and endoscopic findings, diagnosis and management of symptomatic lymphocytic esophagitis patients is challenging for clinicians.”



# Lecture Objectives

---

- Define lymphocytic esophagitis histologically.
- Describe the clinical associations with lymphocytic esophagitis.
- Write clinically relevant notes for our gastroenterology colleagues.



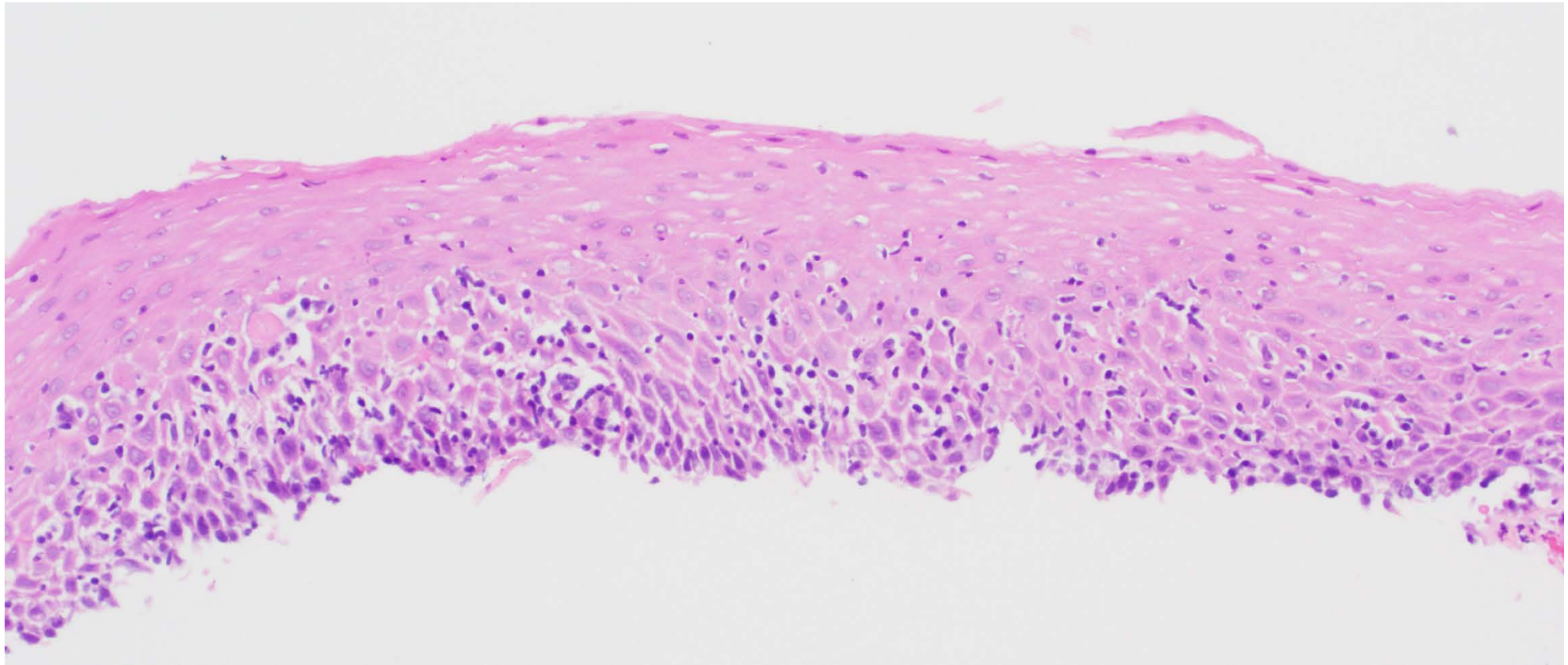
# What Would You Do?

Our Diagnostic Practices



# Case 1

- 45 year old woman with dysphagia, mid-esophageal biopsy.



