MAYO CLINIC

AUSTRALASIAN GASTROINTESTINAL PATHOLOGY SOCIETY

Gastrointestinal Eosinophilia

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Outline

- Esophageal Eosinophilia:
  - What happened to PPI-responsive esophageal eosinophilia?
  - Histologic features of EoE and what should we report?
- Non-esophageal GI tract eosinophilia
  - Differential diagnosis and avoiding pitfalls
  - Diagnosis of primary eosinophilic gastrointestinal diseases

EoE: Evolving definition

AGA INSTITUTE GASTROENTEROLOGY 2007;133:1342–1363

Eosinophilic Esophagitis in Children and Adults: A Systematic Review and Consensus Recommendations for Diagnosis and Treatment

Sponsored by the American Gastroenterological Association (AGA) Institute and North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition

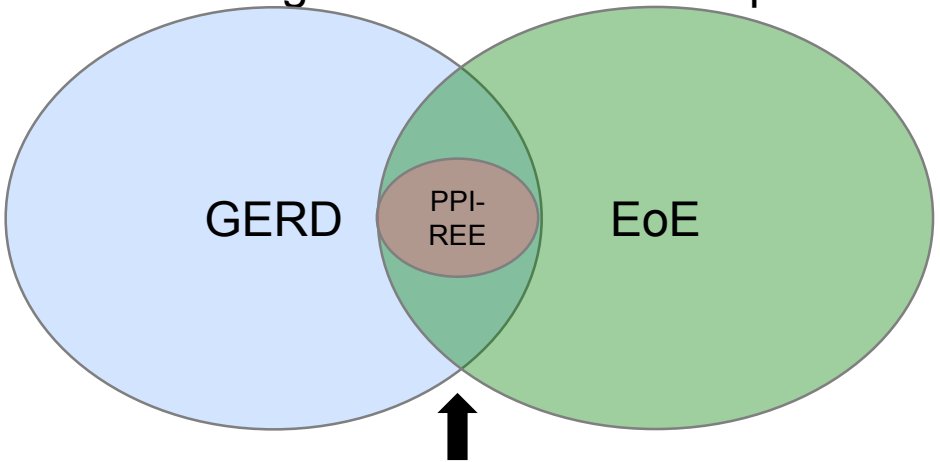
GLENN T. FURUTA,* CHRIS A. LIACOURAS,‡ MARGARET H. COLLINS,§ SANDEEP K. GUPTA,‖ CHRIS JUSTINICH,¶ PHIL E. PUTNAM,# PETER BONIS,** ERIC HASSALL,‡‡ ALEX STRAUMANN,§§ MARC E. ROTHENBERG,‖‖ and Members of the First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees***

Diagnostic Guidelines

Clinical symptoms of esophageal dysfunction
≥15 Eosinophils in 1 high-power field
Lack of responsiveness to high-dose proton pump inhibition (up to 2 mg/kg/day) or
Normal pH monitoring of the distal esophagus

Since 2007: Recognition of a group of patients that look like EoE but respond to PPI

Histologic and Clinical overlap



Assumption that PPI therapy can distinguish these two causes of esophageal eosinophilia

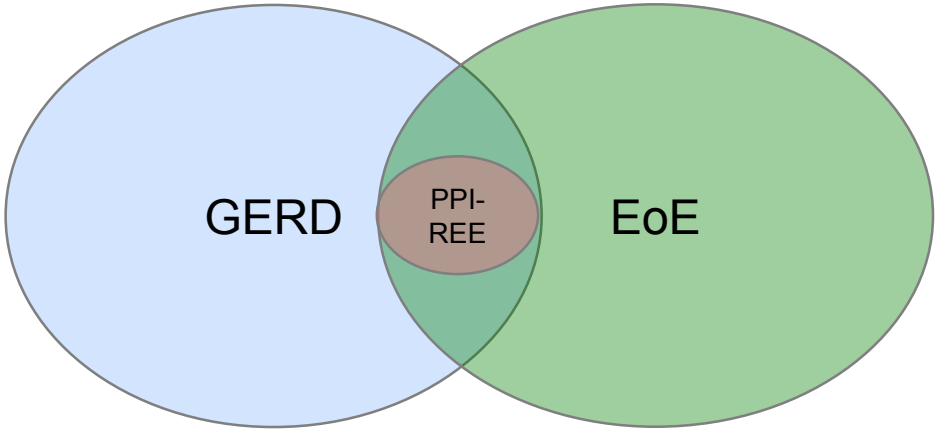
ACG Clinical Guideline: Evidenced Based Approach to the Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis (EoE)

Evan S. Dellon, MD, MPH[1,2], Nirmala Gonsalves, MD[3], Ikuo Hirano, MD, FACG[3], Glenn T. Furuta, MD[4], Chris A. Liacouras, MD[5] and David A. Katzka, MD, FACG[6]

Am J Gastroenterol 2013; 108:679–692;

Recommendations

Proton-pump inhibitor esophageal eosinophilia (PPI-REE) should be diagnosed when patients have esophageal symptoms and have histologic findings of esophageal eosinophilia, but demonstrate symptomatic and histologic response to proton-pump inhibition. At this time, the entity is considered distinct from EoE, but not necessarily a manifestation of GERD. (Recommendation conditional, evidence low)



Transcriptome analysis of proton pump inhibitor–responsive esophageal eosinophilia reveals proton pump inhibitor–reversible allergic inflammation

Ting Wen, PhD,[a] Evan S. Dellon, MD,[b] Fouad J. Moawad, MD,[c] Glenn T. Furuta, MD,[d] Seema S. Aceves, MD, PhD,[e*] and Marc E. Rothenberg, MD, PhD[a*]

Cincinnati, Ohio, Chapel Hill, NC, Bethesda, Md, Aurora, Colo, and La Jolla, Calif

J Allergy Clin Immunol 2015;135:187-97

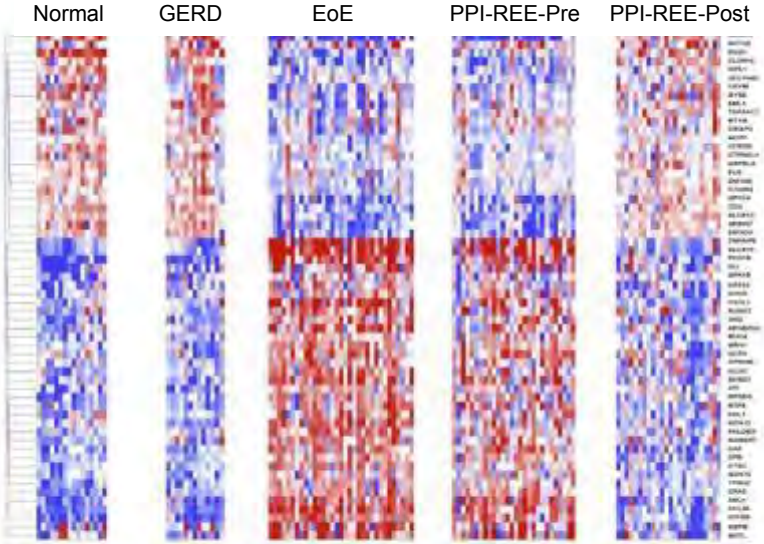


FIG 1. Comparison of esophageal transcriptomes of study cohorts. A total of 114 samples from 5 centers were analyzed by using the EDP. Heat maps were generated on the basis of the 59 EoE genes that passed a greater than 50% call rate of the EDP's 77 significant genes (FS9). *Red* indicates higher expression (upregulation), and *blue* represents lower expression (downregulation). *NL*, Healthy control subjects; *PPI-REE-post*, posttherapy PPI-responsive esophageal eosinophilia; *PPI-REE-pre*, pretherapy PPI-responsive esophageal eosinophilia.

Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis

Javier Molina-Infante,[1] Albert J Bredenoord,[2] Edaire Cheng,[3] Evan S Dellon,[4] Glenn T Furuta,[5] Sandeep K Gupta,[6] Ikuo Hirano,[7] David A Katzka,[8] Fouad J Moawad,[9] Marc E Rothenberg,[10] Alain Schoepfer,[11] Stuart J Spechler,[12] Ting Wen,[10] Alex Straumann,[13] Alfredo J Lucendo,[14] From the PPI-REE Task Force of the European Society of Eosinophilic Oesophagitis (EUREOS)

Table 1 Updated similarities and differences between GORD, PPI-REE and EoE

	GORD	PPI-REE	EoE
Age	Adults>children	Children and young adults	Children and young adults
Gender	Male=Female	Male predominance	Male predominance
Dominant symptom	Heartburn, regurgitation	Dysphagia	Dysphagia
Food impaction	Uncommon	Common	Common
Endoscopic findings	Normal endoscopy (70–80%) Erosions, ulcers, strictures, Barrett's oesophagus, oesophageal adenocarcinoma	Normal endoscopy (<10%) Oedema, rings, exudates furrows, strictures, crêpe-paper oesophagus, narrow calibre oesophagus	Normal endoscopy (<10%) Oedema, rings, exudates, furrows, strictures, crêpe-paper oesophagus, narrow calibre oesophagus
Histology and inflammatory cells	Usually <5–10 eos/HPF Neutrophils, lymphocytes, low-grade eosinophilia	>15 eos/HPF Eosinophils and mast cells	>15 eos/HPF Eosinophils and mast cells
Oesophageal acid exposure on pH monitoring	Mostly positive	Positive and negative	Negative and positive
Primary treatment	Inhibitors of gastric acid secretion, including PPIs, surgical fundoplication	PPI therapy, unclear whether other inhibitors of gastric acid secretion are effective	Topical steroids Elimination diet
Aetiology	Reflux of gastric contents	Unclear	Food/airborne allergens
Type of immune response/ involved chemo/cytocines	Th1 IL-8, MCP-1, RANTES	Th2 Eotaxin-3, IL-5, IL-13	Th2 Eotaxin-3, IL-5, IL-13
EoE transcriptome panel	Not expressed	Similar expression to EoE	Similar expression to PPI-REE
Specific molecular effect of therapy	–	PPIs downregulate Th2 inflammation and normalise EoE gene expression	Topical steroids downregulate Th2 inflammation and normalise EoE gene expression

EoE, eosinophilic oesophagitis; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; PPI, proton pump inhibitor; REE, responsive oesophageal eosinophilia.

Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis

Gut. 2016 Mar;65(3):524-31.

Javier Molina-Infante,[1] Albert J Bredenoord,[2] Edaire Cheng,[3] Evan S Dellon,[4] Glenn T Furuta,[5] Sandeep K Gupta,[6] Ikuo Hirano,[7] David A Katzka,[8] Fouad J Moawad,[9] Marc E Rothenberg,[10] Alain Schoepfer,[11] Stuart J Spechler,[12] Ting Wen,[10] Alex Straumann,[13] Alfredo J Lucendo,[14] From the PPI-REE Task Force of the European Society of Eosinophilic Oesophagitis (EUREOS)

- PPI-REE should no long be considered a distinct entity (better considered a subtype of EoE)
- PPIs are now considered a therapeutic option for EoE

Box 1 Proposal for updated diagnostic criteria for eosinophilic oesophagitis (EoE)

1. *Symptoms of oesophageal dysfunction* (dysphagia/food impaction in adults; abdominal pain, nausea, reflux-like symptoms, feeding difficulties, growth failure, dysphagia in children)
2. *Baseline oesophageal eosinophil-predominant inflammation* (characteristically consisting of a peak value of ≥15 eos/HPF) *limited to the oesophagus*
   - Baseline endoscopy should be preferably performed off proton pump inhibitor (PPI) therapy to better understand the patient profile in case of further response to PPI therapy
   - Other local and systemic causes of oesophageal eosinophilia should be ruled out: eosinophilic gastroenteritis, Crohn's disease, hypereosinophilic syndrome, parasites, drug hypersensitivity, achalasia, vasculitis, pemphigoid, connective tissue disorders and graft-versus-host disease
   - Biopsies from the antrum and/or duodenum should be obtained in all children and in adults with GI symptoms or endoscopic abnormalities
   - A diagnosis of EoE in patients based solely on histology, without clinical and endoscopic features compatible with EoE, might be questionable
   - Routine oesophageal pH monitoring is not recommended in the diagnostic work-up of EoE
   - A majority of patients with EoE will achieve symptom response and histological remission (<15 eos/HPF) on PPI, topical steroid or dietary intervention

Gastroenterology 2018;155:1022–1033

CLINICAL—ALIMENTARY TRACT

Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference

Where we are today

Table 2. EoE Diagnostic Criteria

- 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/mm^2) on esophageal biopsy
  - Eosinophilic infiltration should be isolated to the esophagus.
- Assessment of non-EoE disorders that cause or potentially contribute to esophageal eosinophilia

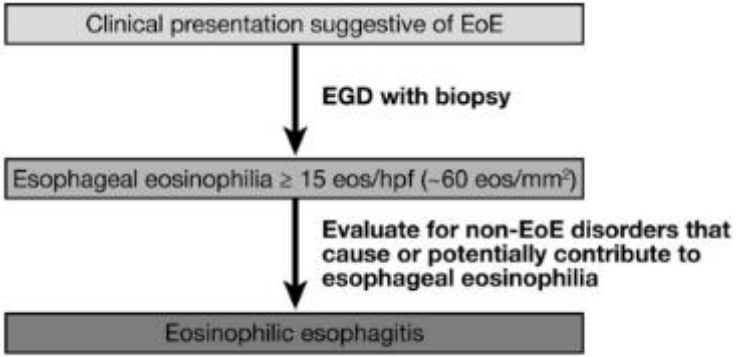


Figure 1. Updated EoE diagnostic algorithm.

- No need to definitively exclude GERD, both can co-exist now.
- Location of eosinophilia within the esophagus no longer matters that much as long as in one hpf it is ≥ 15.

EoE: Increasing prevalence and risk factors

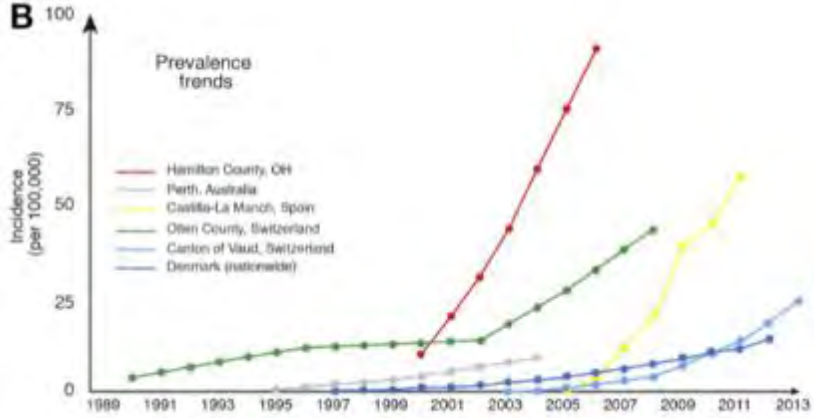
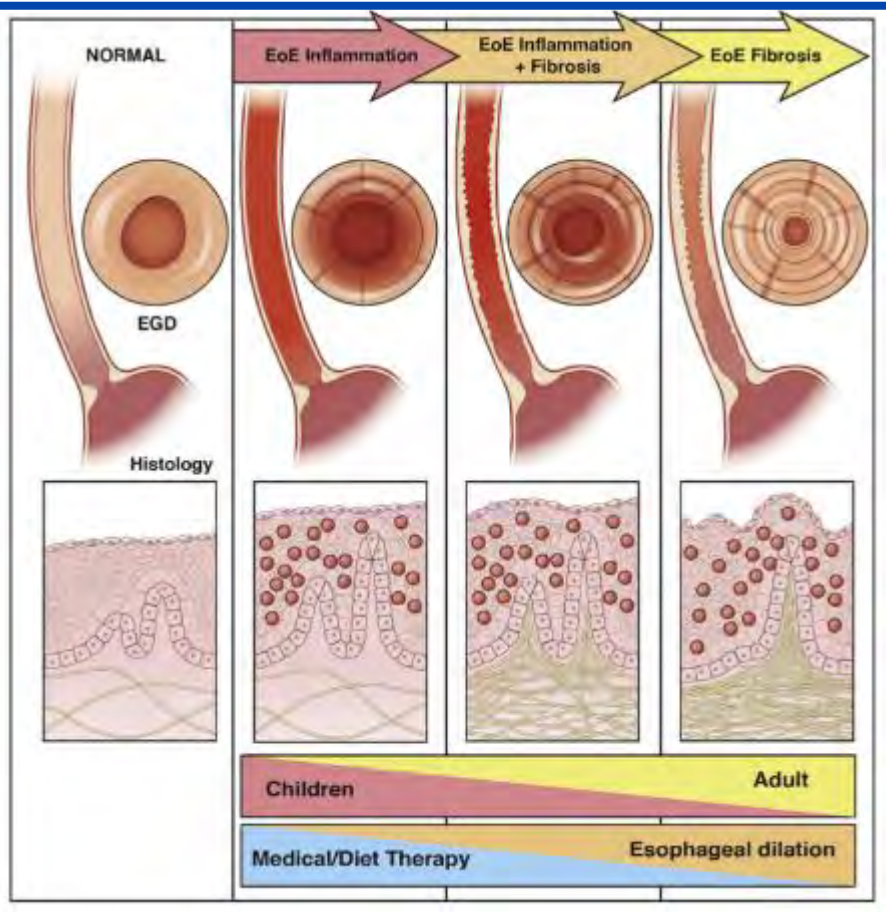


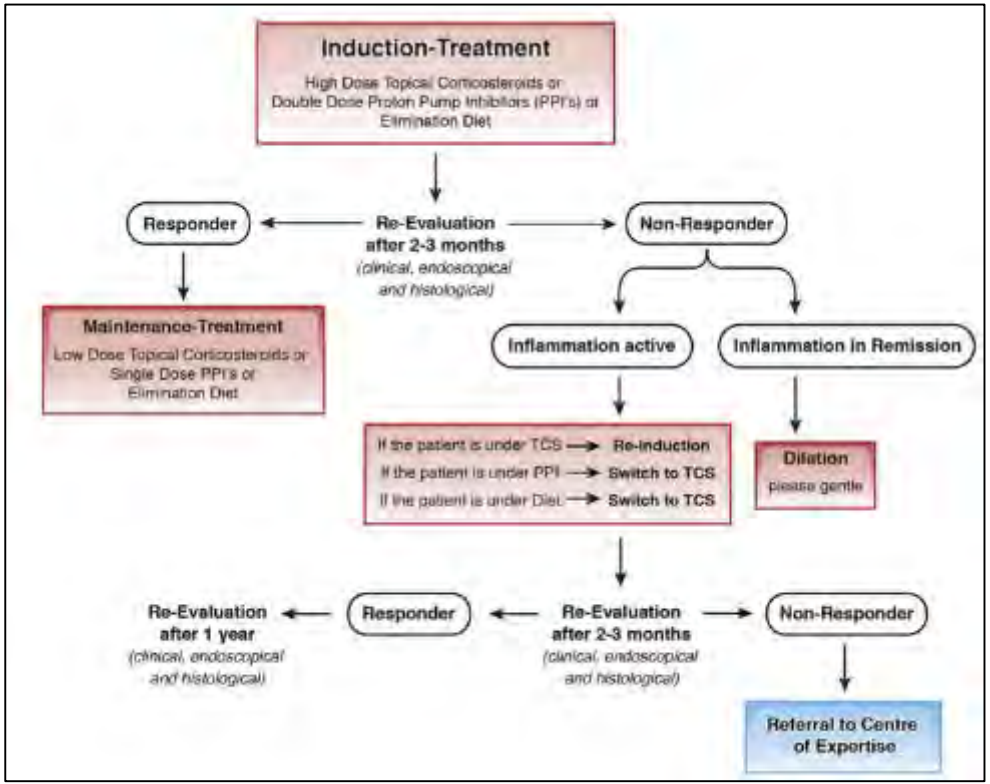
Table 1. Risk Factors for EoE and Disorders Associated With EoE

Risk factor	Comment
Aeroallergens	Might cause EoE or increase disease activity; can cross react with food allergens; may explain seasonal variation in diagnosis
Food allergens	Directly trigger EoE; elimination can lead to disease remission
Helicobacter pylori	Inversely associated with EoE; decrease in *H. pylori* prevalence has accompanied increase in EoE prevalence over the last 20 years; mechanistic data lacking
Infections (herpes simplex virus; mycoplasma)	Associated with EoE; mechanistic data lacking
Oral or sublingual immunotherapy	Causes or induces EoE in certain patients; baseline EoE status for reported cases usually not know prior to immunotherapy
Proton pump inhibitors	Reported to induce IgE antibodies to certain foods
Cold or arid climates	Increased odds of EoE in these climate zones, but not in temperate or tropical zones
Population density	Odds of EoE increase as population density decreases
Early life factors	Antibiotic use, Cesarean section, and preterm delivery increase the odds of pediatric EoE
Connective tissue disorders	Ehlers-Danlos, Marfan syndrome, and Loeys-Dietz syndrome have been associated with EoE
Celiac disease	Associated with EoE; EoE is more common in patients with celiac disease than would be expected
Autoimmune conditions	Inflammatory bowel disease, rheumatoid arthritis, IgA deficiency, multiple sclerosis, and Hashimoto's thyroiditis associated with EoE

Gastroenterology 2018;154:319–332

EoE: Natural history and treatment algorithm





EoE: Current histology recommendations

Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults

United European Gastroenterology Journal
2017, Vol. 5(3) 335–358

13	Al least six biopsies should be taken from different locations, focusing on areas with endoscopic mucosal abnormalities.	Moderate	Strongly in favor
14	The accepted threshold for eosinophil density for the diagnosis of EoE is 15 eosinophils per high power field (standard size of ~0.3 mm^2) in esophageal mucosa, taken as the peak concentration in the specimens examined.	Moderate	Strongly in favor
15	Hematoxylin-eosin staining is sufficient for histological assessment of EoE in routine clinical practice.	Low	Weakly against
16	Besides peak eosinophil count, additional histological features may include eosinophil microabscesses, basal zone hyperplasia, dilated intercellular spaces, eosinophil surface layering, papillary elongation, and lamina propria fibrosis.	Moderate	Weakly in favor
17	Currently, noninvasive biomarkers are not accurate to diagnose or monitor EoE. Some minimal invasive diagnostic tools show promise and merit further evaluation	Moderate	Strongly against
18	Symptoms do not correlate accurately with histologic disease activity, so histology currently continues to be necessary to monitor the disease.	Moderate	Weakly in favor
19	Endoscopic findings alone do not reliably establish a diagnosis of EoE. Their value to assess disease activity needs further evaluation.	Low	Weakly in favor

EoE: Reporting

- What should we report in biopsies taken to exclude/confirm/monitor EoE?