## *Live Content Slide*

*When playing as a slideshow, this slide will display live content*

**Poll: Which of the following most closely matches how you would sign out this case?**



# Placeholder for Results Slide

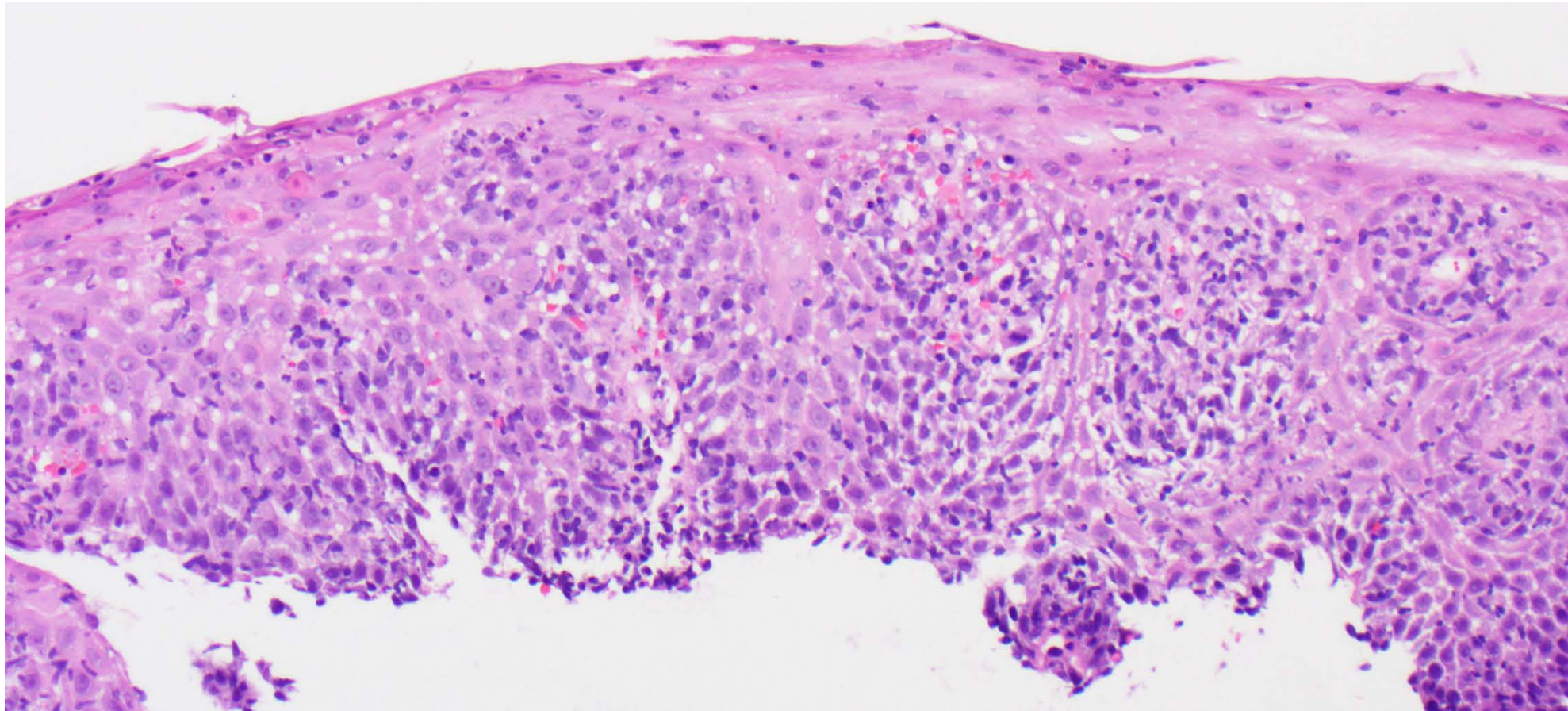
---





# Case 2

- 45 year old woman with dysphagia, mid-esophageal biopsy



## *Live Content Slide*

*When playing as a slideshow, this slide will display live content*

**Poll: Which of the following most closely matches how you would sign out this case?**



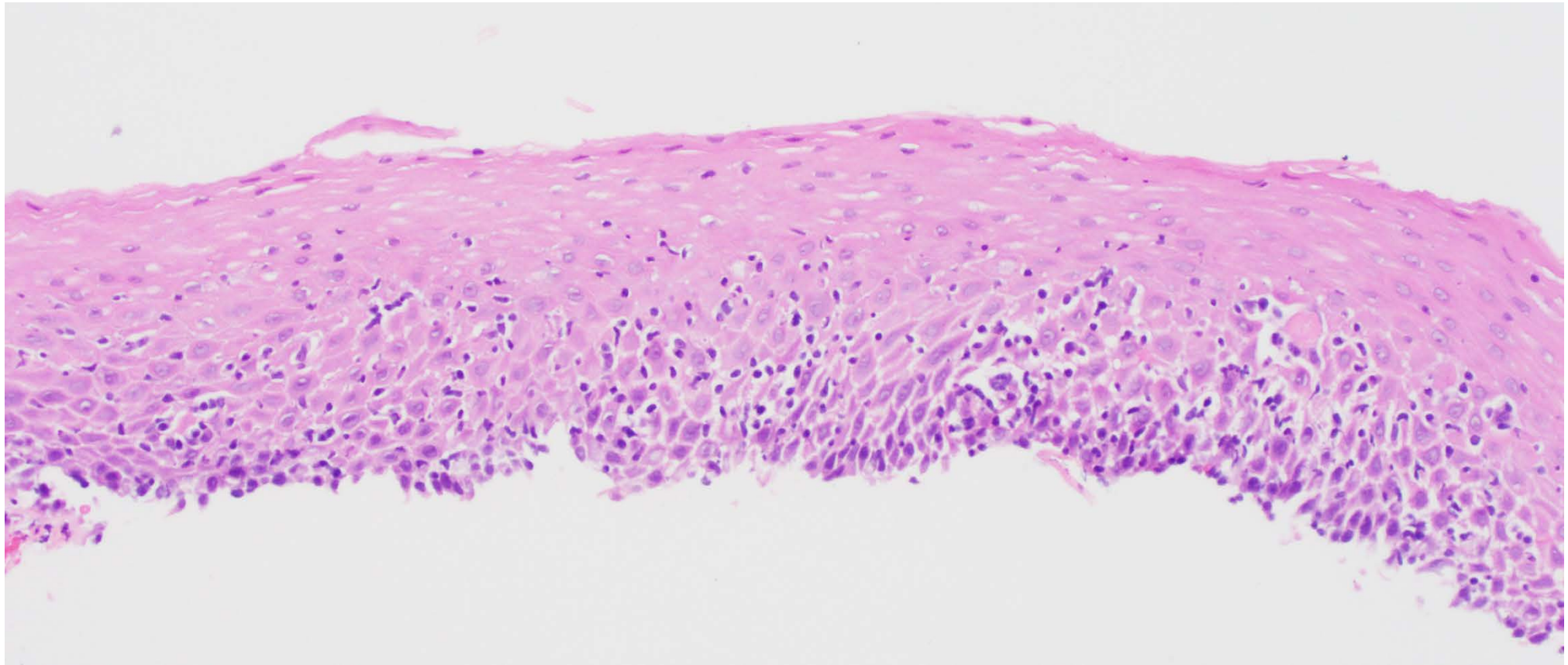
# Placeholder for Results Slide

---



# Case 3

- 9 year old girl with Crohn disease, mid-esophageal biopsy



## *Live Content Slide*

*When playing as a slideshow, this slide will display live content*

**Poll: Which of the following most closely matches how you would sign out this case?**



# Placeholder for Results Slide

---



# What is the “Lymphocytic Esophagitis Pattern”?

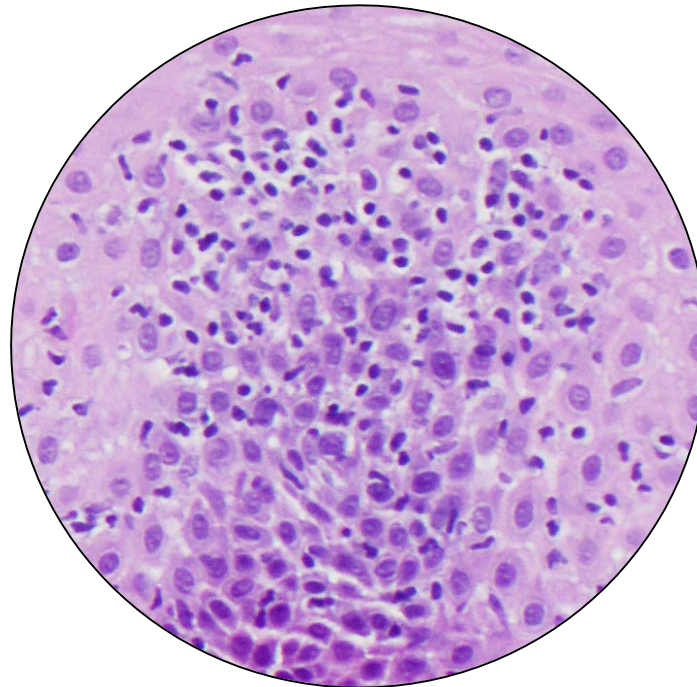
Histologic Features





# Lymphocytosis

- Defined in several retrospective studies
  - “Significant” or “dense” or “increased” intraepithelial lymphocytes, often quantified (e.g. 20 lymphocytes in a 400x field)





# Few Granulocytes

- Defined in several retrospective studies
  - “Significant” or “dense” or “increased” intraepithelial lymphocytes, often quantified (*i.e.* 20 lymphocytes in a 400x field)
  - Rare or absent eosinophils/neutrophils



# ? Spongiosis

- Defined in several retrospective studies
  - “Significant” or “dense” or “increased” intraepithelial lymphocytes, often quantified (*i.e.* 20 lymphocytes in a 400x field)
  - Rare or absent eosinophils/neutrophils
  - +/- peripapillary spongiosis

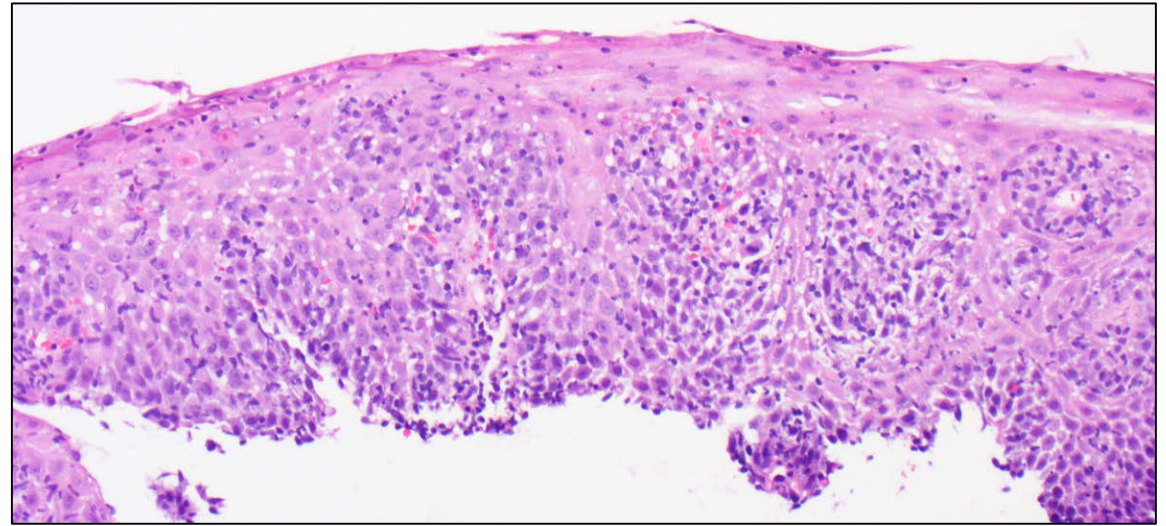
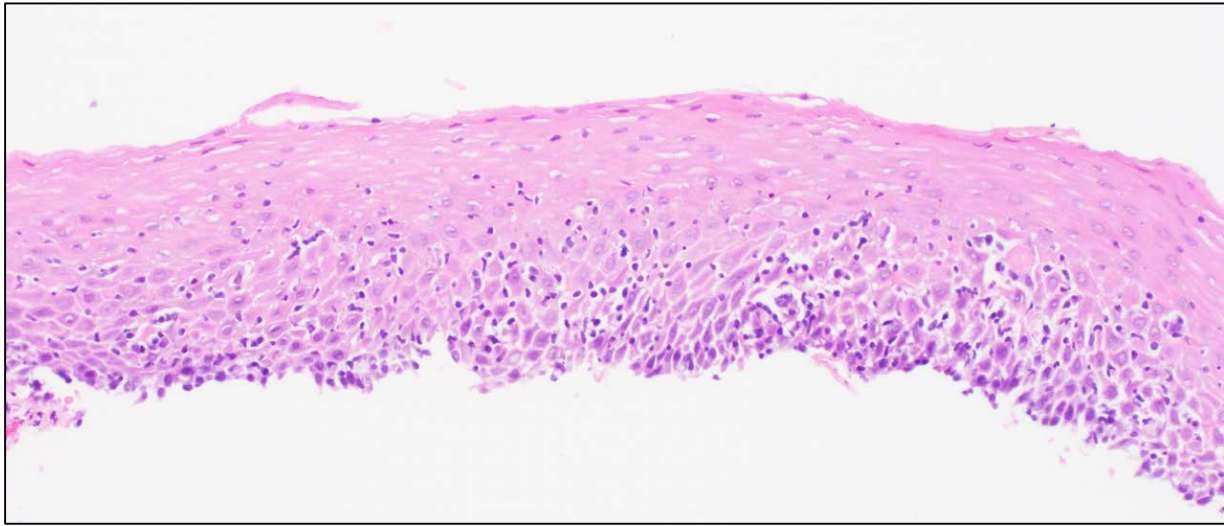