A. Just peak eosinophil count (PEC)

B. Basal cell hyperplasia and PEC

C. All abnormal features seen

D. PEC plus some degree of extent of esophageal eosinophilia by site

E. None of the above

Histological reporting of biopsies

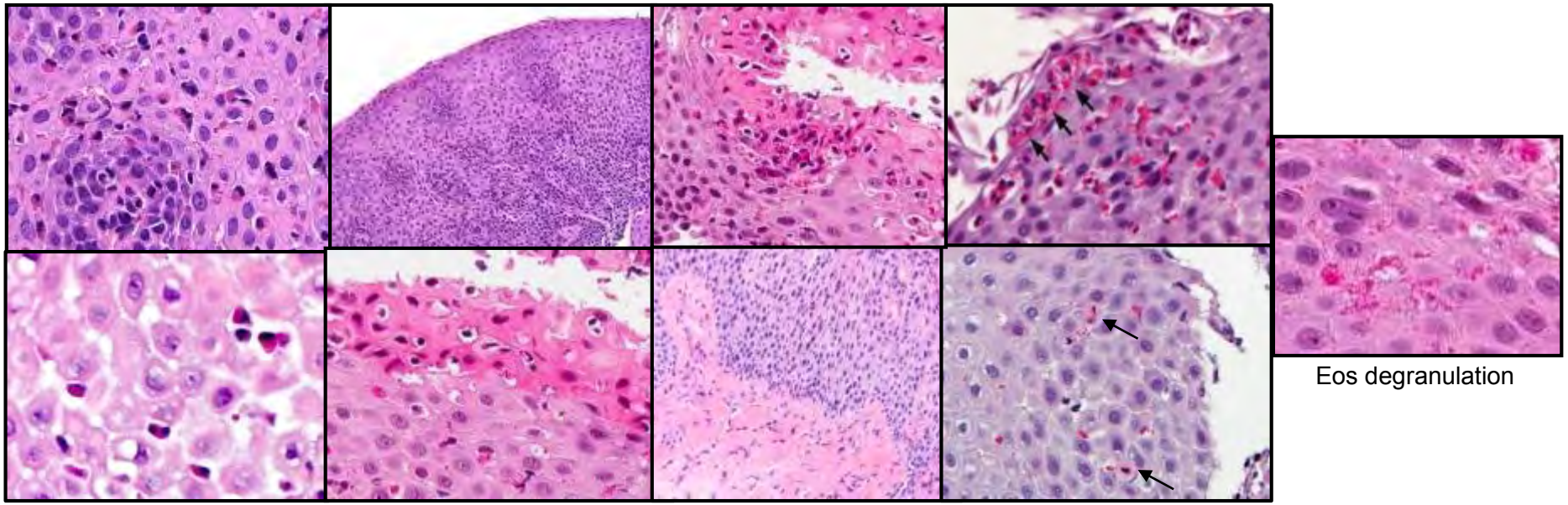
Histological reports should include an eosinophil peak count. They should also include descriptions of the degree of epithelial hyperplasia and spongiosis (e.g., mild, moderate, marked) and should note, if present, eosinophil surface layering and clustering and lamina propria fibrosis, if the lamina propria is present in the biopsies obtained. These reports not only support an initial diagnosis of EoE (or esophagitis with eosinophilia, depending on the relationship of the biopsy to PPI therapy), they also facilitate assessment of response to therapy on subsequent biopsies.

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES 2016;1380(1):204-217

Am J Gastroenterol 2013; 108:679–692

It is important that histologic features besides the absolute eosinophil count, such as eosinophil microabscess formation, superficial layering of eosinophils, extracellular eosinophil granules, basal cell hyperplasia, rete-peg elongation, subepithelial lamina propria fibrosis, and increases in other cell types, such as lymphocytes, be evaluated and noted in pathology reports (47). Although these features are not specific to EoE, they do add information to the overall clinicopathologic assessment of the patient. While preliminary

EoE: Histologic features



Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring

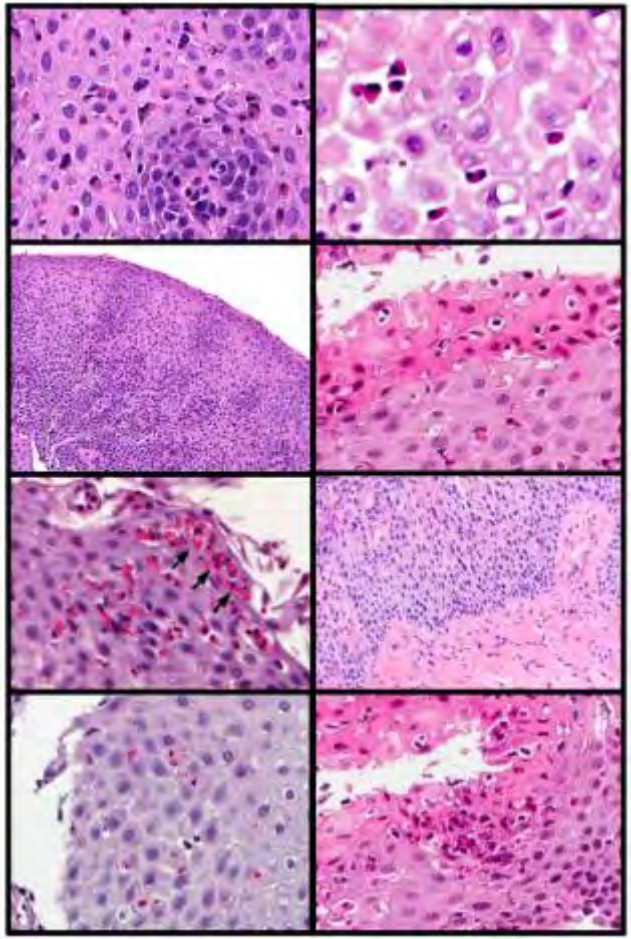
M. H. Collins,[1] L. J. Martin,[2] E. S. Alexander,[3,6] J. Todd Boyd,[1] R. Sheridan,[1] H. He,[2] S. Pentiuk,[4] P. E. Putnam,[4] J. P. Abonia,[5] V. A. Mukkada,[4] J. P. Franciosi,[4] M. E. Rothenberg[5]

Diseases of the Esophagus (2017) **30**, 1–8

EOE specific histologic scoring system (EOEHSS)

- Eosinophil density
- Basal zone hyperplasia
- Dilated intercellular spaces
- Eosinophil abscesses
- Eosinophil surface layering
- Surface epithelial alteration
- Dyskeratotic epithelial cells
- Lamina propria fibrosis

Severity (grade) & extent (stage) scored (0-3)



Reliability of histologic assessment in patients with eosinophilic oesophagitis

Aliment Pharmacol Ther. 2018;47:940–950.

M. J. Warners[1] | C. A. Ambarus[1] | A. J. Bredenoord[1] | J. Verheij[1] | G. Y. Lauwers[2] | J. C. Walsh[3] | D. A. Katzka[4] | S. Nelson[3] | T. van Viegen[3] | G. T. Furuta[5] | S. K. Gupta[6] | L. Stitt[3] | G. Zou[3] | C. E. Parker[3] | L. M. Shackelton[3] | G. R. D'Haens[1,7] | W. J. Sandborn[3,7] | E. S. Dellon[8] | B. G. Feagan[3] | M. H. Collins[9] | V. Jairath[3] | R. K. Pal[10]

- Inter and Intra-rater agreement (measured by ICC) was substantial to almost perfect for PEC and overall EoEHSS:

		Reliability ICC (95% CI)	
Feature		Inter-rater	Intra-Rater
Peak Eosinophil Count		0.86 (0.80, 0.91)	0.92 (0.85, 0.95)
EoEHSS: Grade		0.77 (0.66, 0.84)	0.87 (0.79, 0.91)
EoEHSS: Stage		0.83 (0.74, 0.88)	0.87 (0.80, 0.92)
Eosinophilic Inflammation (EI)			
	Grade	0.82 (0.70, 0.89)	0.86 (0.77, 0.91)
	Stage	0.83 (0.72, 0.89)	0.88 (0.81, 0.93)
Epithelial Basal Zone Hyperplasia			
	Grade	0.50 (0.33, 0.64)	0.68 (0.56, 0.80)
	Stage	0.59 (0.37, 0.72)	0.73 (0.59, 0.85)
Lamina Propria Fibrosis			
	Grade	0.60 (0.46, 0.70)	0.79 (0.69, 0.86)
	Stage	0.63 (0.49, 0.75)	0.76 (0.63, 0.86)

Interpretation: 0–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, 0.81–1 as almost perfect agreement

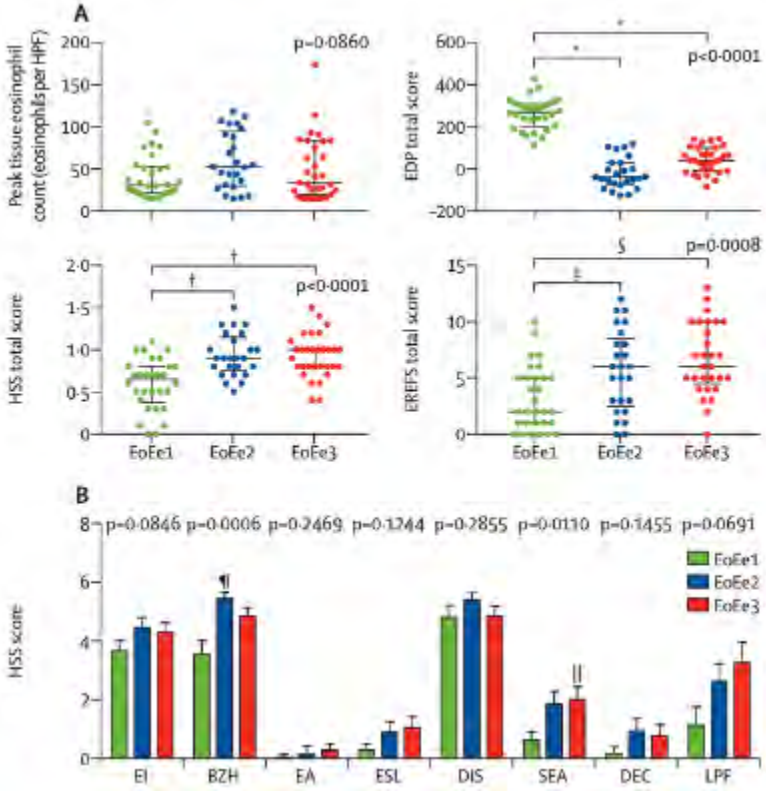
Eosinophilic oesophagitis endotype classification by molecular, clinical, and histopathological analyses: a cross-sectional study

Lancet Gastroenterol Hepatol
2018; 3: 477–88

Tetsuo Shoda, Ting Wen, Seema S Aceves, J Pablo Abonia, Dan Atkins, Peter A Bonis, Julie M Caldwell, Kelley E Capocelli, Christina L Carpenter, Margaret H Collins, Evan S Dellon, Michael D Eby, Nirmala Gonsalves, Sandeep K Gupta, Gary W Falk, Ikuo Hirano, Paul Menard-Katcher, Jonathan T Kuhl, Jeffrey P Krischer, John Leung, Vincent A Mukkada, Jonathan M Spergel, Michael P Trimarchi, Guang-Yu Yang, Nives Zimmermann, Glenn T Furuta, Marc E Rothenberg, on behalf of the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR)

Types based on Gene expression:
EoEe1: Mild
EoEe2: Inflammatory
EoEe3: Fibrostenotic

PEC was not discriminatory but EoEHSS was



New treatment algorithm?

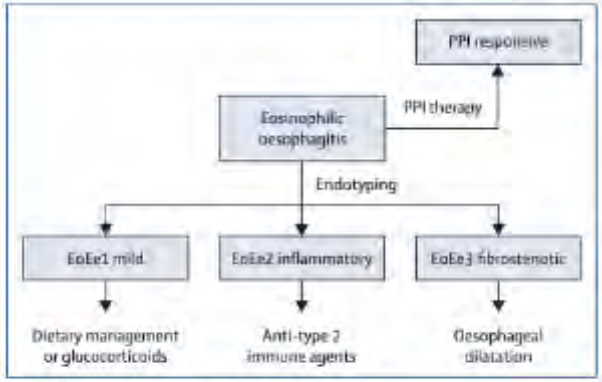
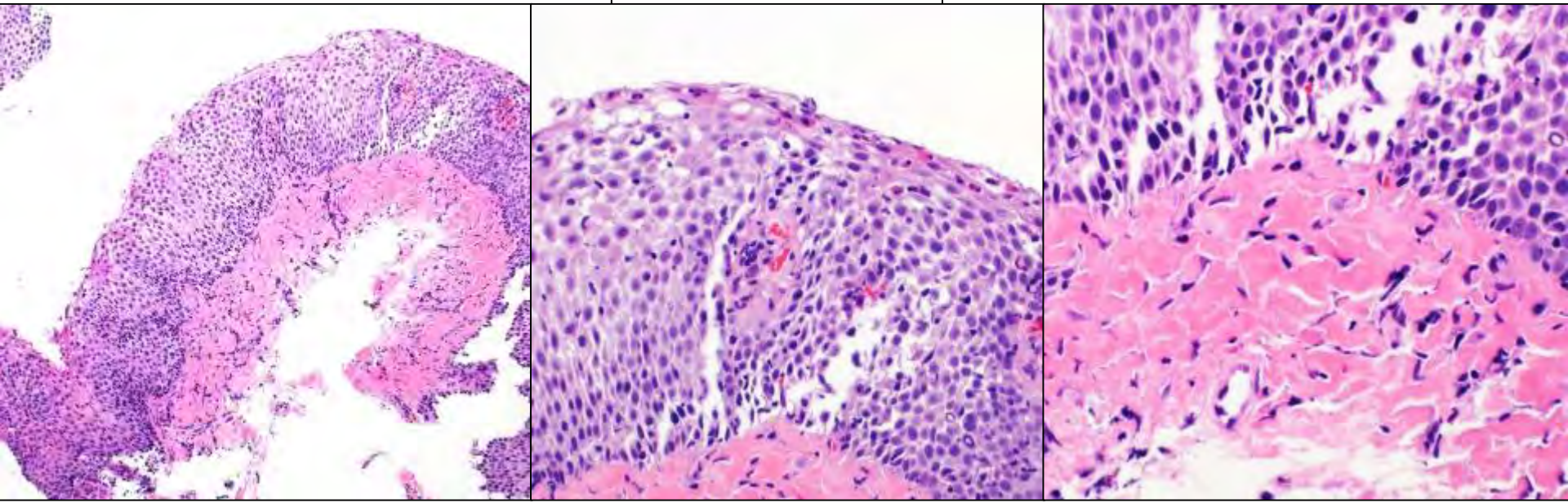


Figure: **Potential clinical application of the EDP**
EDP=eosinophilic oesophagitis diagnostic panel. EoEe=eosinophilic oesophagitis endotype. PPI=proton-pump inhibitor.

Case: PEC doesn't tell the whole story

21 yo male with dysphagia

Max 25 Eos/HPF



Spongiosis, BZH, and lamina propria fibrosis with fairly mild increase in Eos

EoE Reporting: One approach

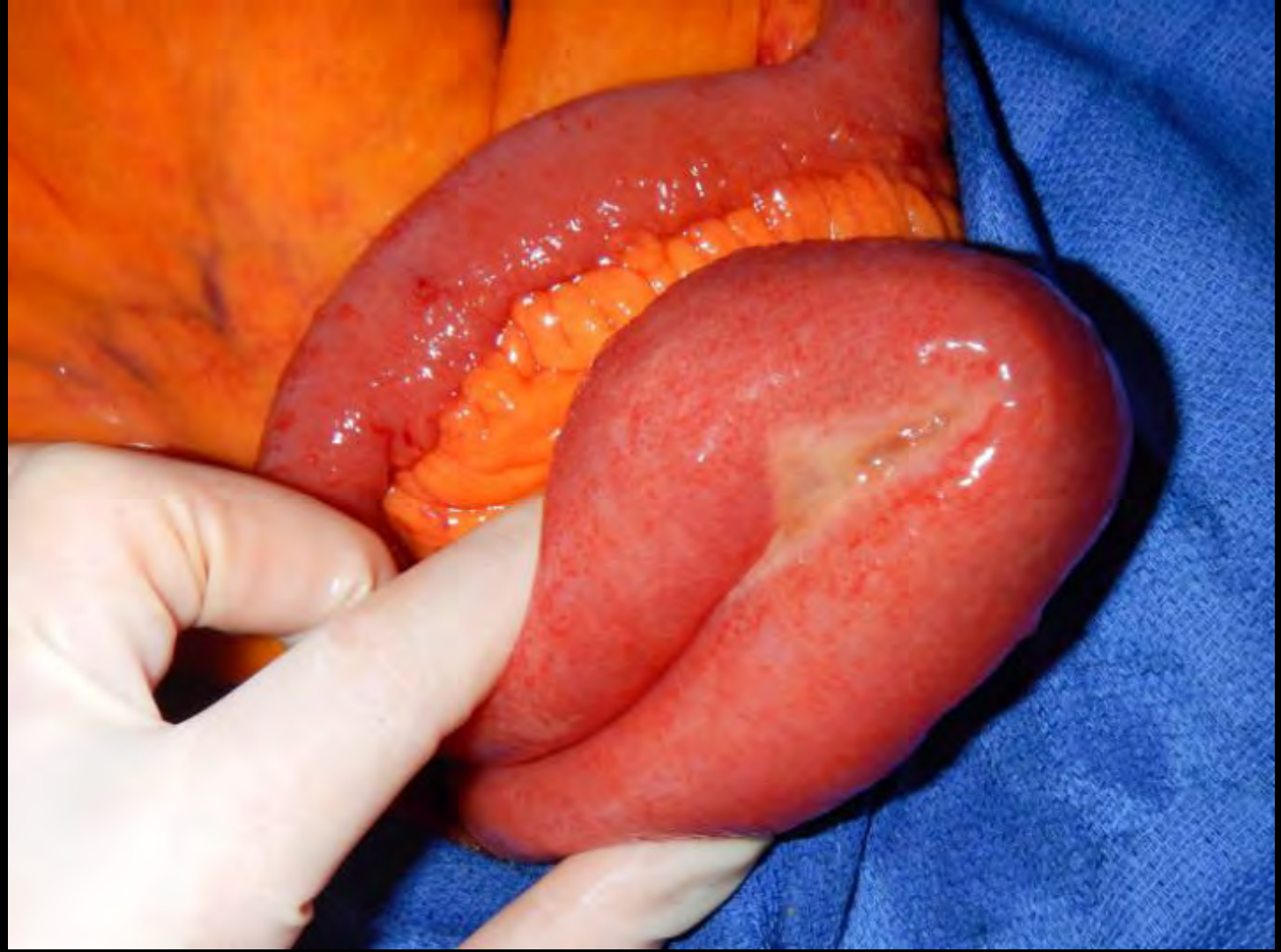
- A diagnosis of EoE should not be based on pathology alone
- Ideal situation:
  - ≥ 6 biopsy fragments from at least 2 sites, ≥ 15 Eos per HPF in seen in at least 1 HPF (96% specific for EoE; Mod Pathol. 2015;28:383–390)
  - Report the PEC
  - Comment: These histologic features could be consistent with EoE in the appropriate clinical and endoscopic setting.
- Otherwise just report the PEC (I count up to 100 per HPF) with or without a comment (depends on clinical info).
- Other potential features to report: extent of eosinophilia, BZH, spongiosis, surface epithelial alteration, and lamina propria fibrosis (if sampled)
  - Full EoEHSS if you so desire….

Outline

- Esophageal Eosinophilia:
  - What happened to PPI-responsive esophageal eosinophilia?
  - Histologic features of EoE and what should we report?
- Non-esophageal GI tract eosinophilia
  - Differential diagnosis and avoiding pitfalls
  - Diagnosis of primary eosinophilic gastritis/gastroenteritis

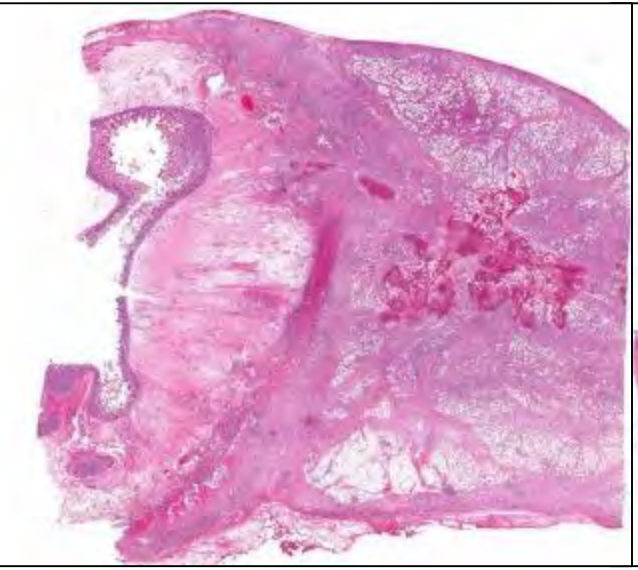
Case

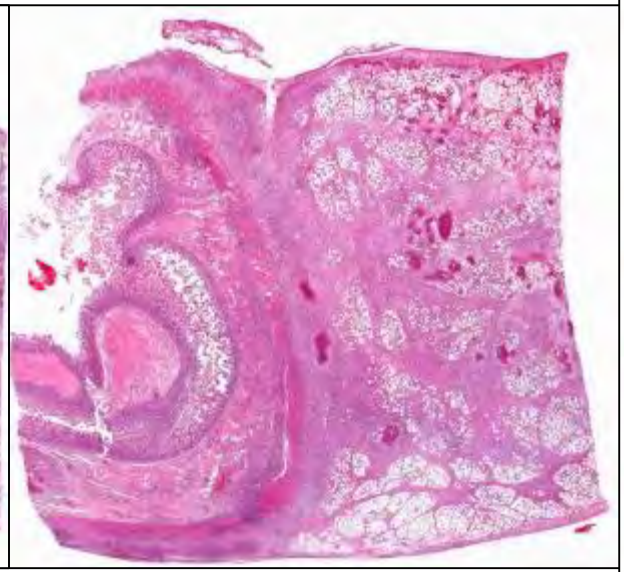
- 56-year-old female with recurrent small-bowel obstructions since 2007. Had a hysterectomy in the early 2000s.
- She modified her diet, which subsided a lot of these attacks. Last “attack” was 2012.
- Now presents with diffuse abdominal pain after “swallowing a lot of air”. Pain is similar to what she has had before. She endorses some emesis x3. Denies any fevers, chills, shortness of breath, or chest pain.
- CT showed a partial small-bowel obstruction involving loops of small bowel in the left hemi-abdomen.