# ? Other Epithelial Damage

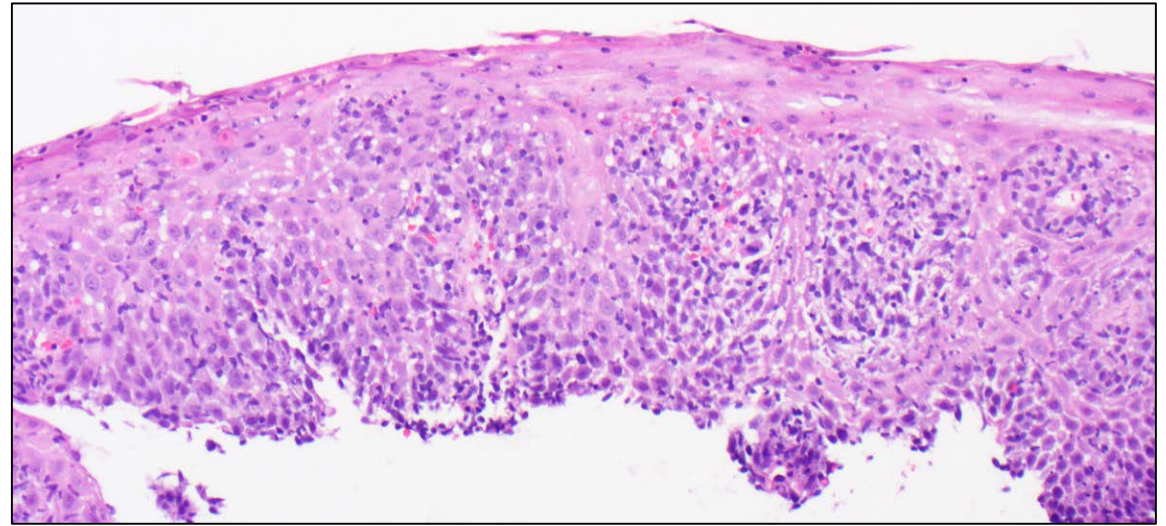
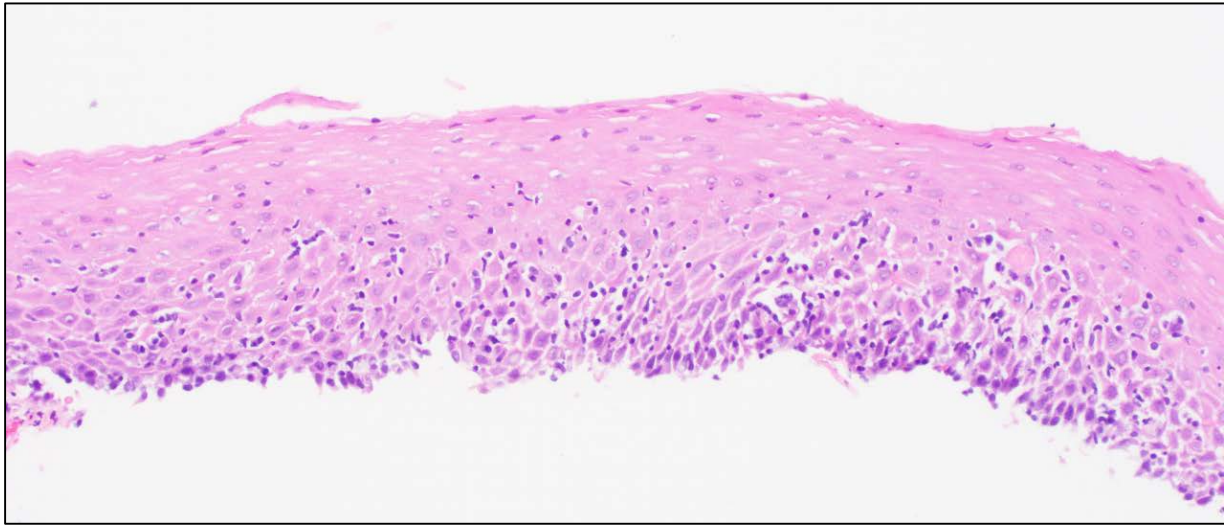
- Defined in several retrospective studies
  - “Significant” or “dense” or “increased” intraepithelial lymphocytes, often quantified (*i.e.* 20 lymphocytes in a 400x field)
  - Rare or absent eosinophils/neutrophils
  - +/- peripapillary spongiosis
  - +/- additional features of squamous epithelial damage (*e.g.* dyskeratotic keratinocytes in “lichenoid” esophagitis)



# Lymphocytic Esophagitis



# Lymphocytic Esophagitis



How many lymphocytes are too many lymphocytes?

# What is “Normal” in the Esophagus?

Within Normal Limits





# How Many Lymphocytes Are “Normal”?

Studies	Population	Distal		Mid		Proximal	
		Avg	Max	Avg	Max	Avg	Max
Haque S. Gut. 2012.	100 patients with “unremarkable squamous mucosa” and no history of GERD	5	12				

# How Many Lymphocytes Are “Normal”?

Studies	Population	Distal		Mid		Proximal	
		Avg	Max	Avg	Max	Avg	Max
Haque S. Gut. 2012.	100 patients with “unremarkable squamous mucosa” and no history of GERD	5	12				
Putra J. AJSP. 2016.	17 asymptomatic volunteers with normal endoscopic appearance and normal acid exposure	24	46	23	41	n/a	n/a



# How Many Lymphocytes Are “Normal”?

Studies	Population	Distal		Mid		Proximal	
		Avg	Max	Avg	Max	Avg	Max
Haque S. Gut. 2012.	100 patients with “unremarkable squamous mucosa” and no history of GERD	5	12				
Putra J. AJSP. 2016.	17 asymptomatic volunteers with normal endoscopic appearance and normal acid exposure	24	46	23	41		
Pittman M. AJSP 2019.	30 healthy patients with a normal esophageal endoscopic appearance	9	35	11	32	8	22



# How Many Lymphocytes Are “Normal”?

Studies	Population	Distal		Mid		Proximal	
		Avg	Max	Avg	Max	Avg	Max
Haque S. Gut. 2012.	100 patients with “unremarkable squamous mucosa” and no history of GERD	5	12				
Putra J. AJSP. 2016.	17 asymptomatic volunteers with normal endoscopic appearance and normal acid exposure	24	46	23	41	n/a	n/a
Pittman M. AJSP 2019.	30 healthy patients with a normal esophageal endoscopic appearance	9	35	11	32	8	22



# Isolated Lymphocytosis Might Be Within Normal Limits

---

- Range of <5-46 lymphocytes per 400x field

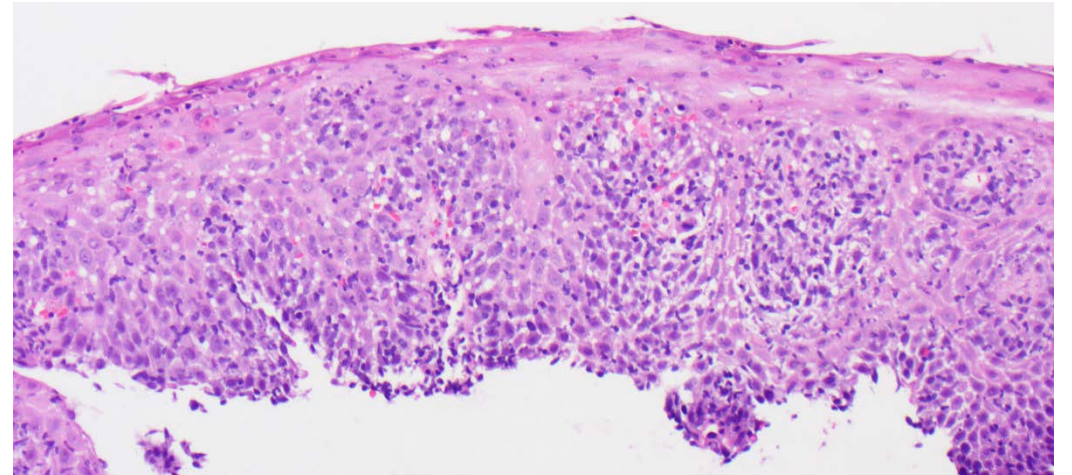
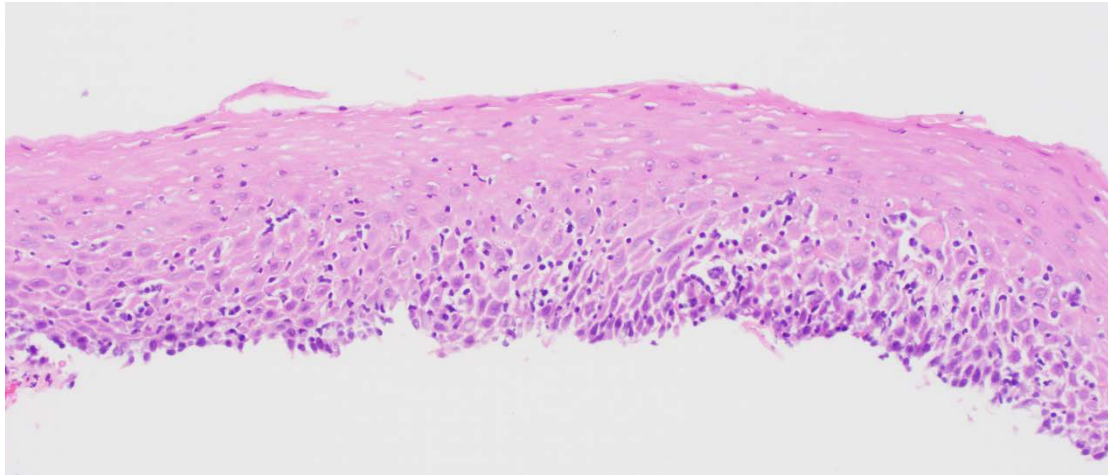
# Lymphocytosis Shouldn't Be Our Only Criterion