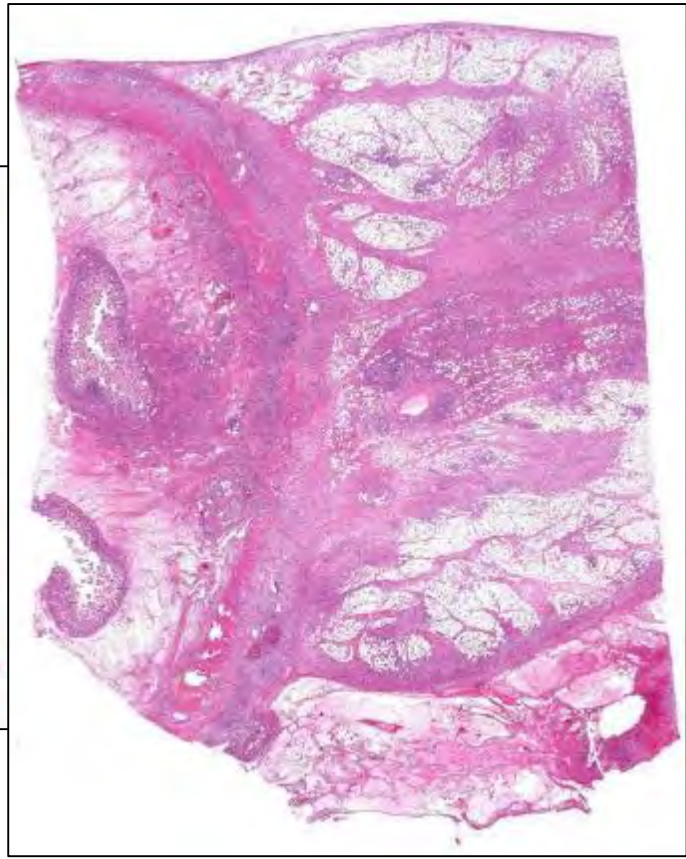


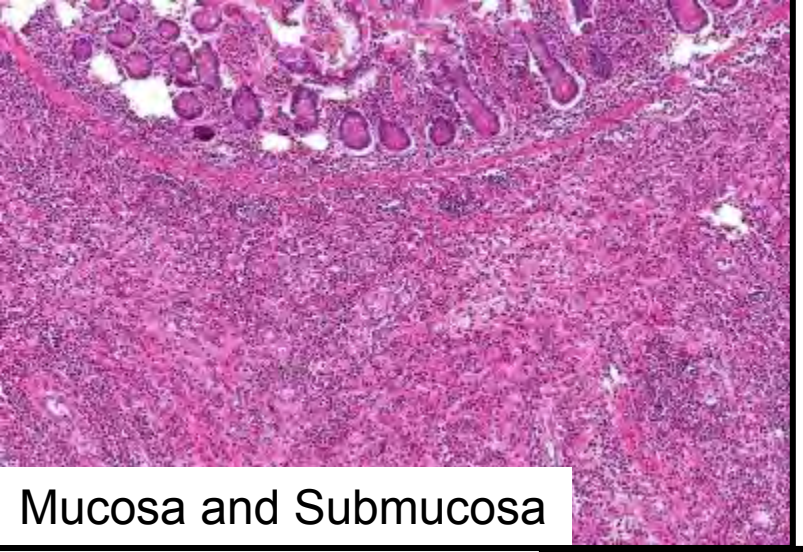
Surgical Pathology specimen

- GROSS DESCRIPTION:
  A. Received fresh labeled “XXXXXXXXXX" and "small bowel" is a 20-cm segment of small bowel that averages 3 cm in external diameter. The bowel mucosa is edematous, but is otherwise intact. In the midportion of the specimen within the mesentery is a poorly-demarcated area of slightly granular gray-white induration that measures 4.8 x 3 x 1.8 cm. Sampled in seven cassettes.
  A1-A4) Samples of mesenteric mass;
  A5) samples from surgical ends of bowel associated with mass;
  A6) sample of mesenteric surgical margin;
  A7) mesenteric lymph node

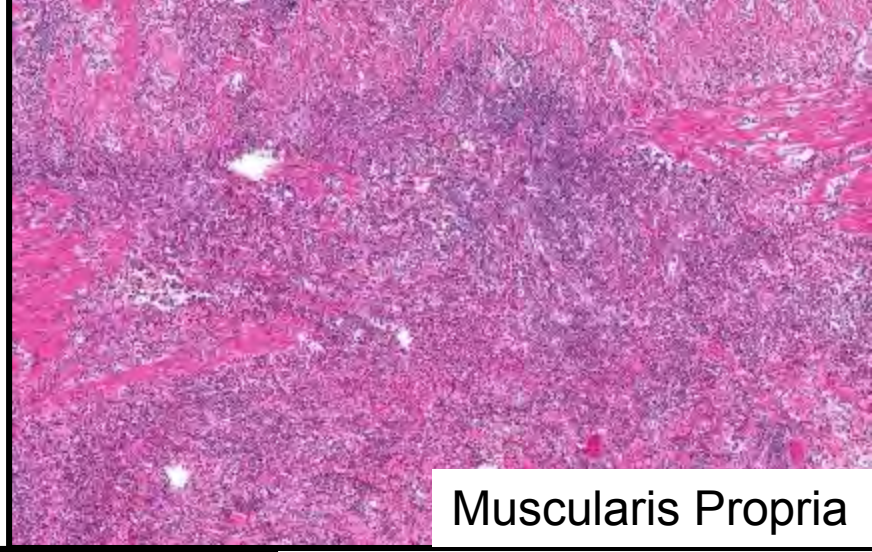








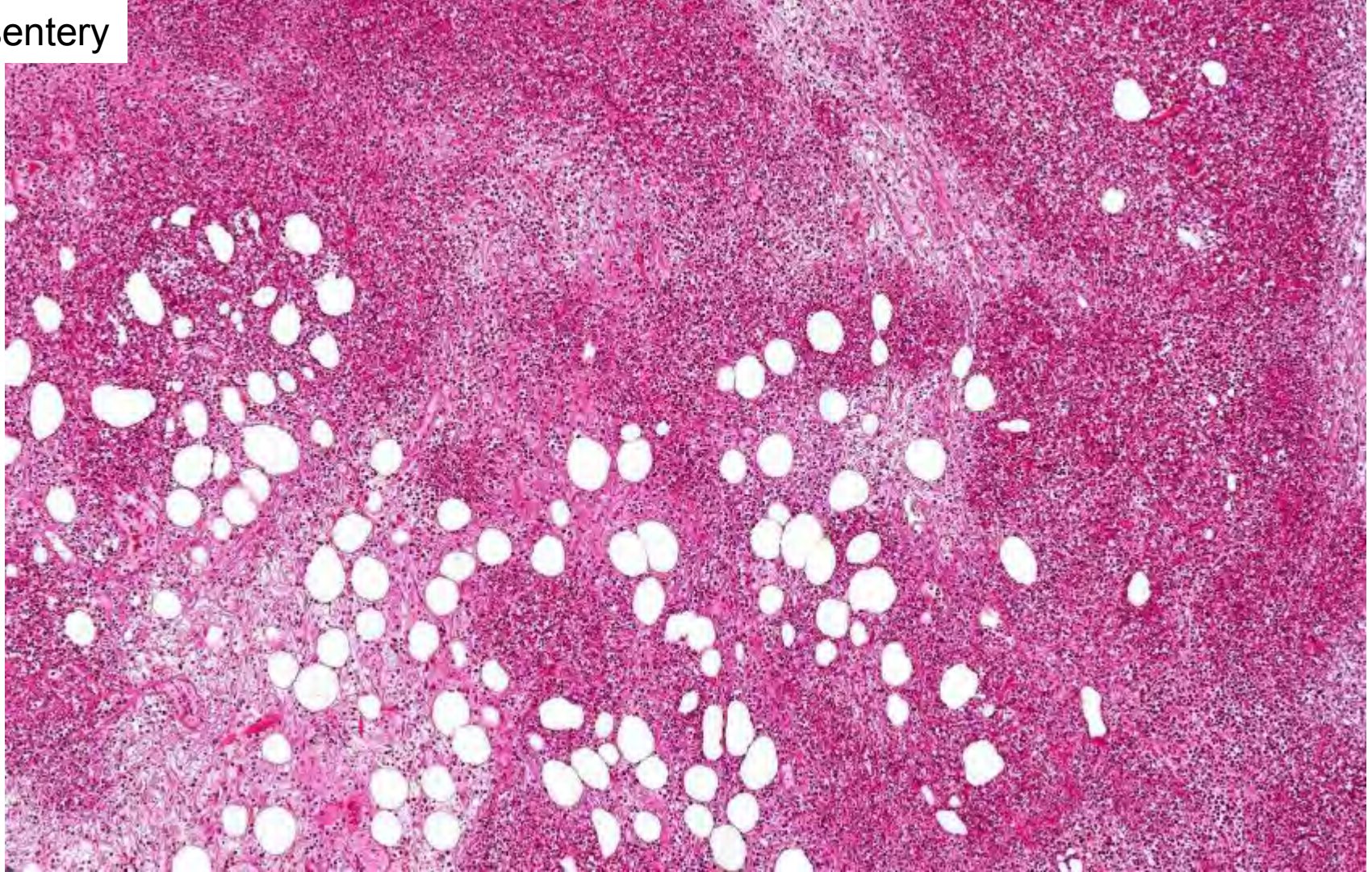
Mucosa and Submucosa

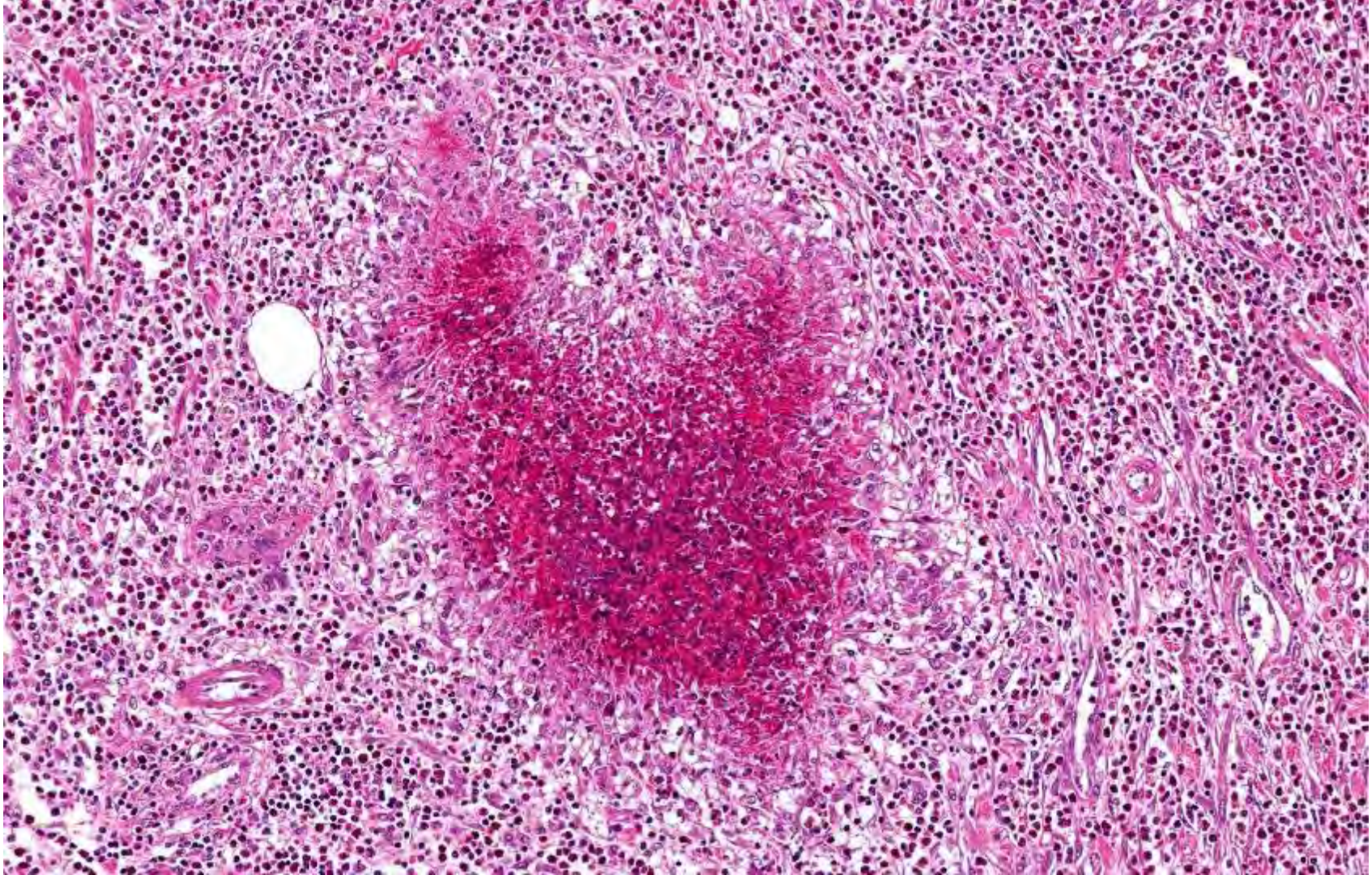


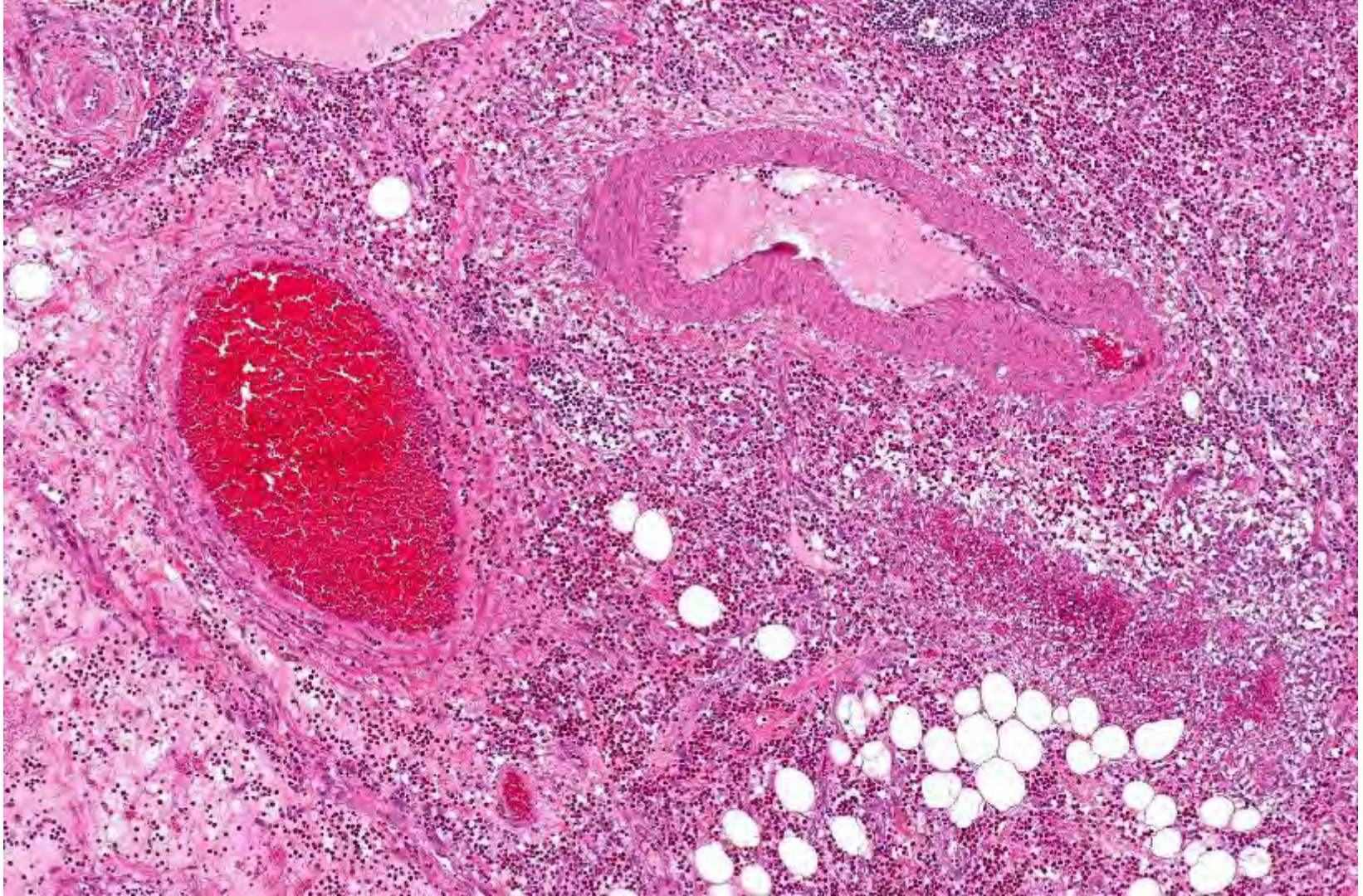
Muscularis Propria

Serosa

Mesentery







Pathologic features

- Marked eosinophilia (with eosinophilic abscesses) present in all layers of the bowel (mucosal, submucosal, muscularis propria, mesentery, and serosa) localized to the area of gross abnormality
- No obvious infections organism
- No apparent vasculitis
- No apparent neoplastic process

Lab Values

	Ref Range & Units	
Lymphocytes	1.00 - 3.40 x10(9)/L	2.20
MCV	82.7 - 96.8 fL	94.8
Eosinophils	0.00 - 0.40 x10(9)/L	1.08 ^
Platelet Count	149 - 375 x10(9)/L	367
Absolute Basophil	0.00 - 0.20 x10(9)/L	0.03
Leukocytes	3.4 - 10.6 x10(9)/L	5.9
Hematocrit	34.9 - 44.5 %	34.7 v
Hemoglobin	12.0 - 15.5 g/dL	11.2 v
Monocytes	0.20 - 0.80 x10(9)/L	0.53
RBC Distrib Width	11.9 - 15.5 %	11.9
Absolute Neutrophils	1.40 - 6.60 x10(9)/L	2.06
Erythrocytes	3.68 - 4.88 x10(12)/L	3.66 v

Peripheral eosinophilia

Question

Which statement is TRUE regarding eosinophilic gastroenteritis?

A. Involvement of the deep layers of the bowel is common in this entity.

B. Altered eosinophil distribution (deep, superficial, or intraepithelial) is more important than the density of eosinophils.

C. Diagnosis requires tissue eosinophilia, symptoms, and exclusion of other causes of increased eosinophilia

Question

Which statement is TRUE regarding eosinophilic gastroenteritis?

A. Involvement of the deep layers of the bowel is common in this entity.

B. Altered eosinophil distribution (deep, superficial, or intraepithelial) is more important than the density of eosinophils.

C. Diagnosis requires tissue eosinophilia, symptoms, and exclusion of other causes of increased eosinophilia

Why are eosinophils so difficult to deal with?

- Sometimes they are a normal component of the mucosa and we should ignore them
- Sometimes they are part of the disease process affecting the GI tract and we should ignore them
- Sometimes they are a red herring and distract us from the true process that is going on, resulting in a missed diagnosis
- Sometimes they are the primary mediators of the disease and should be emphasized in our reports

Normal distribution of Eosinophils

Virchows Arch (2018) 473:313–320

Table 2 Mean number (± standard deviation), range and maximum number of eosinophils in each gastrointestinal segment

Gastrointestinal segment		Lamina propria				Epithelium			
		Eos/HPF	Eos/mm^2			Eos/HPF	Eos/mm^2		
		Mean ± SD	Mean ± SD	Range	Max	Mean ± SD	Mean ± SD	Range	Max
Oesophagus ($n = 33$)		N/A	N/A	N/A	N/A	0 ± 0	0 ± 0	0	0
Fundus ($n = 13$)	Superficial	0.2 ± 0.2	0.8 ± 0.9	0–3	3	0 ± 0	0 ± 0	0	0
	Deep	0.2 ± 0.6	0.9 ± 2.3	0–8	8	0 ± 0	0 ± 0	0	0
Corpus ($n = 13$)	Superficial	0.1 ± 0.1	0.2 ± 0.6	0–2	2	0 ± 0	0 ± 0	0	0
	Deep	0.3 ± 1.0	1.1 ± 3.9	0–14	14	0 ± 0	0 ± 0	0	0
Antrum ($n = 16$)	Superficial	0.2 ± 0.4	0.7 ± 1.7	0–6	6	0 ± 0	0 ± 0	0	0
	Deep	1.9 ± 3.0	7.8 ± 12.4	0–42	42	0 ± 0	0 ± 0	0	0
Bulb ($n = 13$)		4.4 ± 4.2	18.1 ± 17.0	0–50	50	0.2 ± 0.5	0.9 ± 2.0	0–7	7
D2 ($n = 13$)		3.6 ± 3.0	14.4 ± 12.0	2–42	42	0.3 ± 0.5	1.4 ± 2.1	0–7	7
Ileum ($n = 16$)		12.6 ± 8.6	51.5 ± 35.3	3–111	111	0.8 ± 0.7	3.4 ± 2.9	0–9	9
Caecum ($n = 16$)		12.7 ± 8.2	51.8 ± 33.5	2–125	125	1.0 ± 0.9	4.2 ± 3.7	0–13	13
Ascending colon ($n = 16$)		10.0 ± 6.7	40.9 ± 27.4	3–88	88	0.7 ± 0.7	3.0 ± 3.0	0–9	9
Transverse colon ($n = 14$)		8.4 ± 5.4	34.3 ± 21.9	4–69	69	0.7 ± 0.8	3.0 ± 3.1	0–11	11
Descending colon ($n = 15$)		9.9 ± 6.5	40.0 ± 26.6	1–92	92	0.8 ± 0.6	3.0 ± 2.7	0–10	10
Sigmoid colon ($n = 17$)		6.3 ± 4.4	25.8 ± 17.8	0–56	56	0.6 ± 0.6	2.3 ± 2.3	0–8	8
Rectum ($n = 17$)		3.3 ± 2.5	13.9 ± 10.1	0–44	44	0.4 ± 0.6	1.8 ± 2.4	0–9	9

Stomach

Small bowel

Colon

GIT eosinophilia: Differential Dx

- Primary eosinophilic GI diseases
- Secondary eosinophilia due to systemic disease and neoplasms
- GI inflammatory diseases associated with increased eosinophils

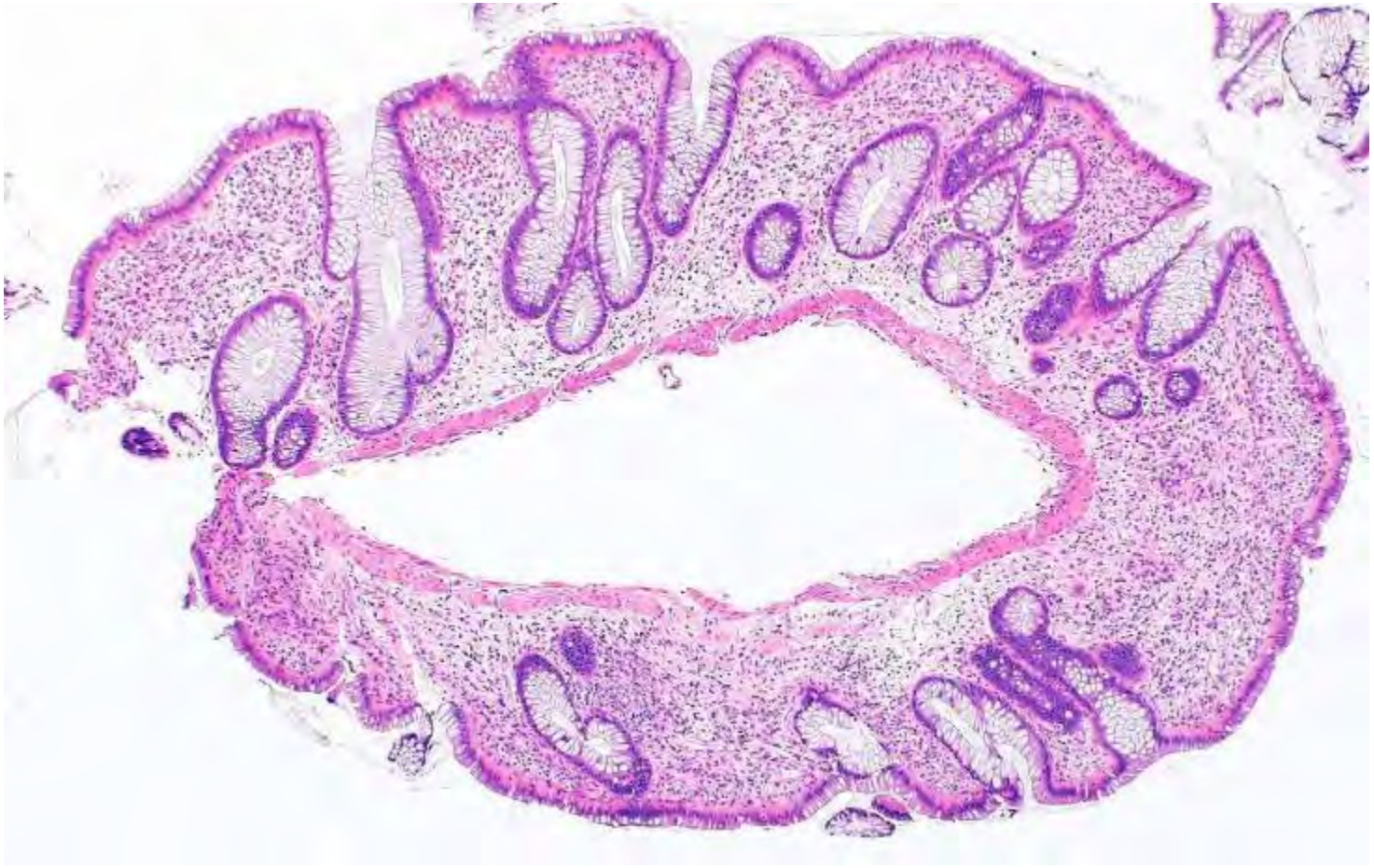
Secondary GI Eos: Systemic Causes and Tumors

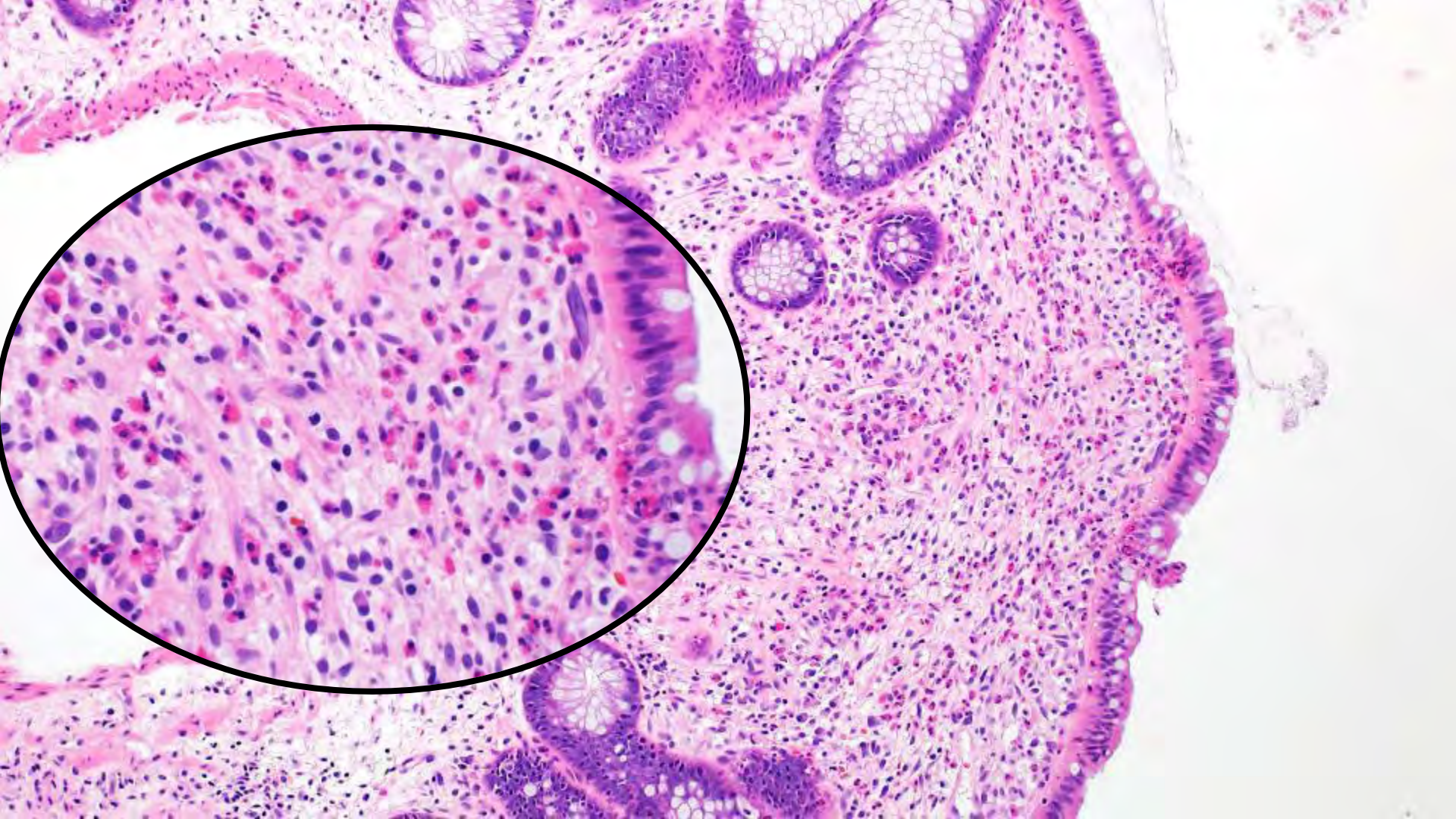
- Infections (mucosal to transmural)
- Hypersensitivity reaction (predominately mucosal and submucosal)
- Neoplasms (mucosal to transmural)
- Connective tissue disease (mucosal to transmural)
- Vasculitis (mucosal to transmural)
- Hypereosinophilic syndrome (mucosal to transmural)

Secondary GI eosinophilia: Systemic causes

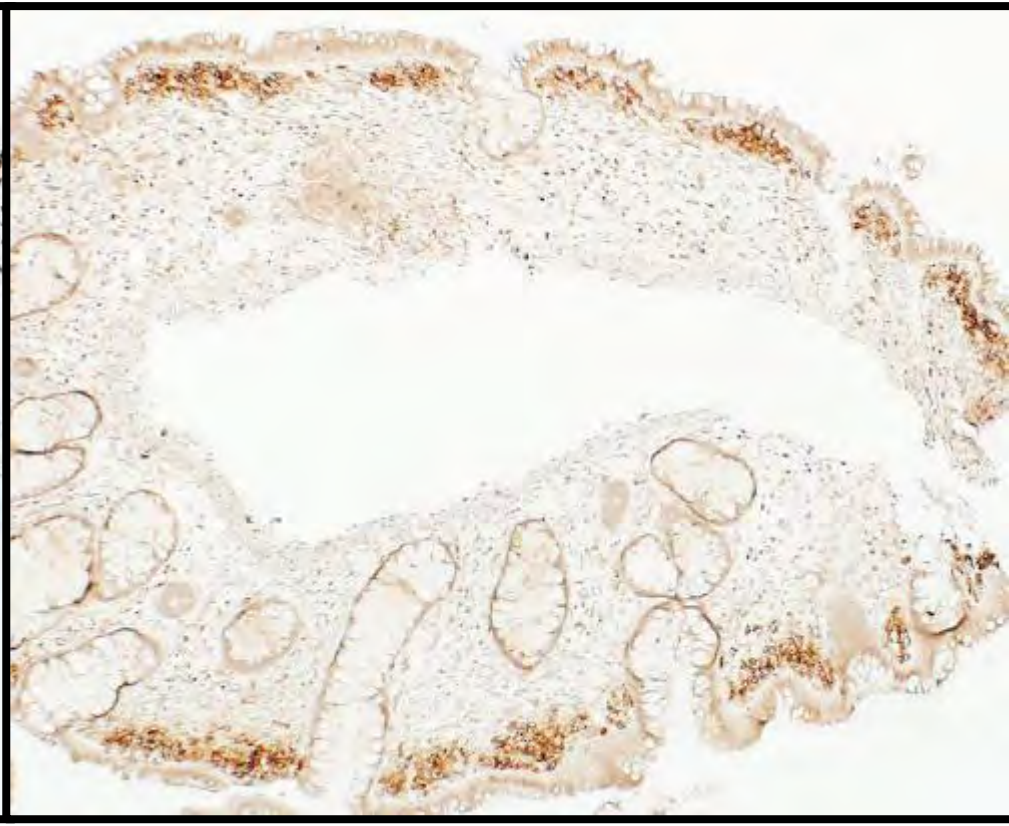
- 65 yo male with AML s/p allogeneic stem cell transplant with diarrhea. Undergoes a colonoscopy to evaluate for GVHD.

A polyp was also biopsied





CD117



CD25

A Clinicopathologic Study of 24 Cases of Systemic Mastocytosis Involving the Gastrointestinal Tract and Assessment of Mucosal Mast Cell Density in Irritable Bowel Syndrome and Asymptomatic Patients

Leona A. Doyle, MD, Golrokh J. Sepehr, MD,* Matthew J. Hamilton, MD,†‡ Cem Akin, MD, PhD,†‡ Mariana C. Castells, MD,†‡ and Jason L. Hornick, MD, PhD*‡*

(*Am J Surg Pathol* 2014;38:832–843)

Prominent eosinophilic infiltrates were seen in 44% of involved colonic/ileal biopsies (Fig. 6) and 16% of duodenal biopsies but not in any of the involved gastric biopsies. Other histologic findings were observed in 28% (19/67) of biopsies involved by mastocytosis: architectural distortion in 4 colonic biopsies, chronic duodenitis in 3 biopsies, villous blunting in 4 small intestinal biopsies,

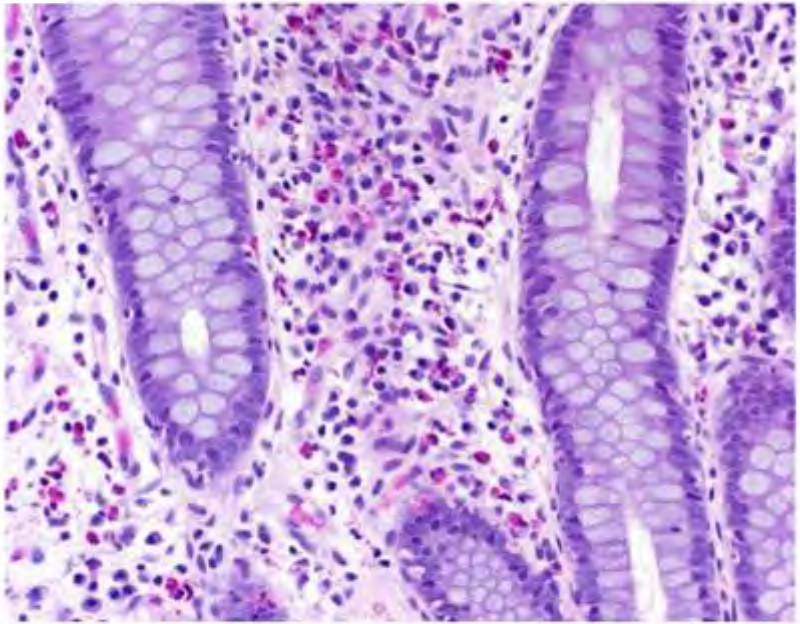
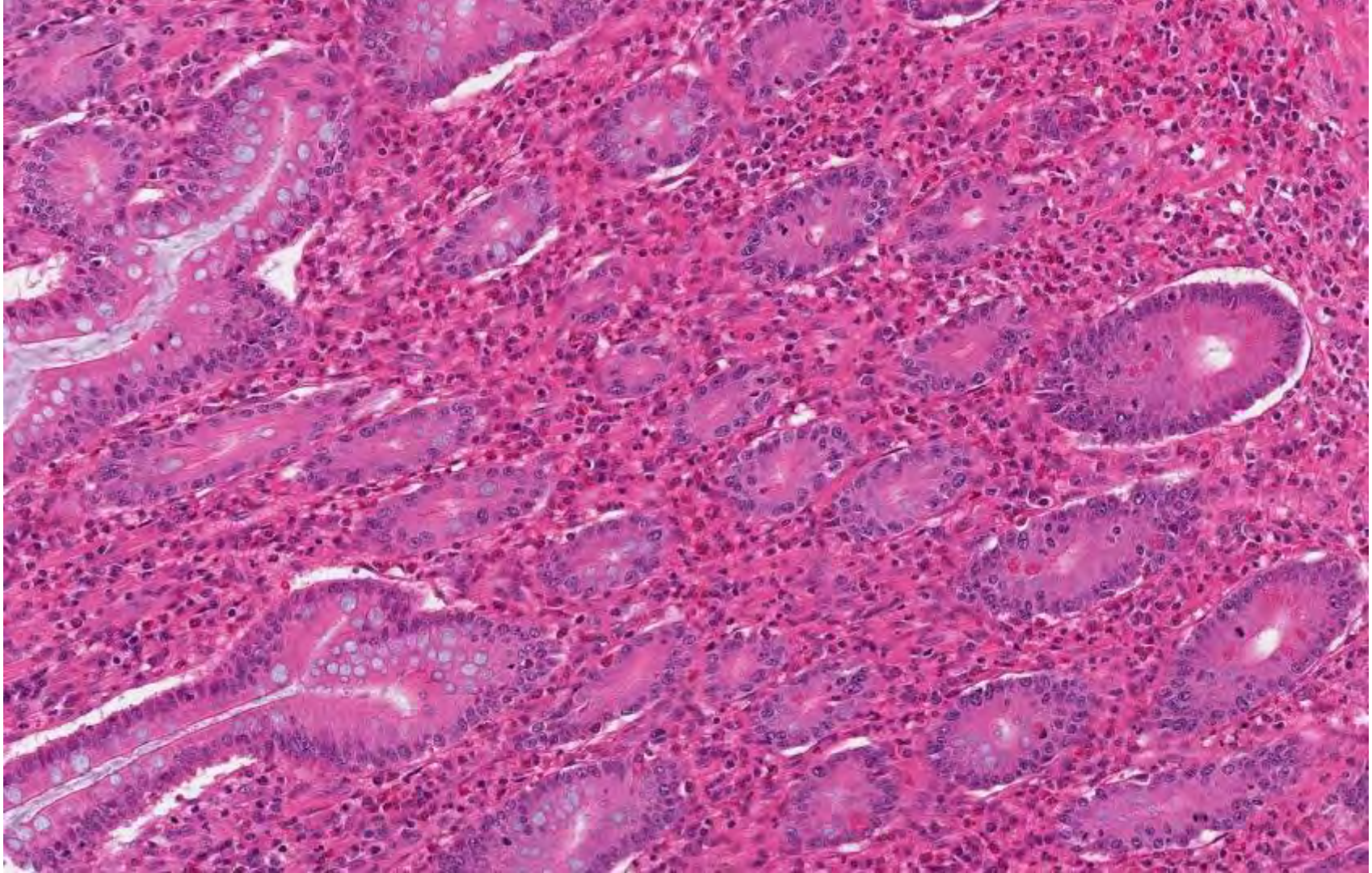
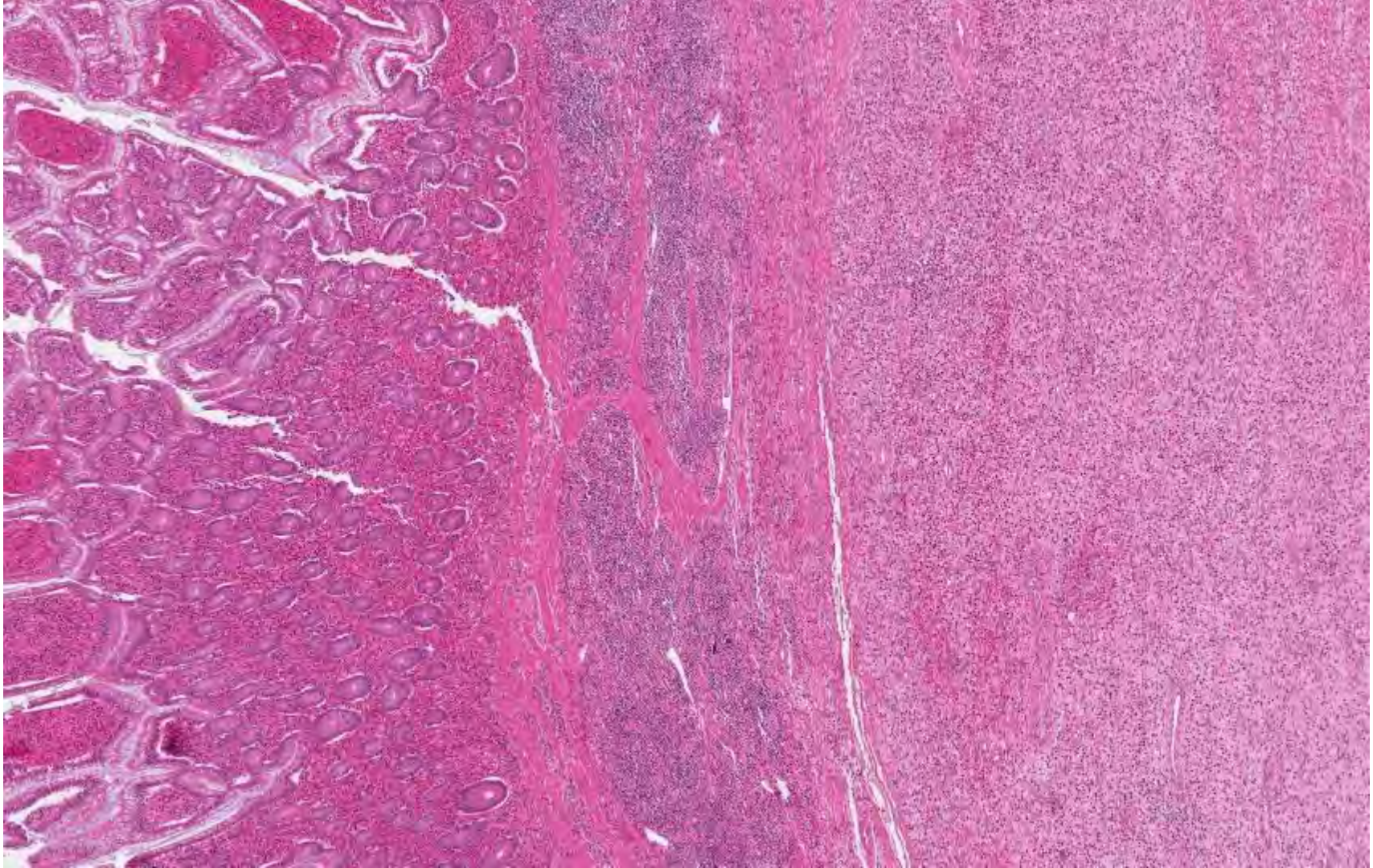


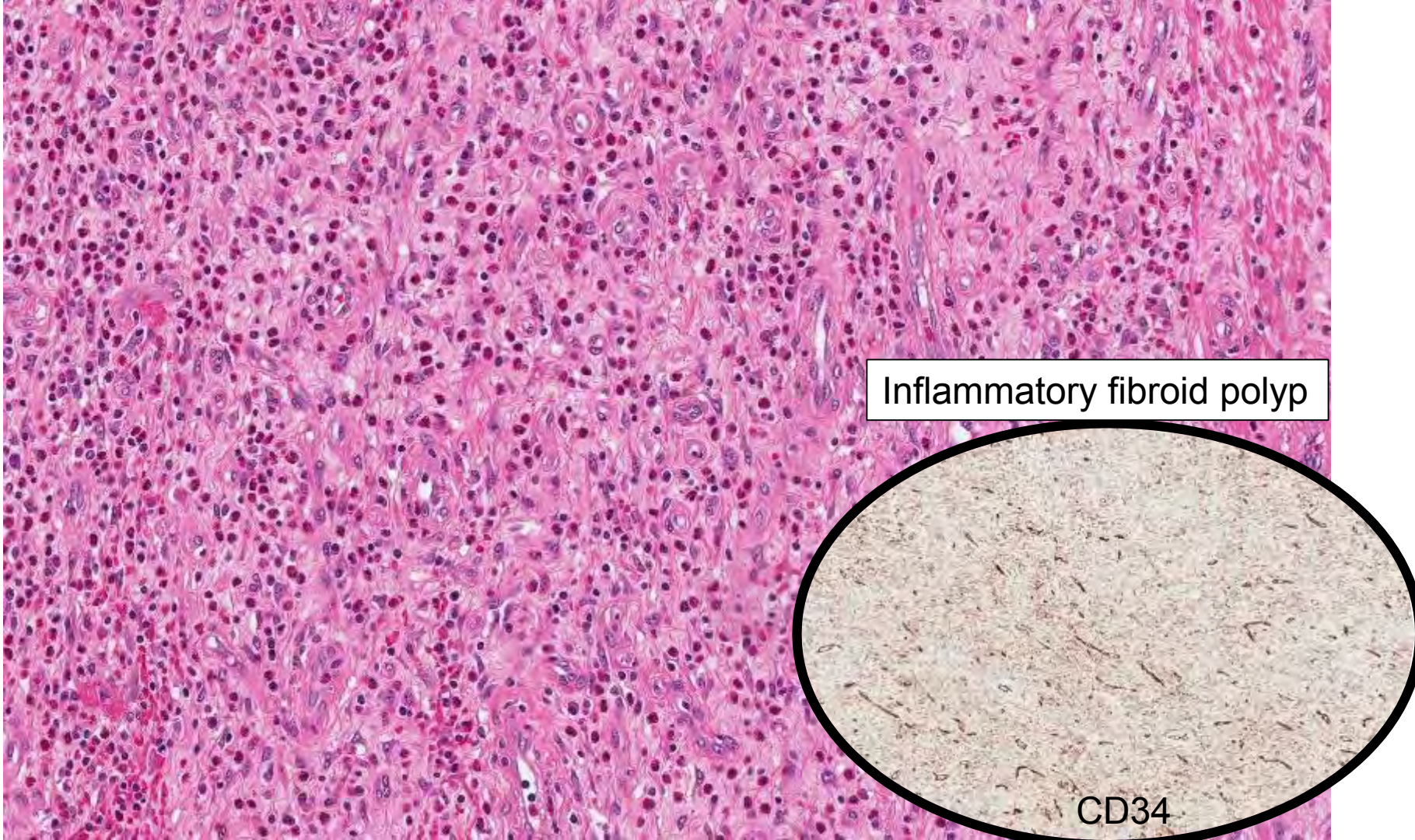
FIGURE 6. Prominent lamina propria eosinophils are common in colonic biopsies involved by systemic mastocytosis and may mask the mast cell infiltrate.

Secondary GI eosinophilia

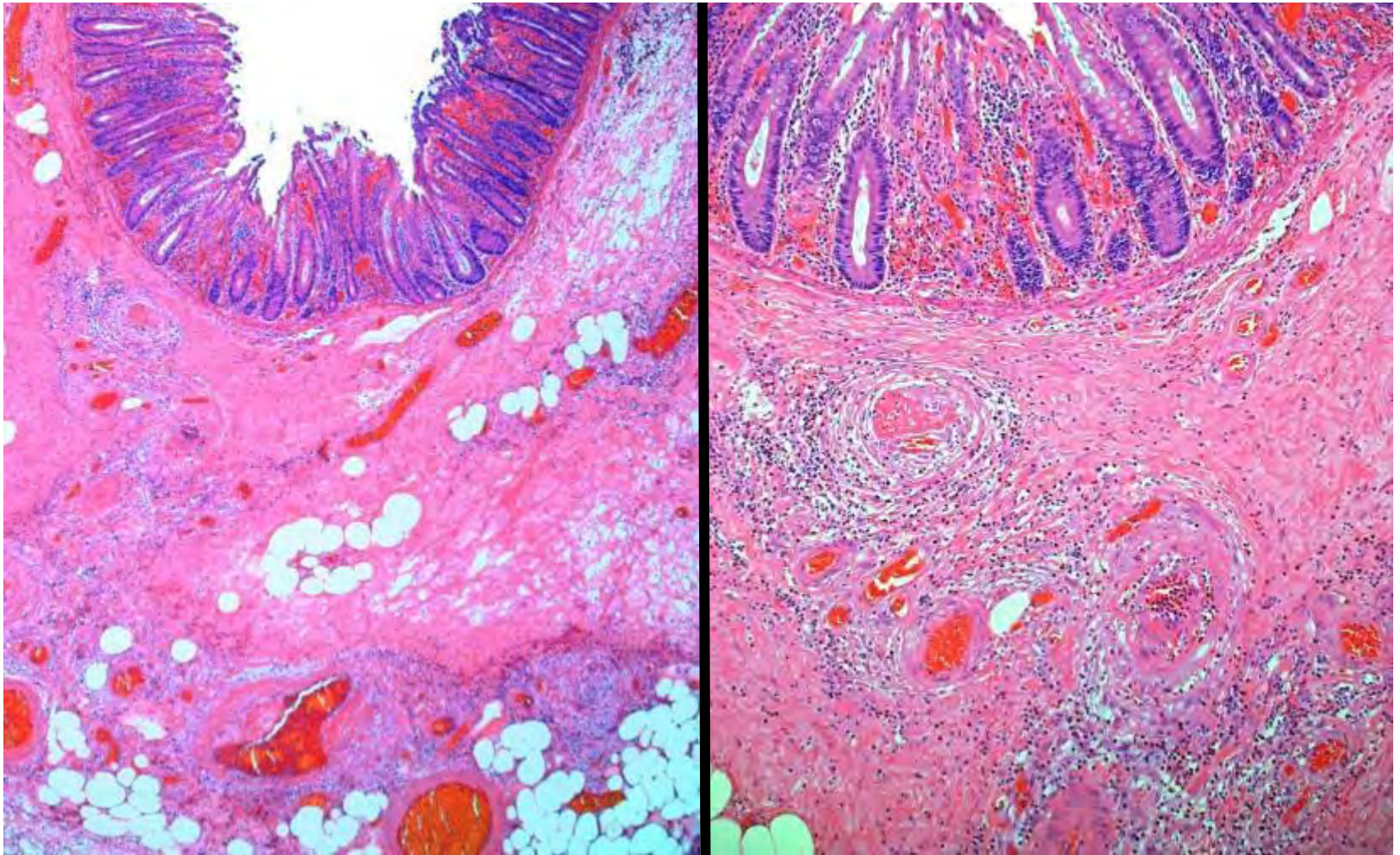
- 45 yo male with a small bowel mass.