---

- How many lymphocytes are too many?
  - Not quite the right question
  - What else do we see with the lymphocytes?
    - Spongiosis
    - Basal cell hyperplasia
    - Dyskeratotic keratinocytes

# Histologic Definition of the Lymphocytic Esophagitis Pattern

- The presence of significantly increased intraepithelial lymphocytes and evidence of epithelial damage in the absence of significant granulocytes



- But.....

# Does Pattern = Final Diagnosis?

---

- Should we be making a diagnosis of lymphocytic esophagitis on all cases with this pattern?

# What is the Clinical Scenario?

Putting the “Clinico” in Clinicopathologic



# The “Lymphocytic Esophagitis” Pattern is Nonspecific

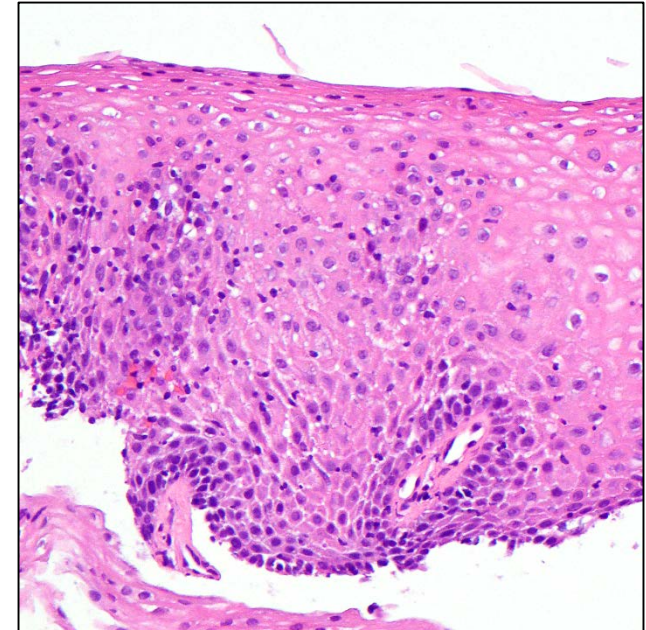
- “With no formal definition and a variety of clinical presentations and endoscopic findings, diagnosis and management of symptomatic lymphocytic esophagitis patients is challenging for clinicians.”





# GERD with Lymphocytes

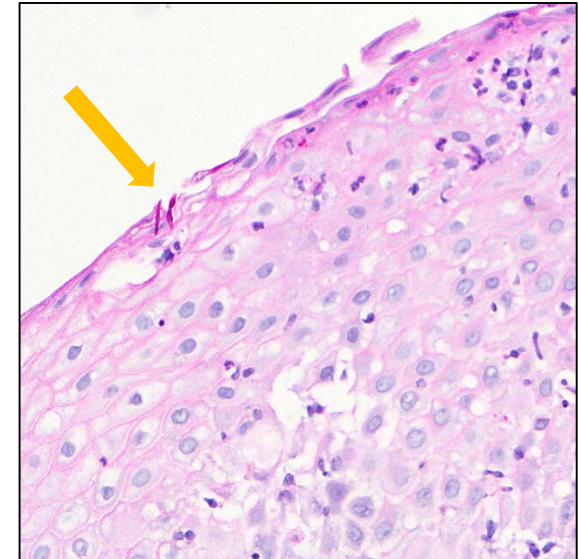
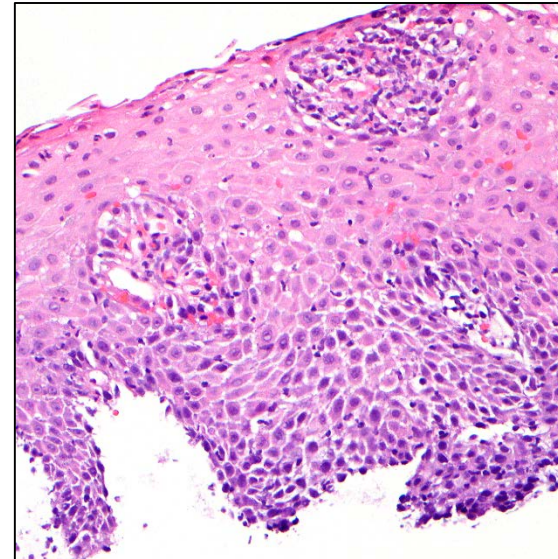
- Gastroesophageal reflux disease
  - Cytokines
  - Attract T-lymphocytes
- GERD more common than LE



Souza RF, et al. 2009. *Gastroenterology*.  
Souza RF, et al. 2017. *Curr Opin Pharmacol*.