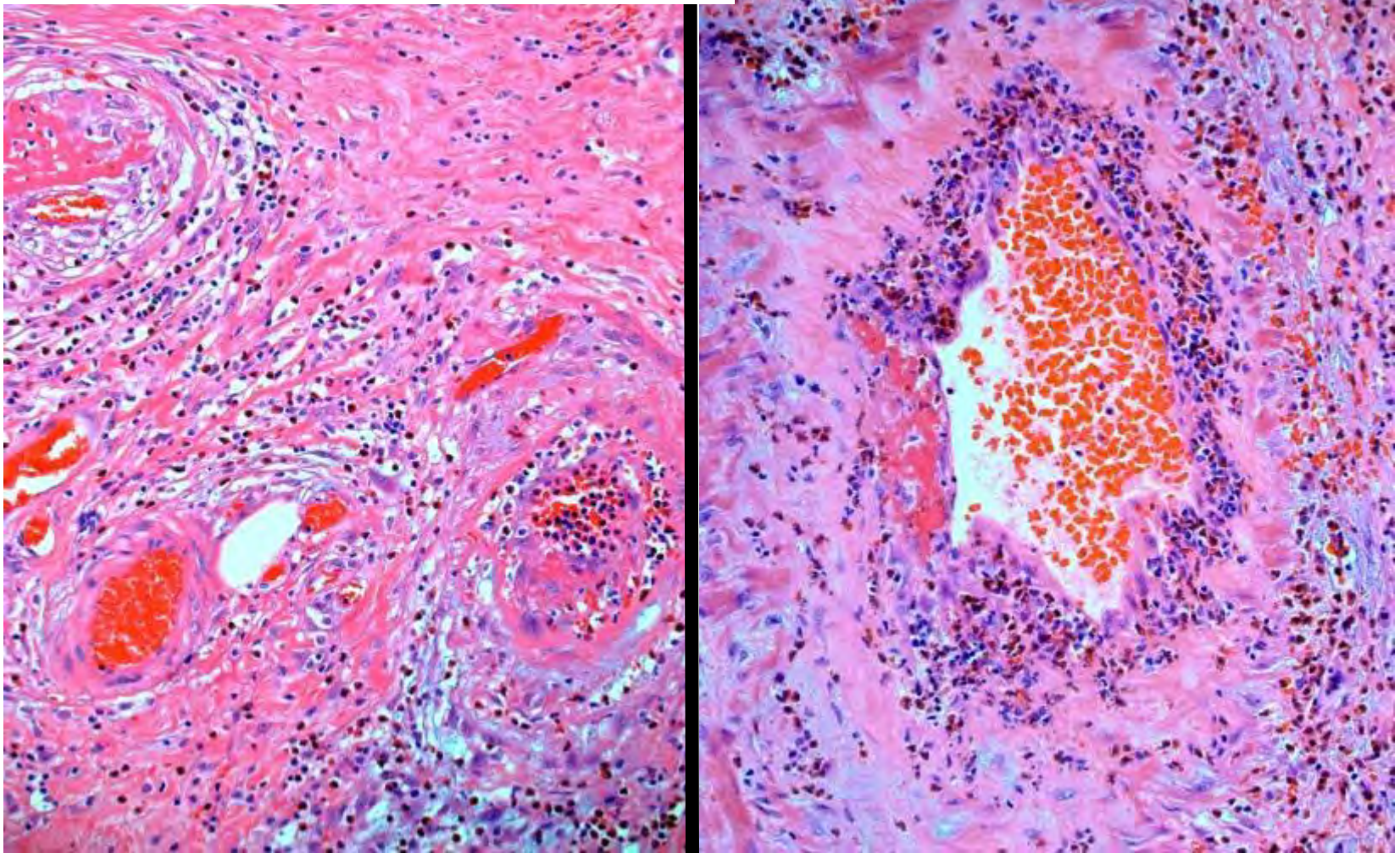



Inflammatory fibroid polyp
CD34

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): Photos courtesy of John Hart



Churg-Strauss: Photos courtesy of John Hart



Eosinophilic gastrointestinal disorders associated with autoimmune connective tissue disease

Marie Lecouffe-Desprets[a,b], Matthieu Groh[a], Bruno Bour[c], Claire Le Jeunne[a], Xavier Puéchal[a,*]

20 cases of CTD with GI eosinophilia are described:

- 95% present with eosinophilic gastritis or enteritis (EoE is rare)
- Abdominal pain, N/V, diarrhea and obstructive symptoms are common

Table 2
Main characteristics of eosinophilic gastrointestinal disorders associated with autoimmune connective tissue disease reported in the literature.

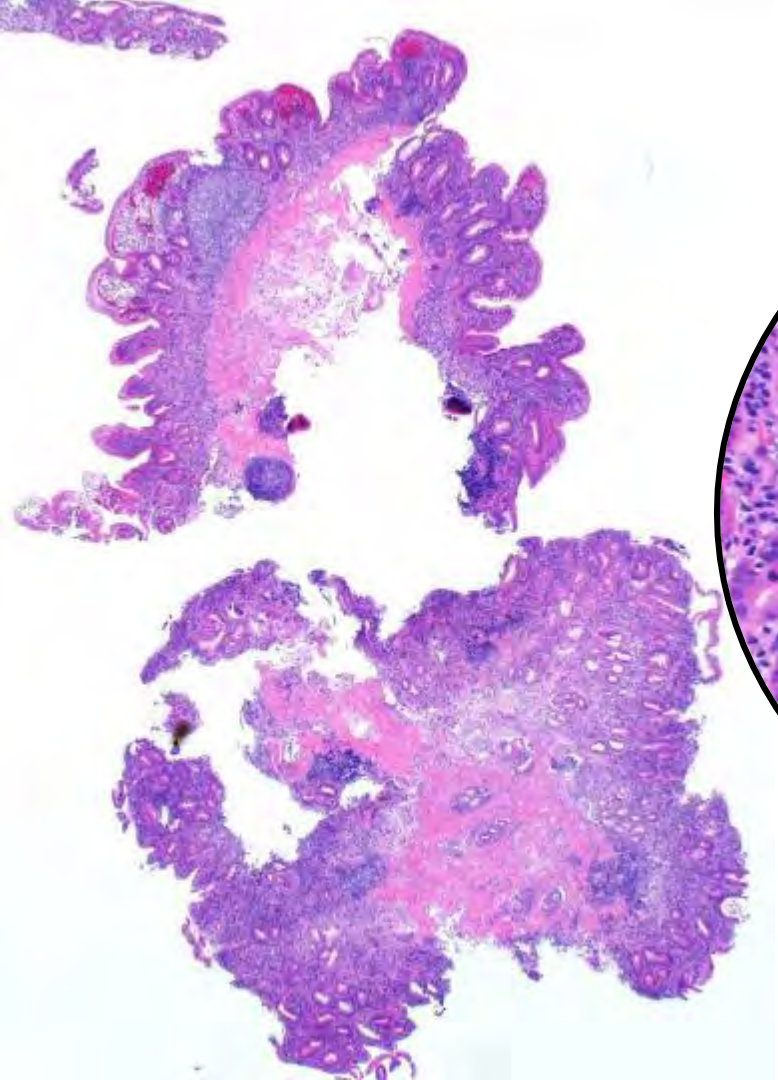
General features	
Median age (range)	47 years (10–71)
Gender (male/female)	4/16
Atopy history (NS)	0/5 (15/20)
Autoimmune connective tissue disease (CTD)	
SLE	7/20 (35%)
Rheumatoid arthritis	4/20 (20%)
Systemic sclerosis	3/20 (15%)
Dermato- or polymyositis	3/20 (15%)
Primary Sjögren's syndrome	1/20 (5%)
Overlap syndrome	2/20 (10%)
Diagnosis of CTD compared to EGID diagnosis	
Before	9/19
Concomitant	9/19
After	1/19
Pathological findings	
Intestinal biopsy available	19/20 (95%)
Digestive wall eosinophilic infiltration	19/19 (100%)
Mucosa or submucosa	15/19 (79%)
Muscularis propria	8/19 (42%)
Serosa or subserosa	4/19 (21%)
No digestive wall infiltration	0/19 (0%)
No intestinal biopsy	1/20 (5%)

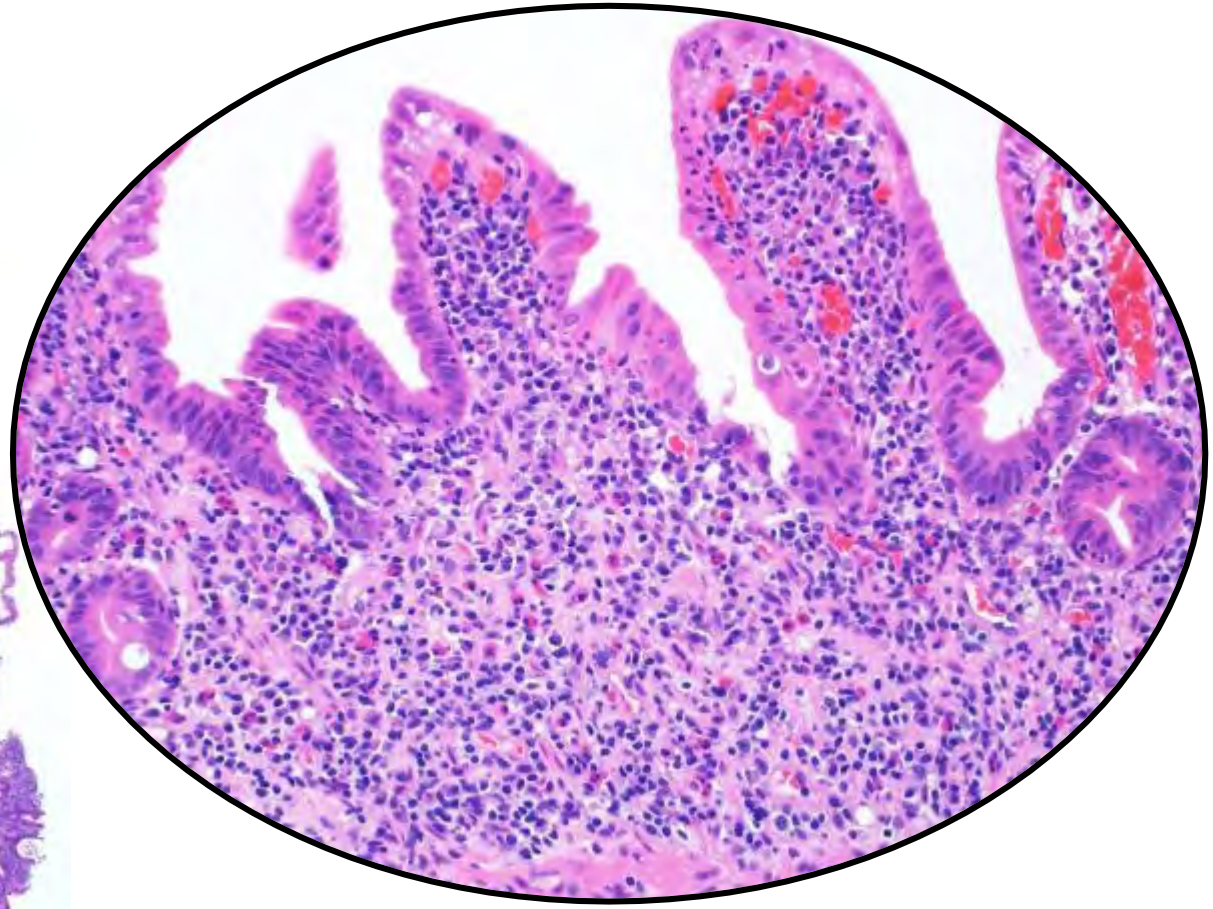
GIT diseases associated with eosinophilia

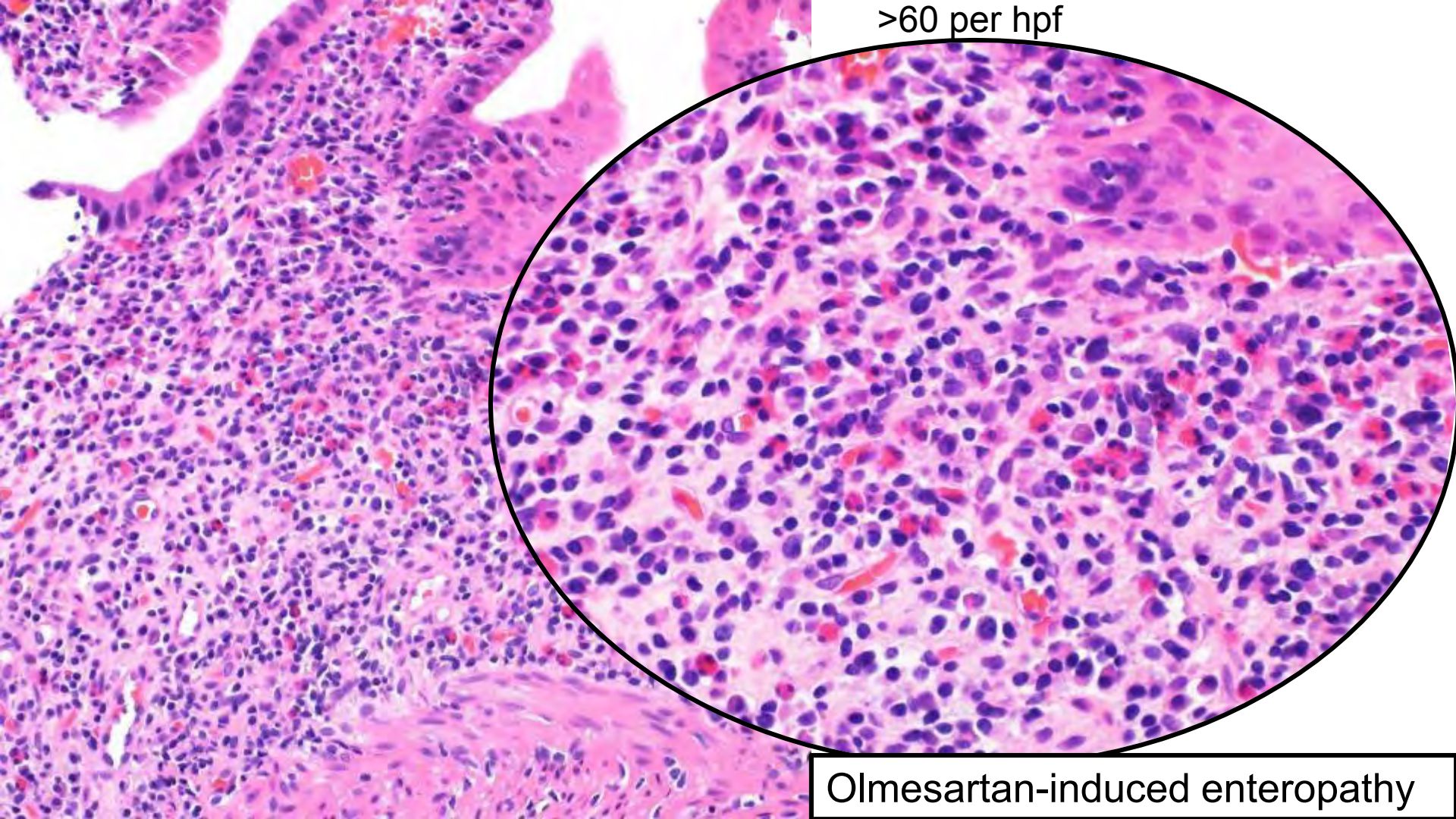
- Inflammatory bowel disease
- Collagenous colitis
- Gastro-esophageal reflux
- Celiac disease (some cases)
- *H. pylori* infection (some cases)
- Medication injury
- Functional dyspepsia (mild increase?)

GIT diseases associated with eosinophilia

- 60 yo male with 2 year history of watery diarrhea. Diagnosed with celiac disease on outside biopsies and has tried a gluten free diet with only minimal success. Patient is HLA DQ2+ and has a weakly positive tTG.