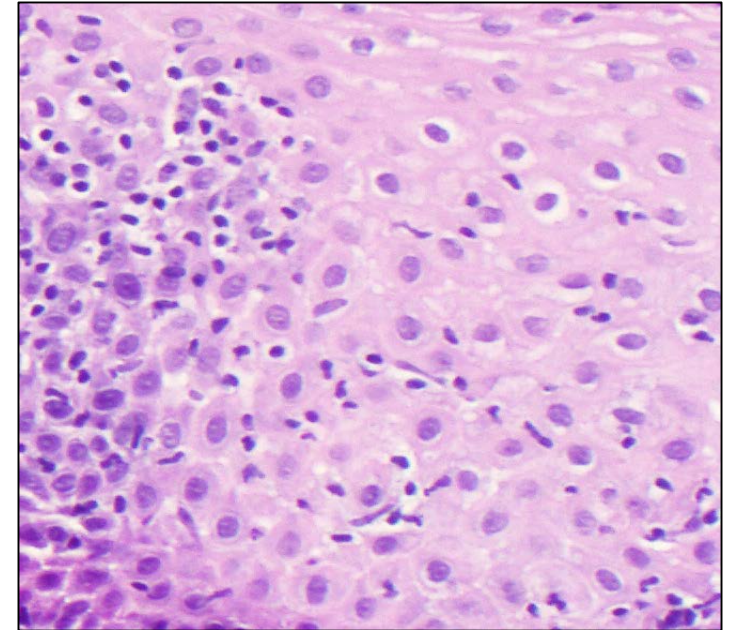
# Candida with Lymphocytes

- Gastroesophageal reflux disease
  - Cytokines
  - Attract T-lymphocytes
- Candida esophagitis
  - +/- Superficial neutrophils
  - Special stains (PAS-d) helpful



# Stasis with Lymphocytes

- Gastroesophageal reflux disease
  - Cytokines
  - Attract T-lymphocytes
- Candida esophagitis
  - +/- Superficial neutrophils
  - Special stains (PAS-d) helpful
- Motility Disorders
  - Achalasia and non-achalasia
  - Usually CD4-predominant infiltrate



# Crohn Disease with Lymphocytes

---

- Known association between Crohn disease and histologic lymphocytic esophagitis
  - Rubio, et al:
    - 7 of 11 (64%) pediatric patients with lymphocytic esophagitis had concurrent Crohn disease
  - Ebach, et al:
    - 17 of 60 (28%) pediatric patients with Crohn disease had concurrent lymphocytic esophagitis



# Crohn Disease with Lymphocytes

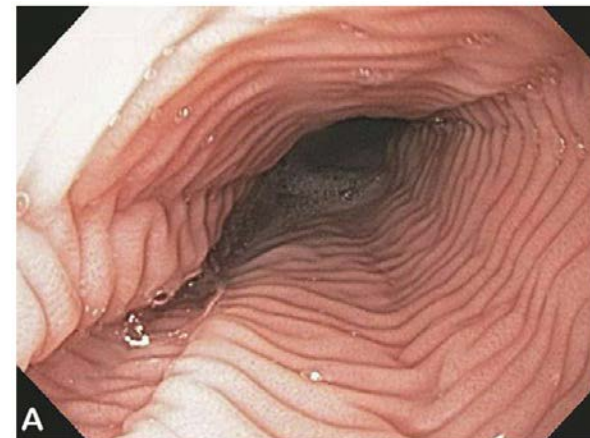
- Known association between Crohn disease and histologic lymphocytic esophagitis
  - Rubio, et al:
    - 7 of 11 (64%) pediatric patients with lymphocytic esophagitis had concurrent Crohn disease
  - Ebach, et al:
    - 17 of 60 (28%) pediatric patients with Crohn disease had concurrent lymphocytic esophagitis
- Lymphocytic esophagitis is a manifestation of underlying Crohn disease in children
- What about adults?





# Typical Patient with Lymphocytic Esophagitis

- Usually middle-aged to older women
- Usually presenting with dysphagia
- Often with rings or furrows on endoscopic exam
- No underlying associated diseases\*\*\*



Haque S, et al. 2012.



Cohen S, et al. 2012. *J Clin Gastroenterol*.

Haque S, Genta RM. 2012. *Gut*.

Pasricha S, et al. 2016. *Dig Dis Sci*.

# Other Disease Associations in Adults?

---

- Common:
  - GERD
  - Candida
  - Stasis
    - Dysmotility
    - Ablation therapy

# Other Disease Associations in Adults?

Common:

- GERD
- Candida
- Stasis
  - Dysmotility
  - Ablation therapy



# Lymphocytic Esophagitis May Represent Immune-Mediated Disease in Adults

---

- 61 adult patients with “lymphocytic esophagitis”
  - Average 56 years old
  - 72% women
- 41 (67%) had an underlying immune-mediated condition or immunodeficiency
  - 18 (30%) with Crohn disease (compared to 8% in control group)
  - 14 (23%) had a connective tissue disease
  - 14 (23%) managed with a biologic agent



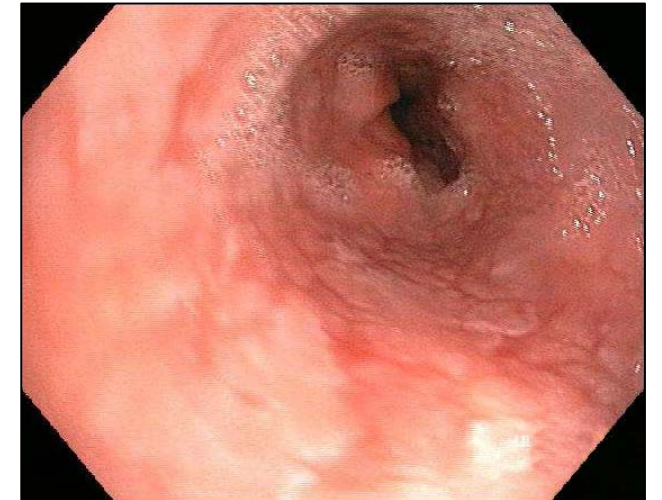
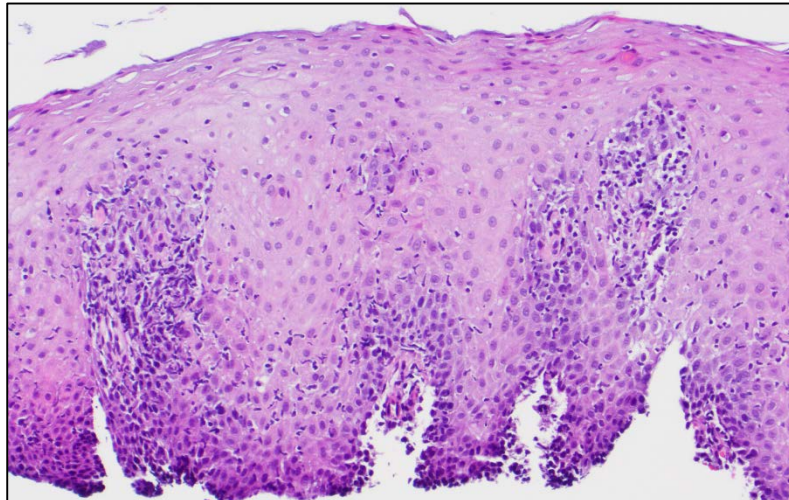
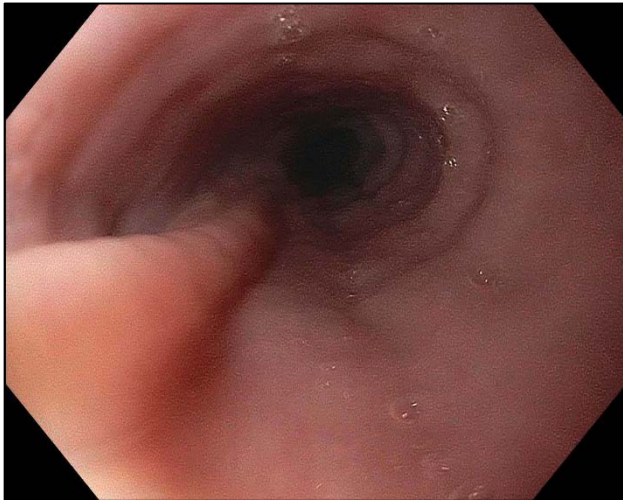
# What does it all Mean?