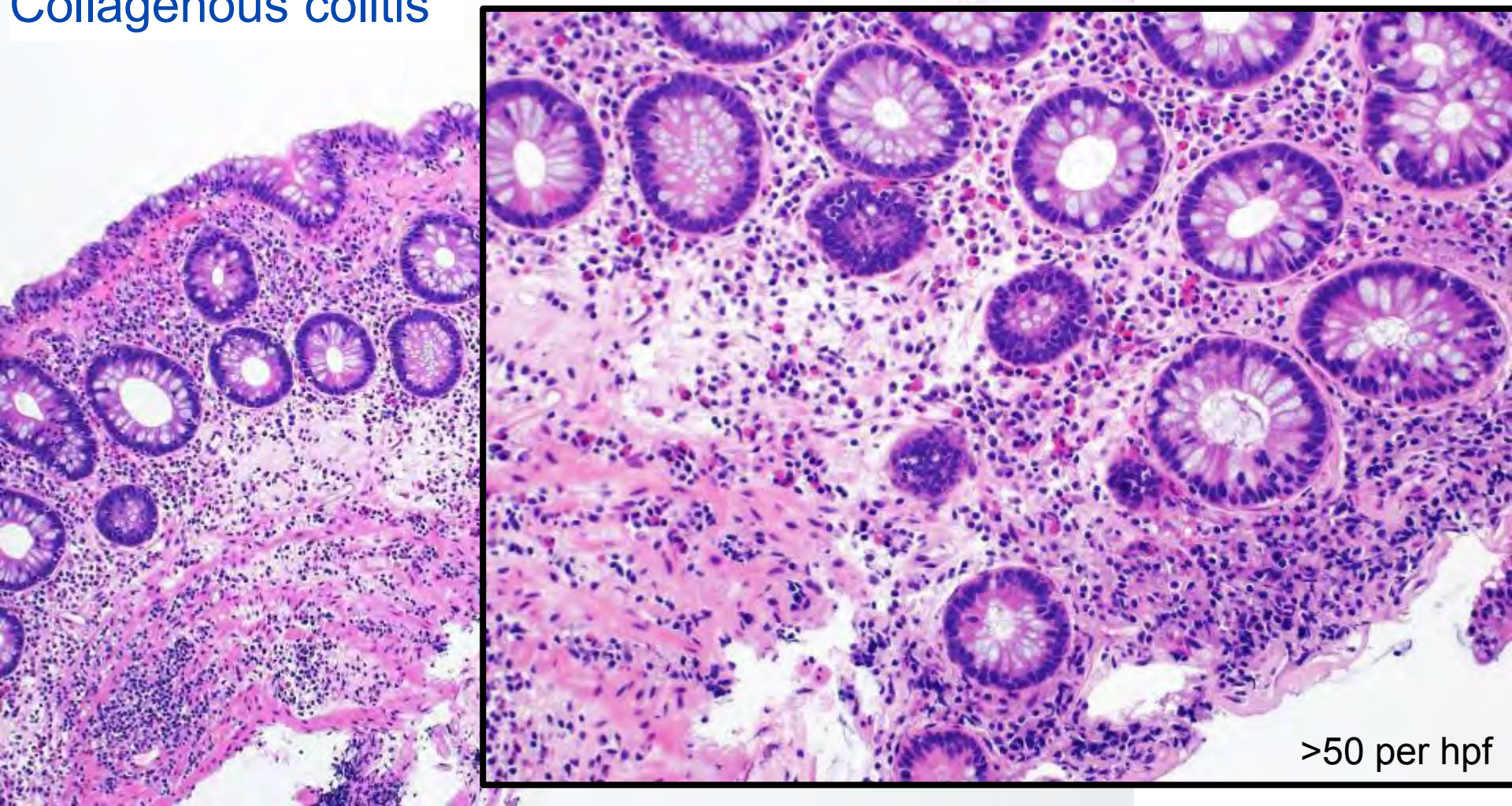




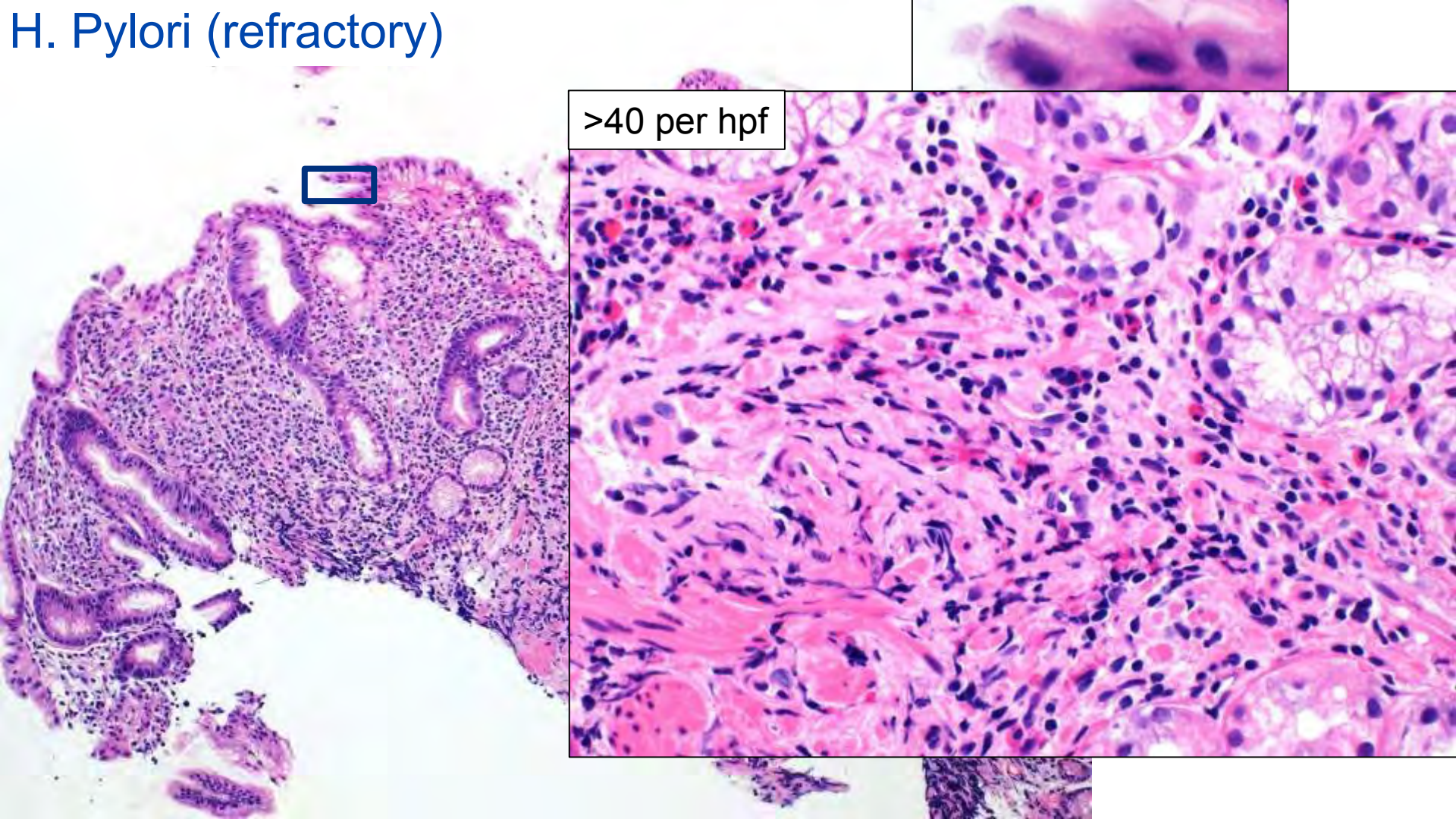


Olmesartan-induced enteropathy

Collagenous colitis

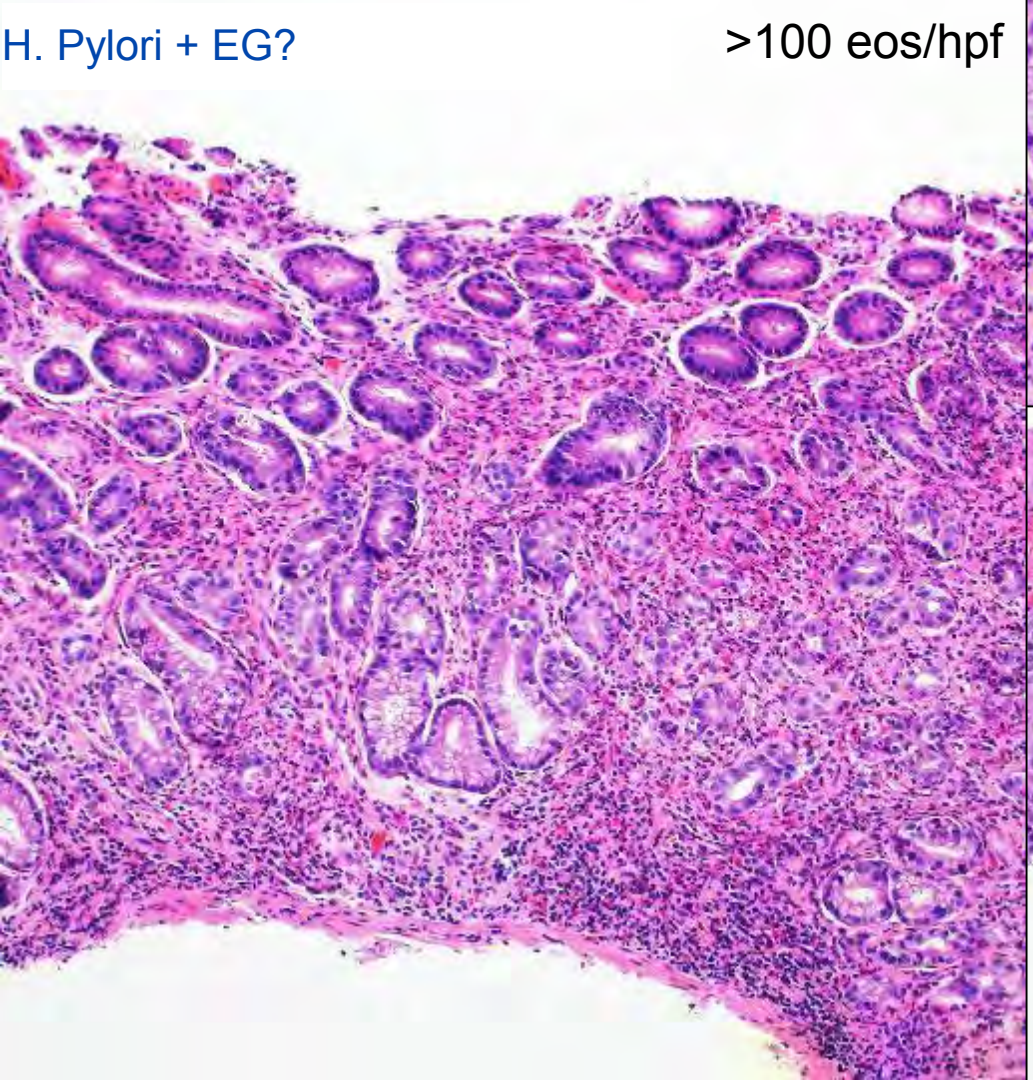


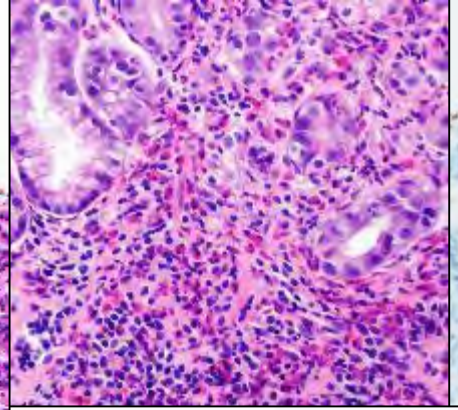
H. Pylori (refractory)

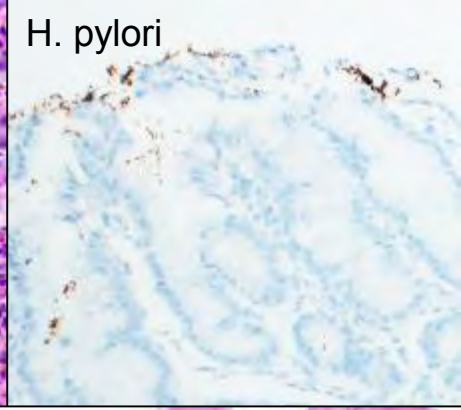


H. Pylori + EG?

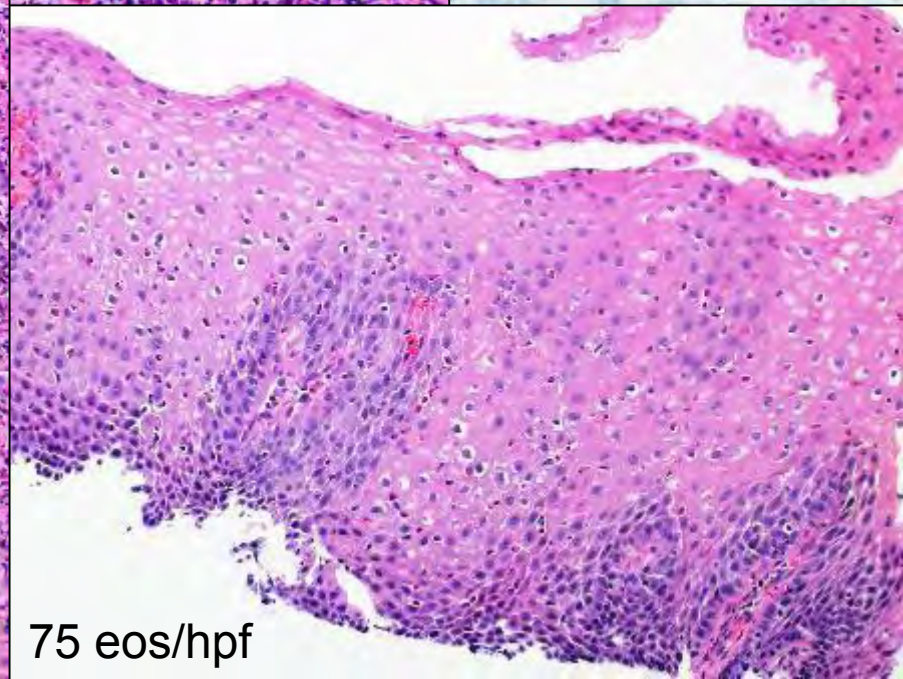
>100 eos/hpf





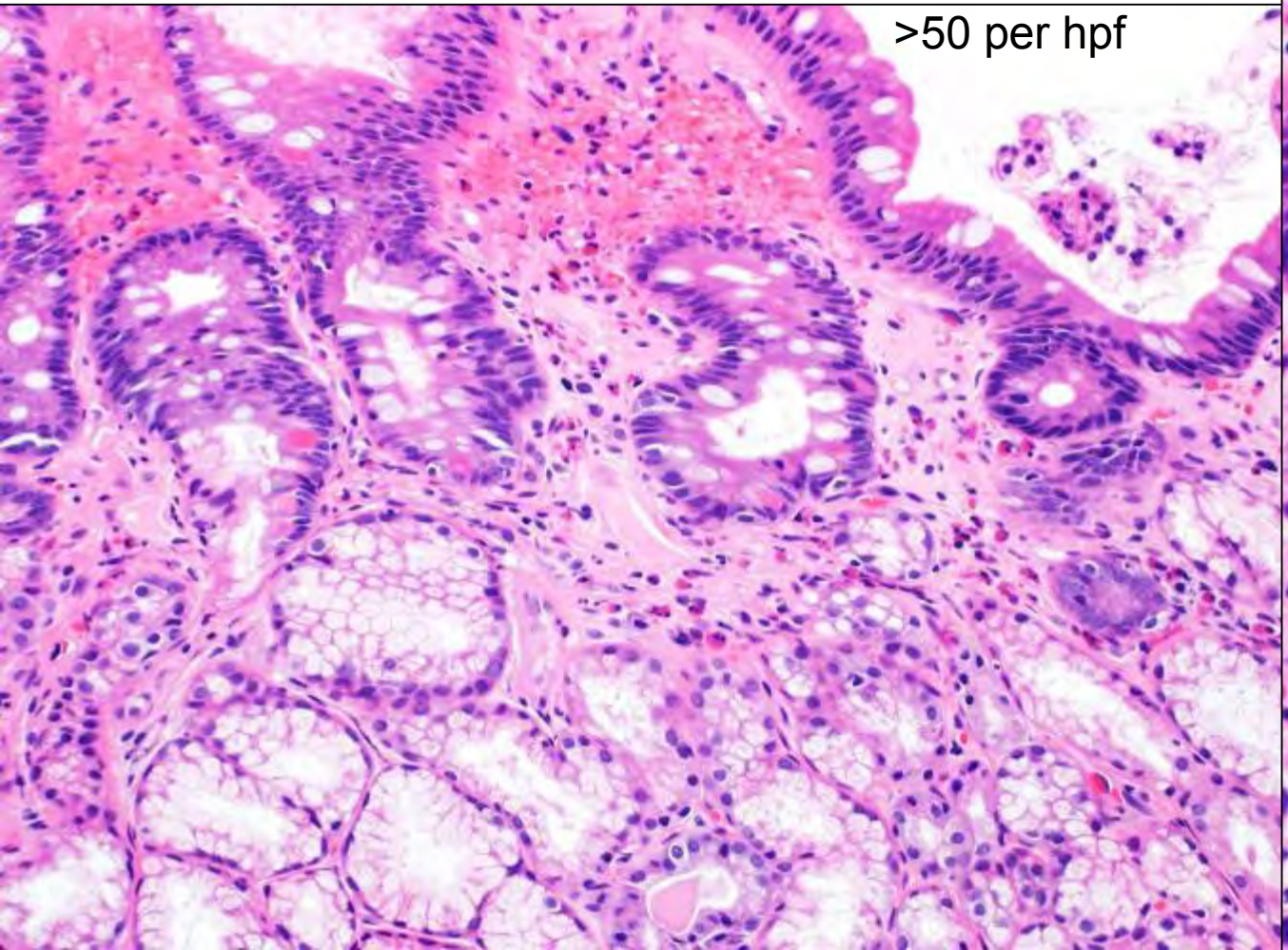


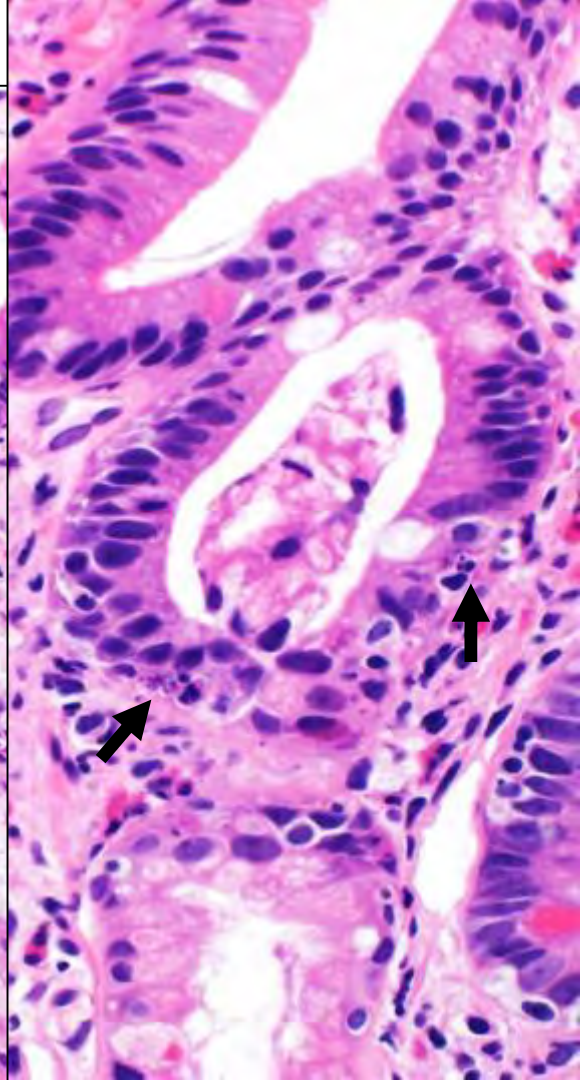
H. pylori



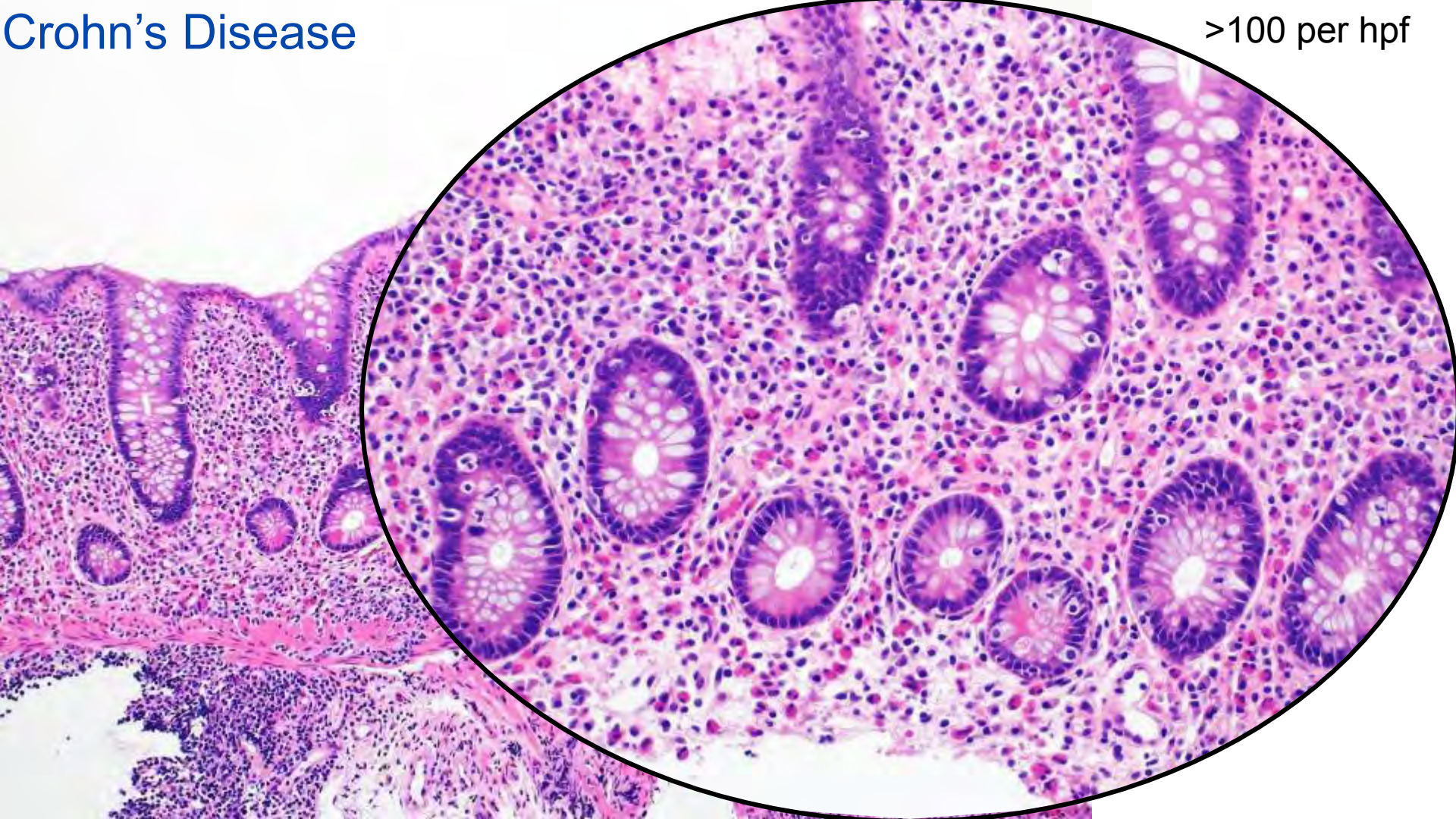
75 eos/hpf

GVHD

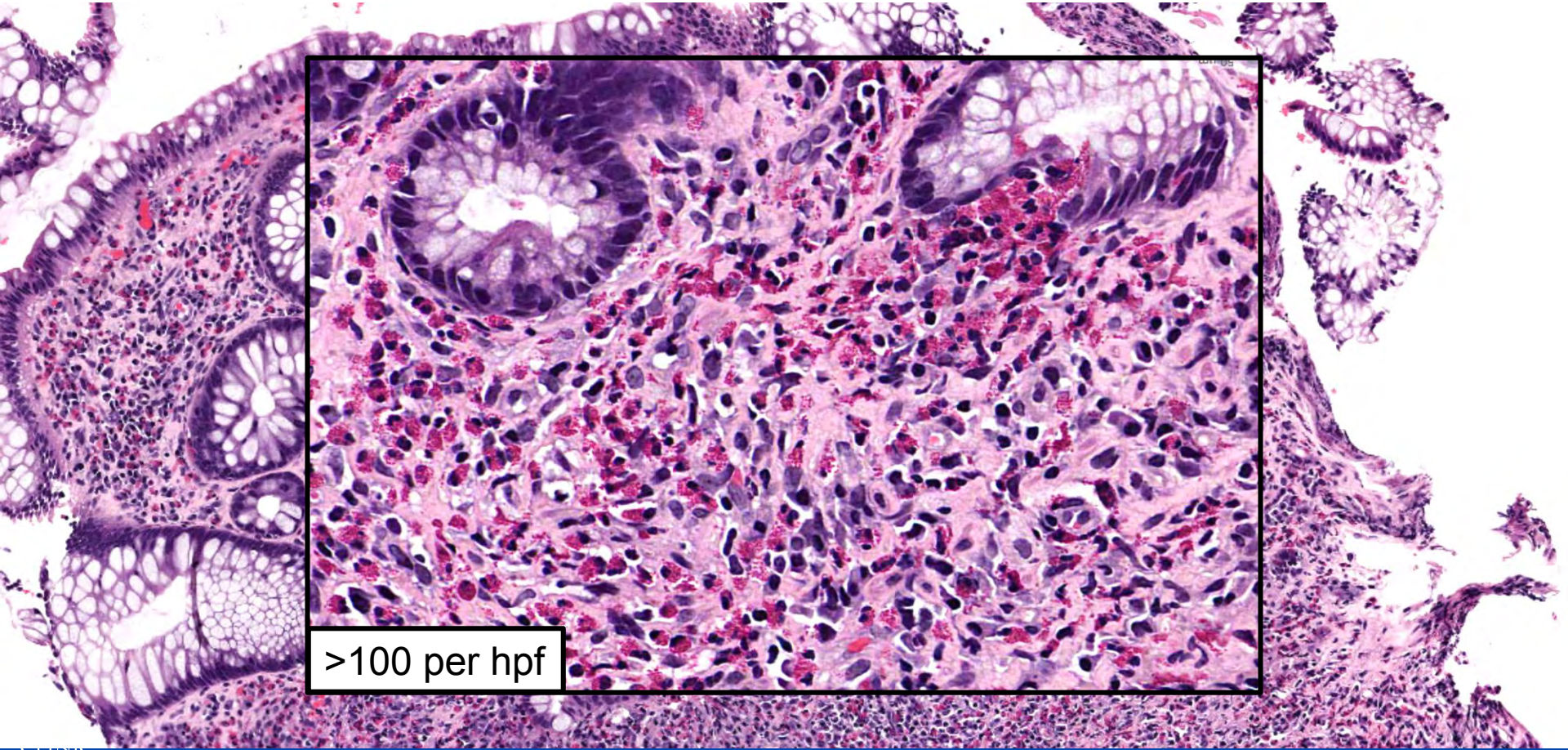




Crohn's Disease



UC



Eosinophils in IBD: What does it mean?

Severe eosinophilic infiltration in colonic biopsies predicts patients with ulcerative colitis not responding to medical therapy

Colorectal Dis. 2014 Dec;16(12):O420-30.