Wrap it up, Pittman



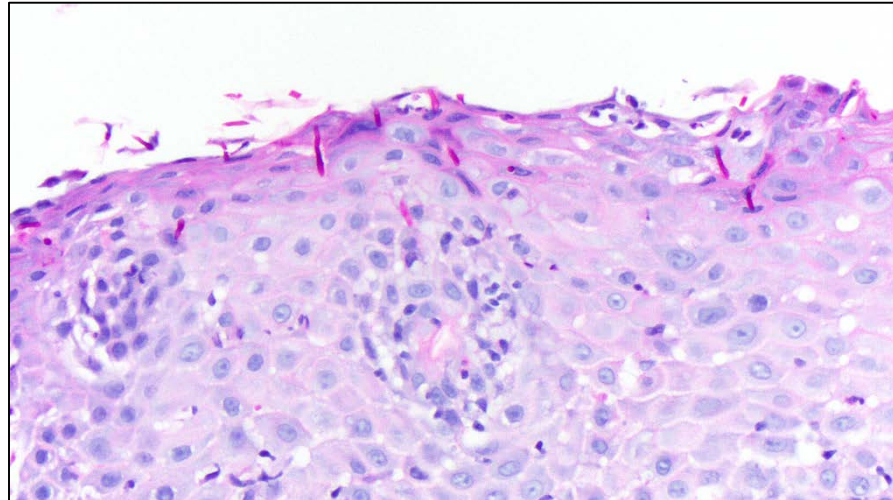
# Lymphocytic Esophagitis as a Diagnosis

- Lymphocytic esophagitis is real clinicopathologic disorder
- Treatment is a proton-pump inhibitor +/- oral fluticasone



# Lymphocytic Esophagitis as a Diagnosis

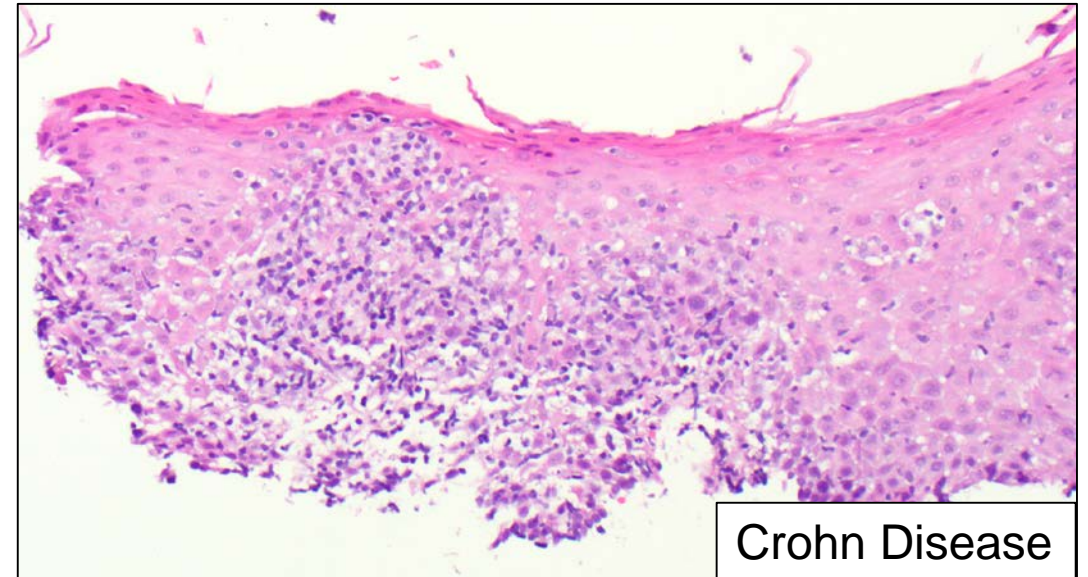
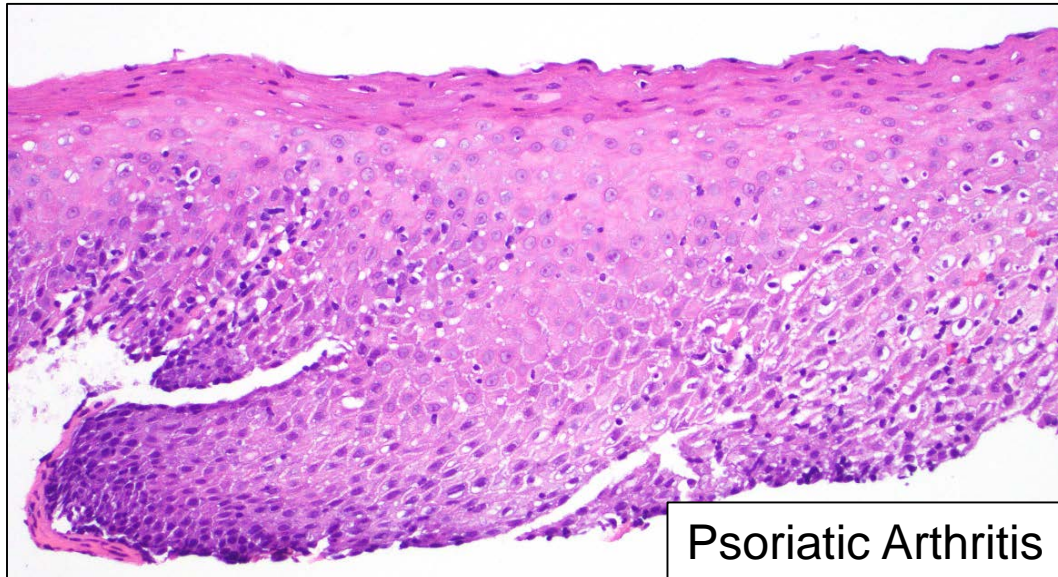
- **Be wary** of diagnosing Lymphocytic Esophagitis when
  - 1) The findings are probably reflux related (distal biopsy, reflux symptoms, etc)
  - 2) The patient has a known dysmotility disorder
  - 3) The patient has an infectious esophagitis