P. Zezos*†, K. Patsiaoura‡, A. Nakos*, A. Mpoumponaris*, T. Vassiliadis*, O. Giouleme*, M. Pitiakoudis§, G. Kouklakis† and N. Evgenidis*

*Division of Gastroenterology, 2nd Propaedeutic Department of Internal Medicine, "Hippokration" General Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece, †Gastrointestinal Endoscopy Unit, Democritus University of Thrace, University General Hospital of Alexandroupolis, Alexandroupolis, Greece, ‡Department of Pathology, "Hippokration" General Hospital, Thessaloniki, Greece and §2nd Department of Surgery, Democritus University of Thrace, University General Hospital of Alexandroupolis, Alexandroupolis, Greece

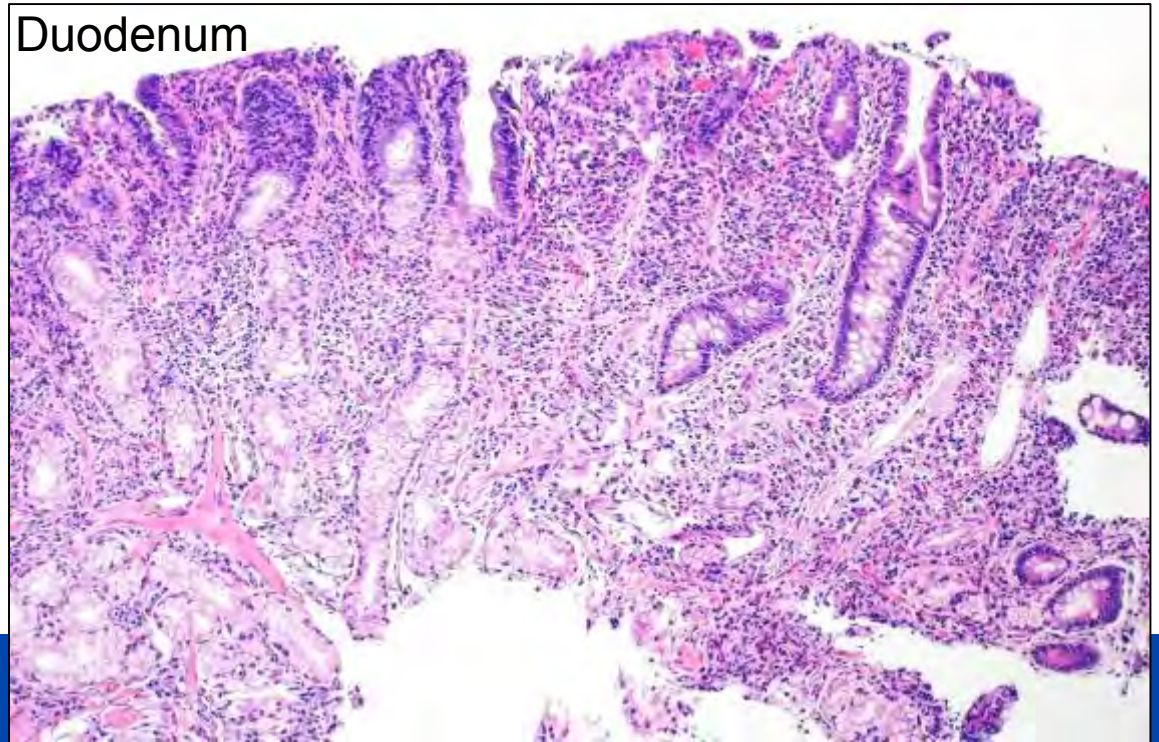
Mucosal Eosinophilia Is an Independent Predictor of Vedolizumab Efficacy in Inflammatory Bowel Diseases

Inflamm Bowel Dis. 2019

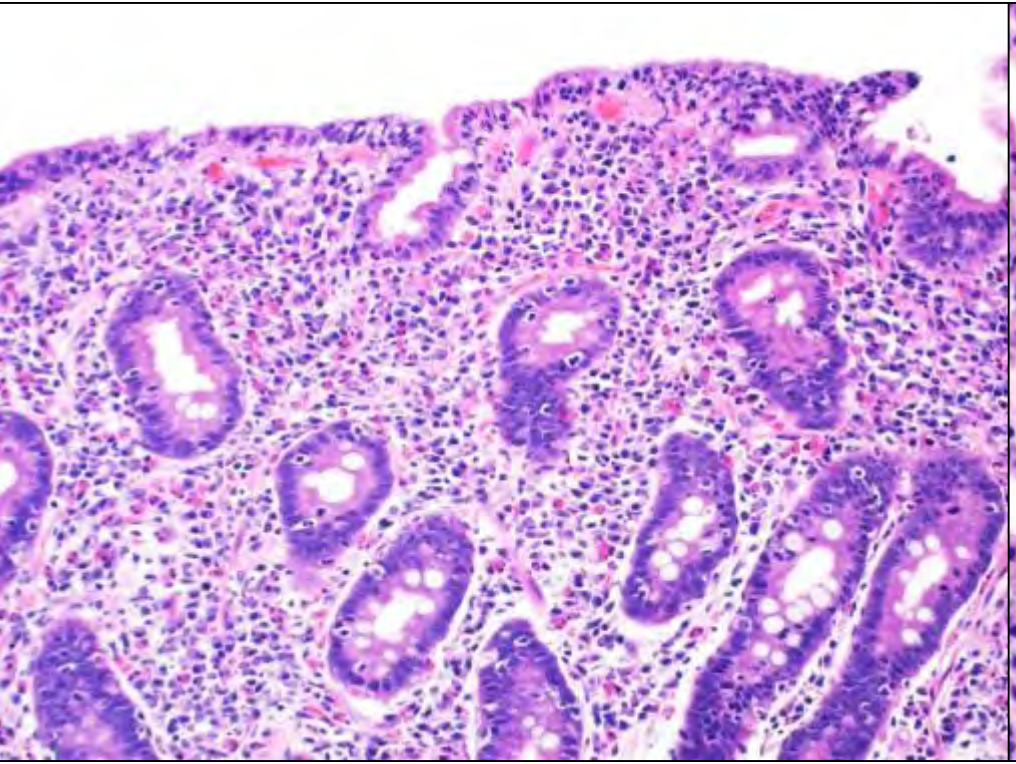
Erin M. Kim, Cara Randall, MD,§ Renee Betancourt, MD,§ Staci Keene, MD,§ Amy Lilly, MD,§ Mark Fowler, MD,§ Evan S. Dellon, MD, MPH,*,†,‡ and Hans H. Herfarth, MD, PhD*,†,‡*

GIT diseases associated with eosinophilia

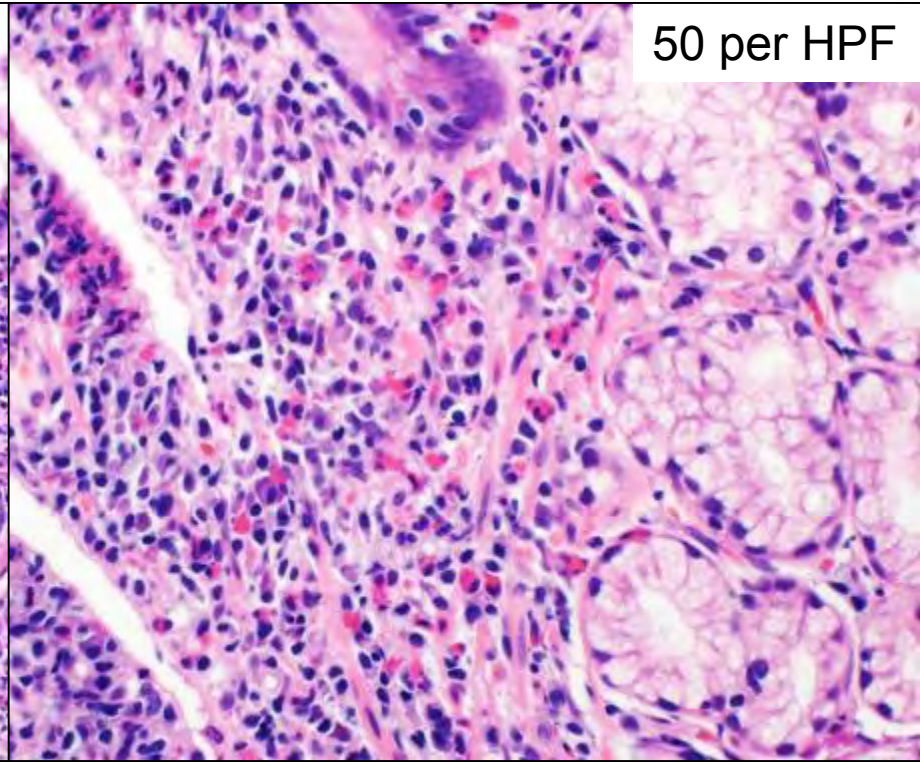
- 30 yo female with diarrhea and weight loss.



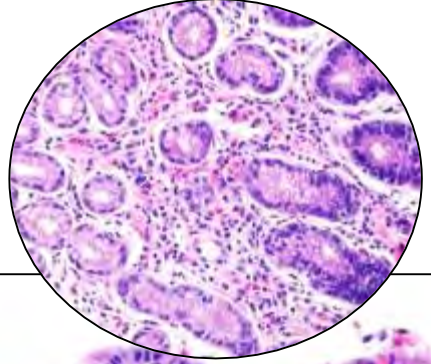
Increased IELs, villous blunting

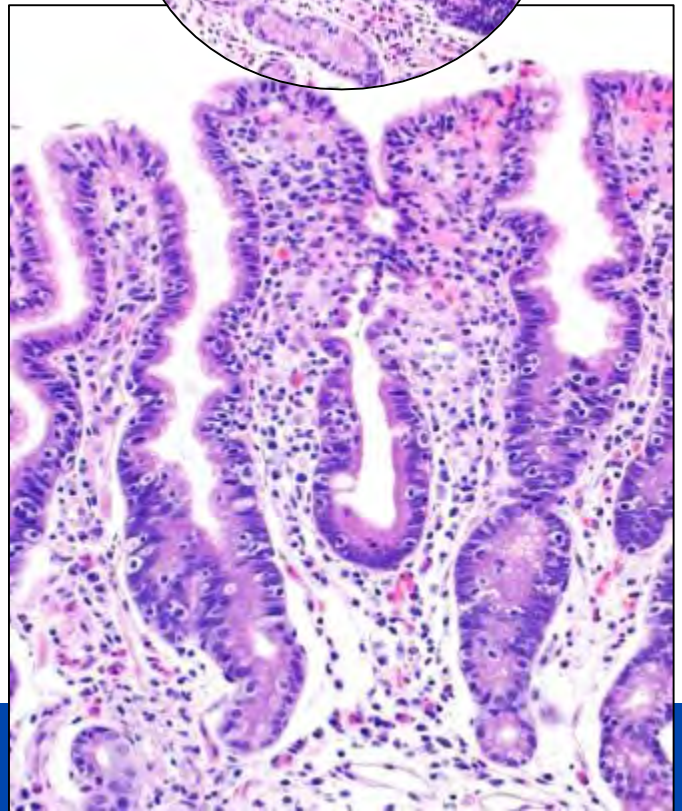


Increased Eosinophils

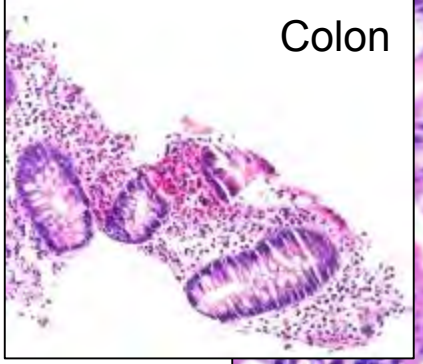


Stomach: LG and patchy increased Eos

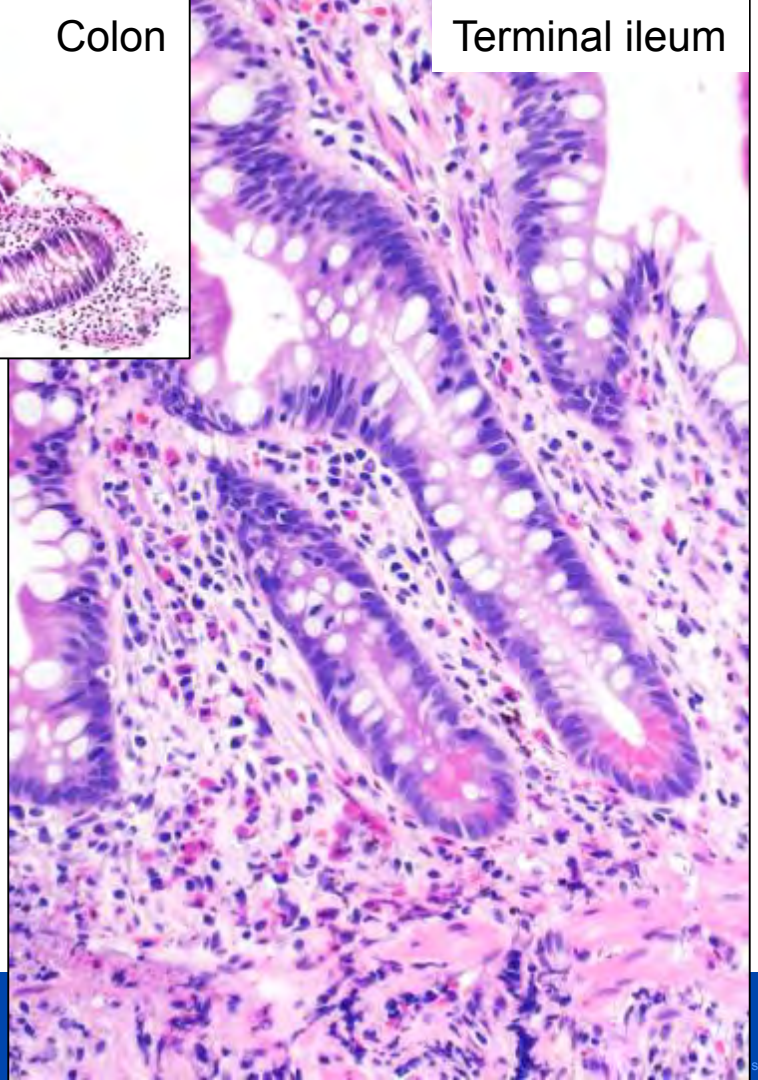




Colon



Terminal ileum



Gastrointestinal Pathology in Celiac Disease

Am J Clin Pathol 2012;138:42-49
DOI: 10.1309/AJCPE89ZPVJTSPWL

A Case Series of 150 Consecutive Newly Diagnosed Patients

Ian S. Brown, MBBS, FRCPA,[1,2] Jason Smith, MBBS,[1,3] Christophe Rosty, MD, PhD, FRCPA[1,4]

Table 4
Pathologic Characteristics of Duodenal Mucosa With Regard to Different Corazza Stages of Celiac Disease

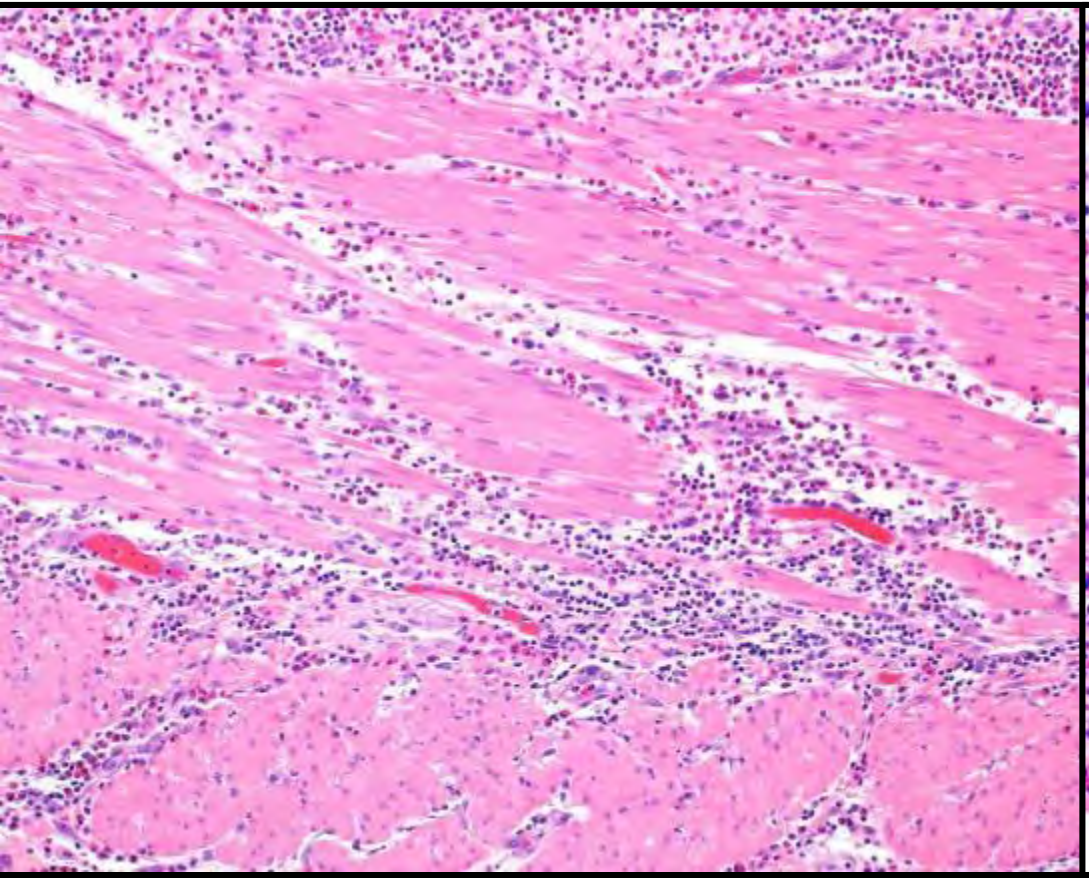
Characteristic	Corazza Stage A1	Corazza Stage B1	Corazza Stage B2	*P* Value
Mean ± SD age, y	45.4 ± 18.6	38.6 ± 18.5	36.7 ± 21.1	.51
Mean ±SD IEL count/100 epithelial cells	61.7 ± 22.6	82.9 ± 21.2	94.7 ± 26.6	<.0001
Lymphoplasmacytic infiltrate				
Grade 0	5	7	1	<.0001
Grade 1	2	49	7	
Grade 2	0	2	21	
Neutrophilic infiltrate				
Grade 0	6	43	16	<.0001
Grade 1	1	14	47	
Grade 2	0	1	22	
Mean ± SD eosinophil count/hpf	6.7 ± 5.3	11.9 ± 6.1	17.1 ± 9.6	<.0001
No. (%) of superficial enterocyte changes	0	27/59 (46.6)	76/85 (89.4)	<.0001
Mean ± SD Paneth cell count/hpf	19.1 ± 6.4	15.7 ± 7.9	14.0 ± 8.1	.17
Subepithelial collagen band thickening	0	14/58 (24.1%)	54/85 (63.8%)	<.0001

up to 50/hpf (mean, 14.6) **Image 1B**. An eosinophil count of more than 20/hpf was found in 37 cases overall (24.7%). No increased eosinophil counts in peripheral blood or in the mucosa of other intestinal parts were found in these patients. Higher eosinophil count or increased neutrophil density had a strong statistical association with advanced Corazza stage ($P < .0001$) (Table 4).

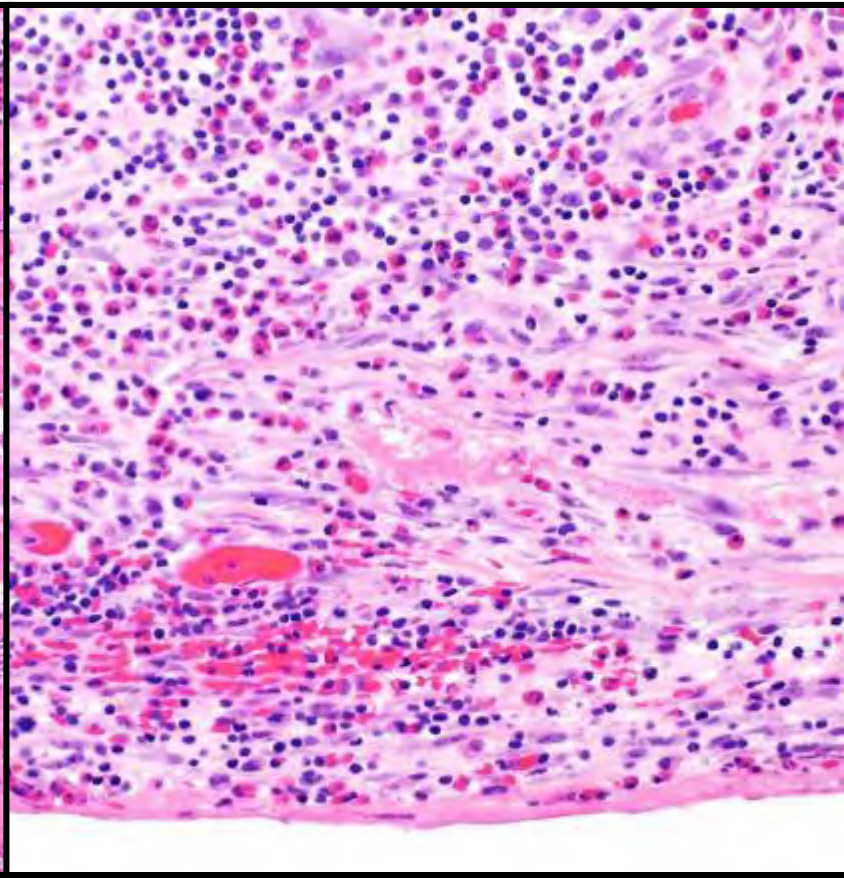
Eosinophilic gastritis/gastroenteritis/colitis

- Definition (Talley et al. Gut 1990; 31; 54–58)
  - GI symptoms
  - Evidence of tissue eosinophilia in the GI tract
  - No evidence of other local or systemic secondary causes of eosinophilia
- Prevalence: 2-8/100,000 (increasing)
- About 75% are atopic (asthma, eczema, food allergy)
- Symptoms depend on location of eosinophils: Klein classification (Medicine (Baltimore) 1970; 49; 299–319.)
  - Mucosal: Pain, diarrhea, nausea/vomiting
  - Mural: Abdominal pain, obstructive symptoms
  - Serosal: Abdominal bloating
- Treatment: Immune suppression and/or dietary modification

Mural involvement



Serosal involvement



Primary eosinophilic GI diseases

Table 4. Proposed quantitative criteria for eosinophilic gastritis and eosinophilic gastroenteritis

Author(s)	Diagnosis	Criteria
Hurrell *et al.*[75]	Histological eosinophilic gastritis	≥30 eosinophils per HPF in at least five separate HPFs (if *Helicobacter pylori* is present, eosinophilia must persist for several months post-eradication)
Collins[74]	Eosinophilic gastritis	≥30 eosinophils per HPF in at least five separate HPFs
Ko *et al.*[69]		
Bischoff and Ulmer[73]		
Collins[74]		
Collins[74]		nding colon or >64 eosinophils per HPF in the rectosigmoid colon
Turner *et al.*[81]	Colonic eosinophilia	>50 eosinophils per HPF in the right colon >35 eosinophils per HPF in the transverse colon >25 eosinophils per HPF in the left colon

HPF, High-power field.

Definition used in recent clinical trial: Eosinophilia of the gastric mucosa ≥30 eosinophils/HPF in 5 HPFs and/or eosinophilia of the duodenal mucosa ≥30 eosinophils/HPF in 3 HPFs, without any other cause for the eosinophilia.

Histopathology. 2017 Aug;71(2):177-199.