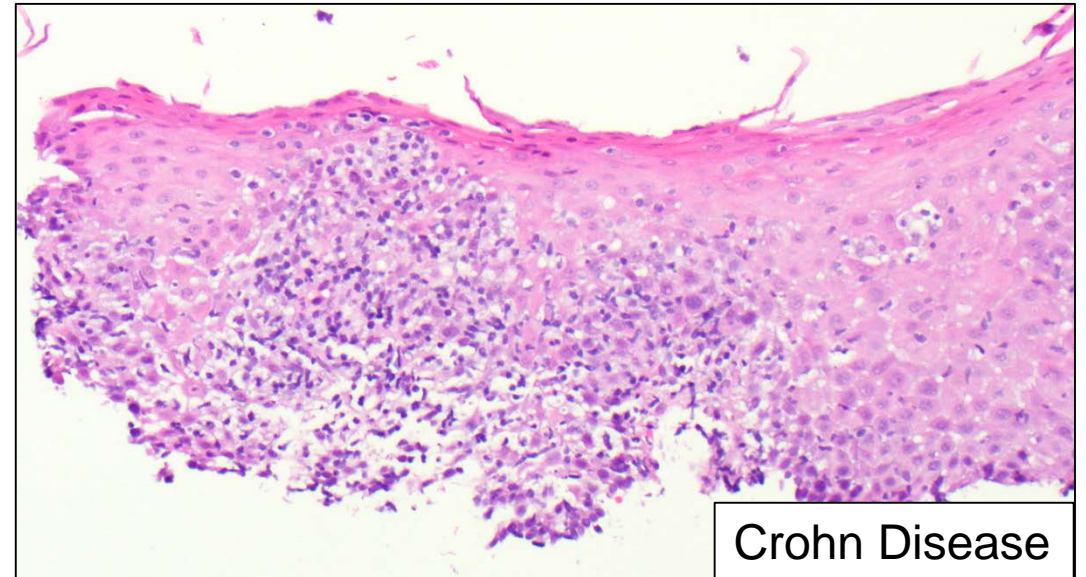
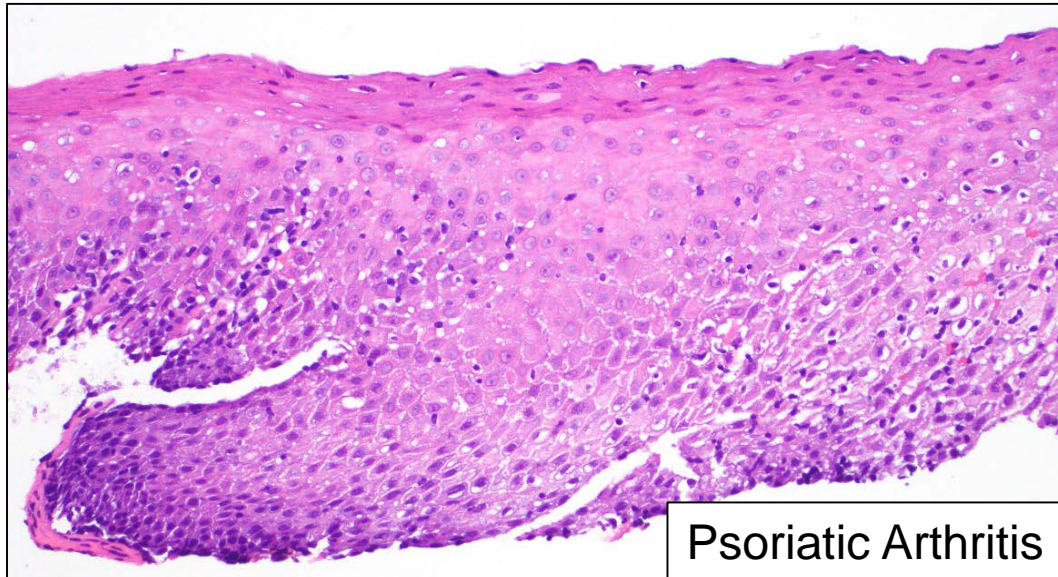
# Lymphocytic Esophagitis as a Diagnosis

- **Do** diagnose lymphocytic esophagitis when
  - 1) The patient has an associated disease state that fits



# Lymphocytic Esophagitis as a Diagnosis

- **Do** diagnose lymphocytic esophagitis when
  - 1) The patient has an associated disease state that fits
  - 2) The patient's clinical history is unknown but the LE pattern is present at multiple levels in the esophagus (with a note\*\*)



# **\*\*Sample Sign-Out, Unknown History**

---

Lymphocytic esophagitis; see note.

Note: Intraepithelial lymphocytosis and associated epithelial damage are seen at multiple levels in the esophagus. This histologic pattern has been associated with achalasia and non-achalasia motility disorders, immune-mediated disorders (Crohn disease, rheumatologic arthritis), immunodeficiency syndromes (common variable immunodeficiency), certain medications (thiazides), and prior mucosal injury (ablation). A stain for PAS-d is negative for fungal organisms.





# Still Unknown

---

- Is there an association with biologic drugs (the “mabs” and “mibs”)
- What is lymphocytic-eosinophilic esophagitis?
- Do asymptomatic patients or patients without endoscopic changes need treatment?
- What is the best therapy for patients with lymphocytic esophagitis?
- If chronic, could lymphocytic esophagitis lead to strictures?





# Take Home Points

---

- Intraepithelial lymphocytes are found in the esophagus in a variety of conditions.
- The lymphocytic esophagitis pattern should have both lymphocytosis and evidence of epithelial injury.
- Lymphocytic esophagitis is associated with immune-mediated and immunodeficiency disorders.
- Further study of appropriate patient groups is necessary to understand when and how to treat.



# Thank You