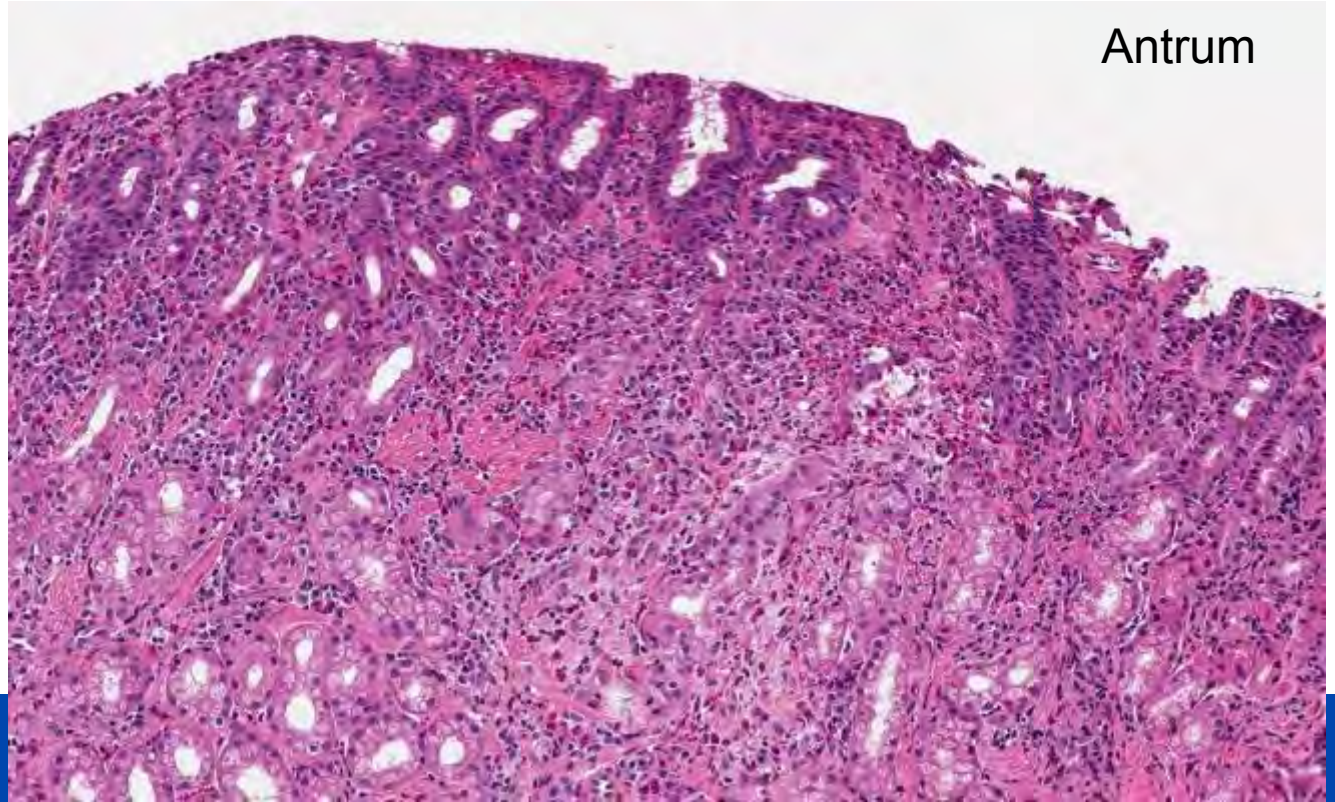
Eosinophilic gastritis/gastroenteritis/colitis

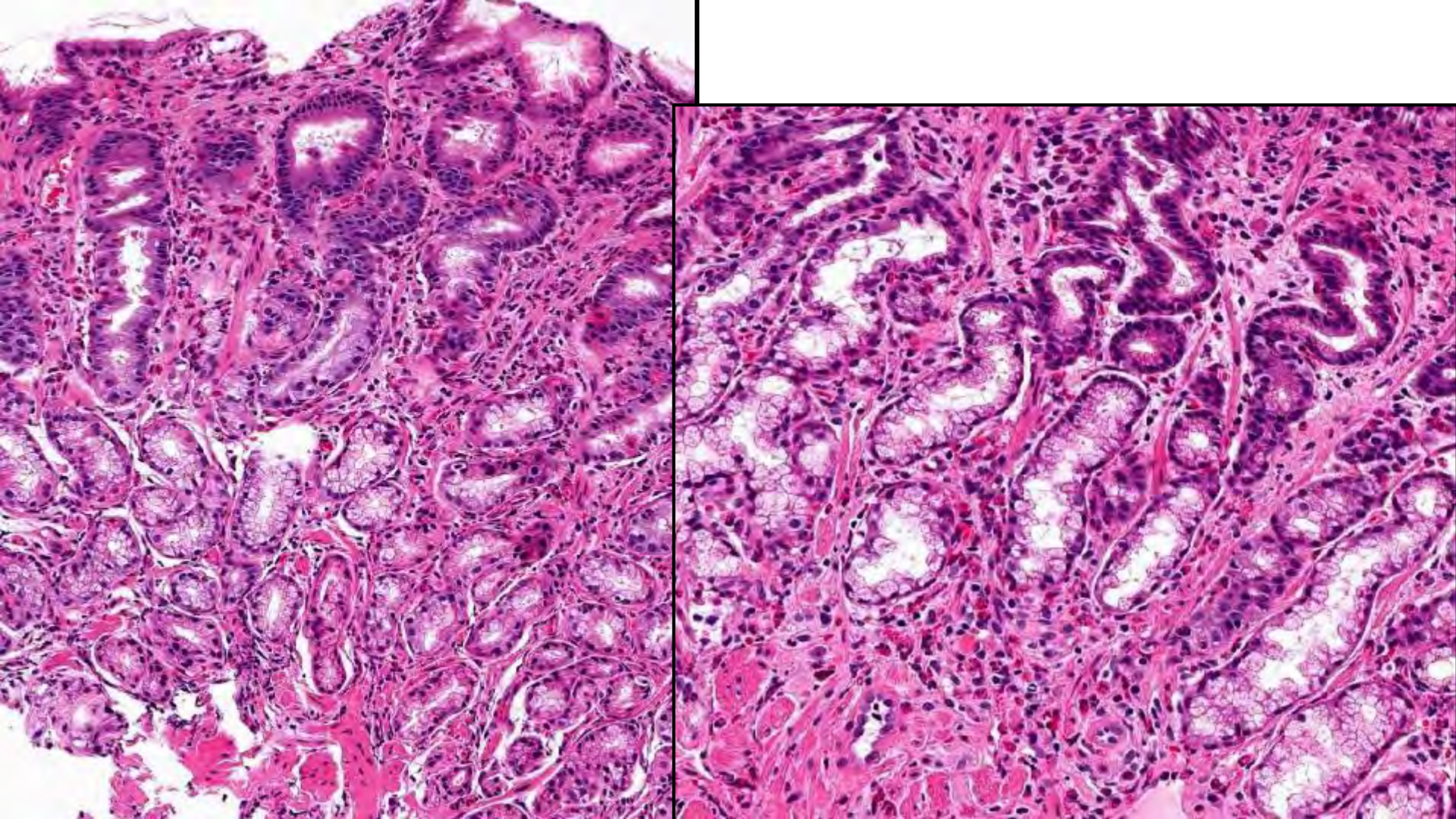
- More than just the density of Eos?
- Does location within the mucosa help?
  - Superficial: Gastroenterol. Clin. North Am. 2014; 43; 257–268 and Pediatr Dev Pathol 2006; 9; 210-218.
  - Deep (muscularis mucosae/submucosal): Mod. Pathol. 2011; 24; 556–563.
  - Intraepithelial: Mod. Pathol. 2011; 24; 556–563.

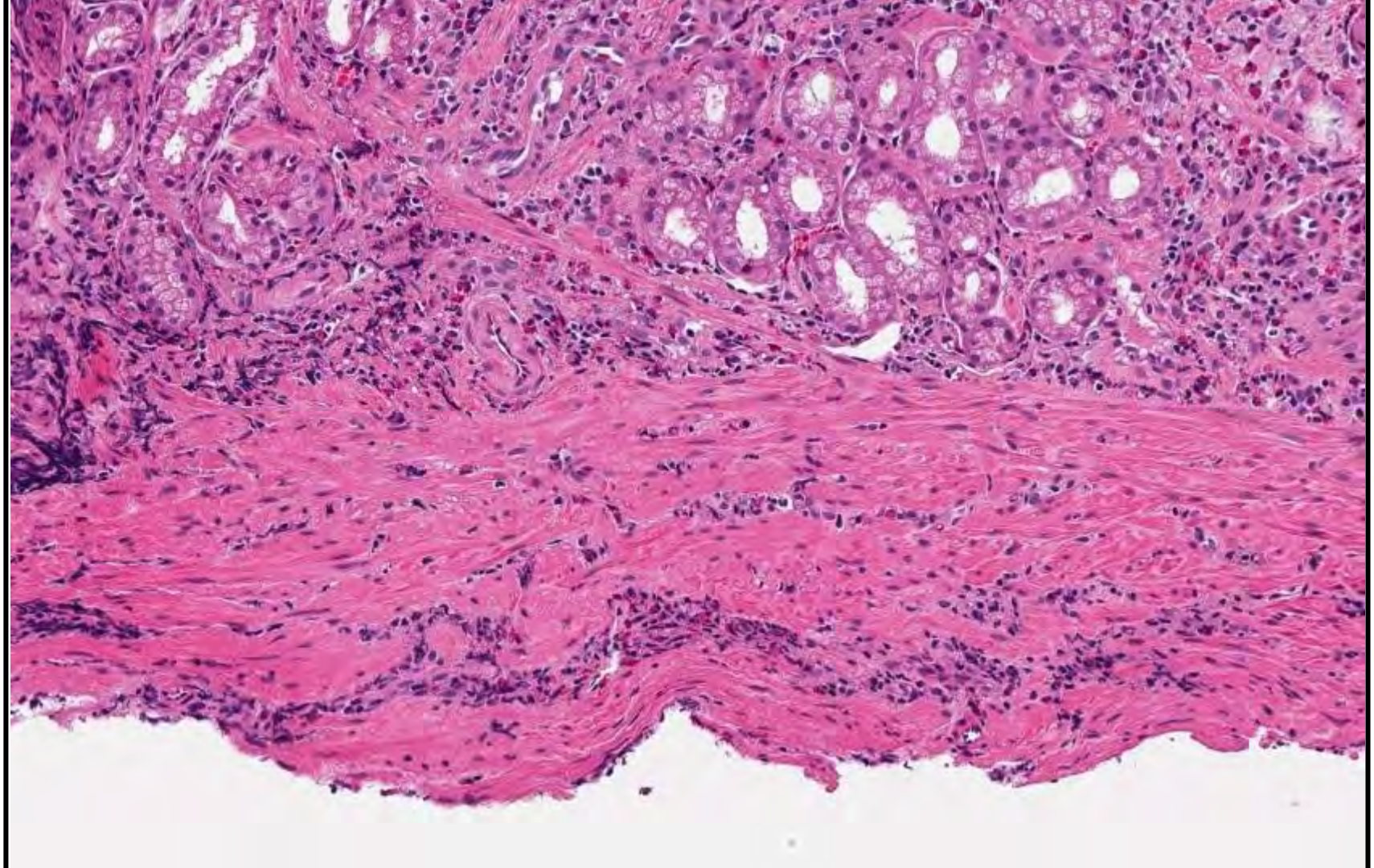
Location is not as helpful as density

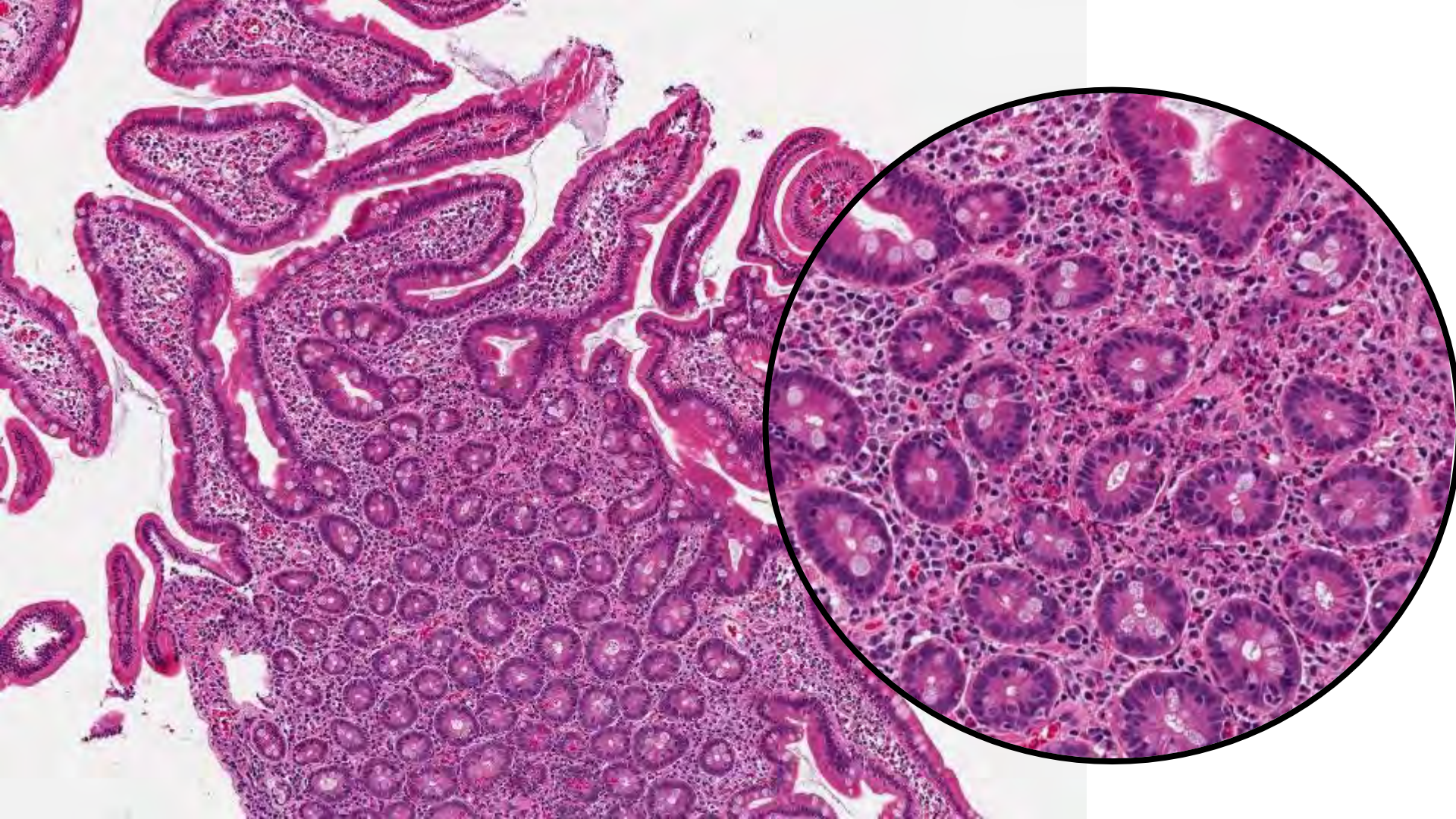
Primary eosinophilic gastroenteritis

- 48 yo female with abdominal pain, nausea, and vomiting.

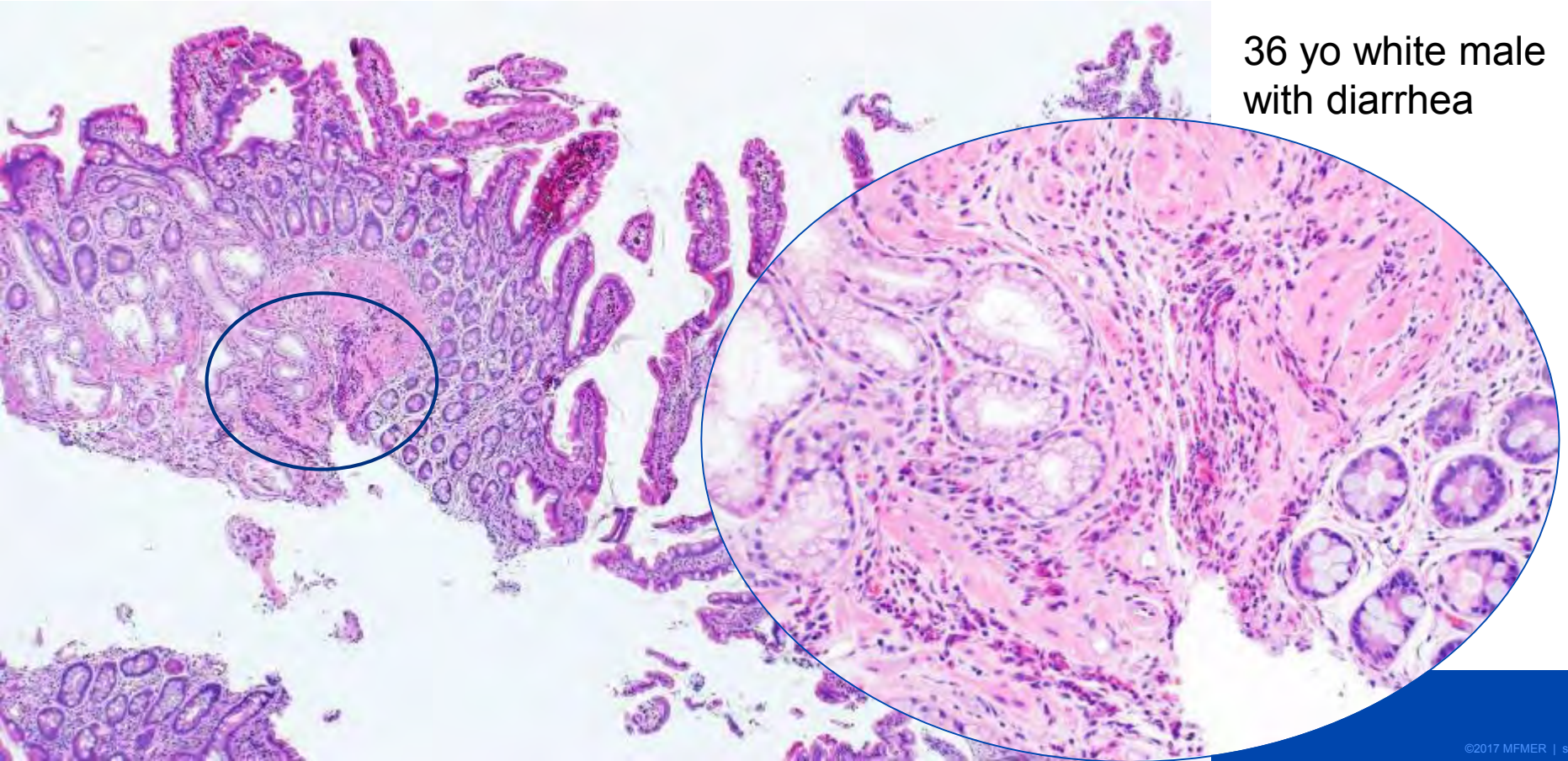




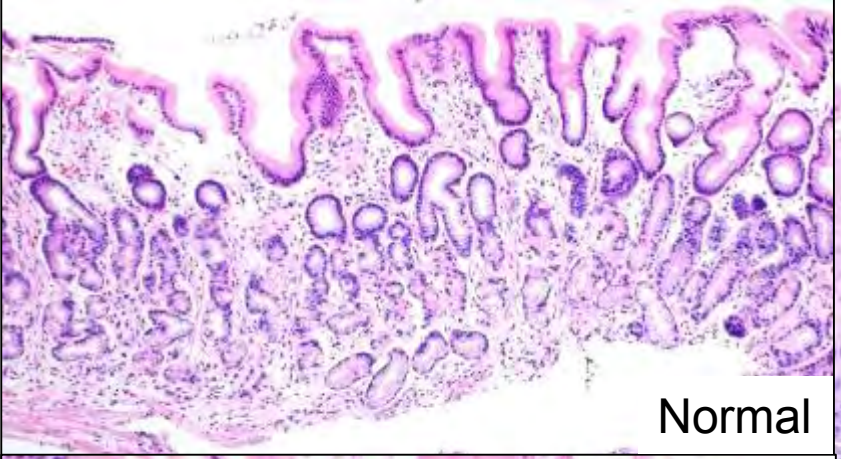


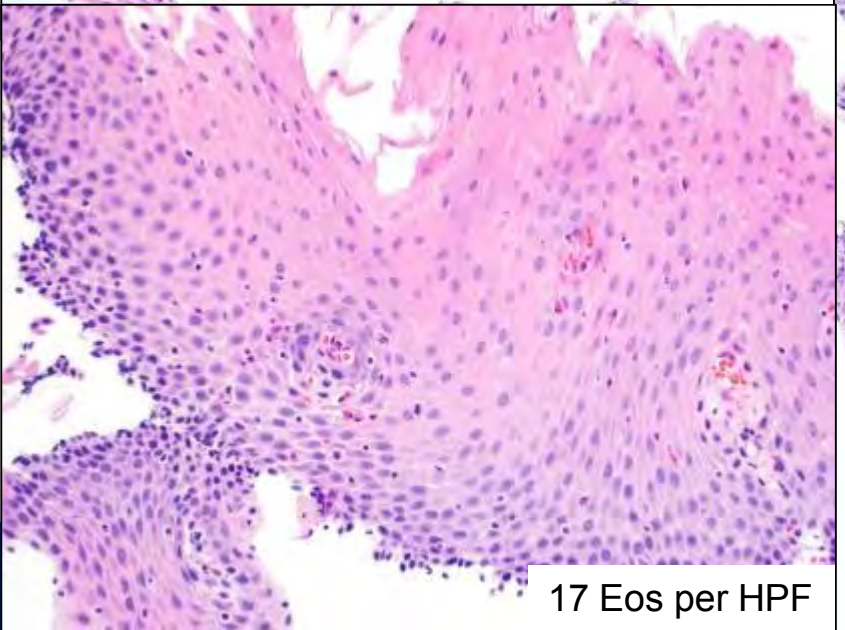


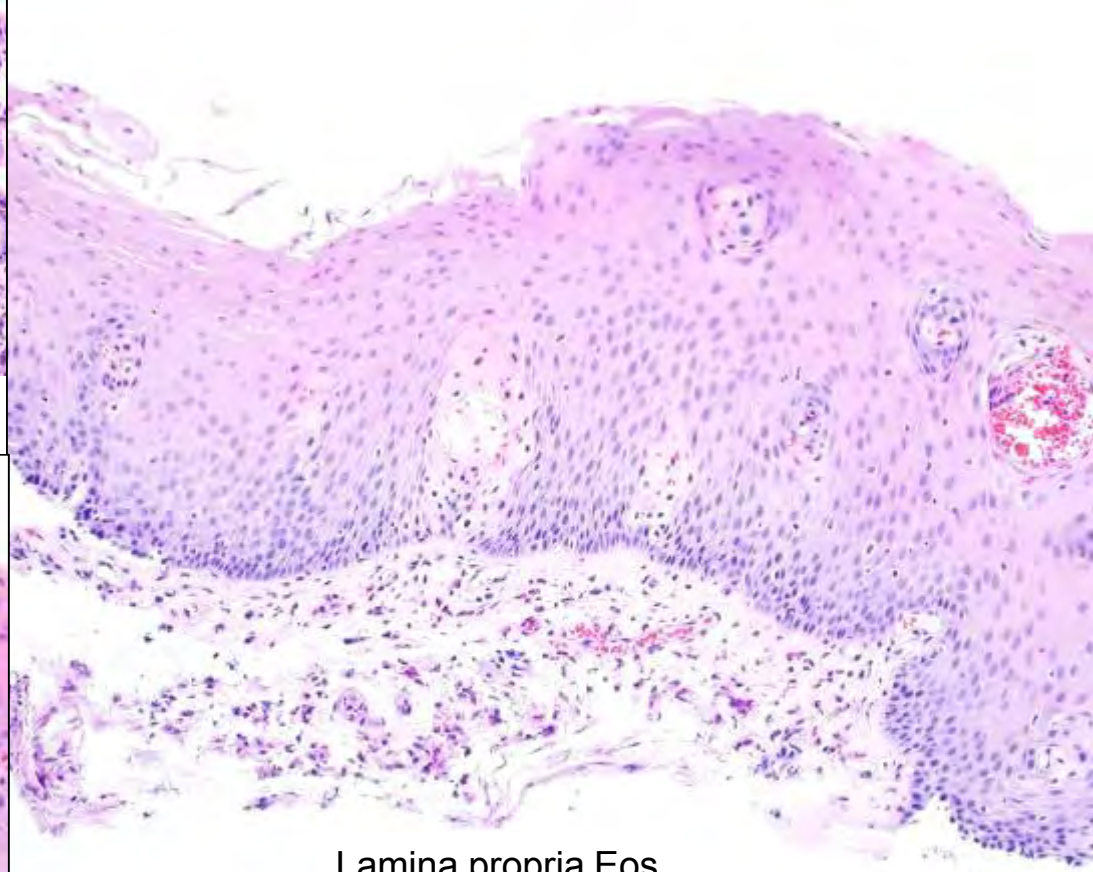
Primary eosinophilic gastroenteritis



36 yo white male with diarrhea



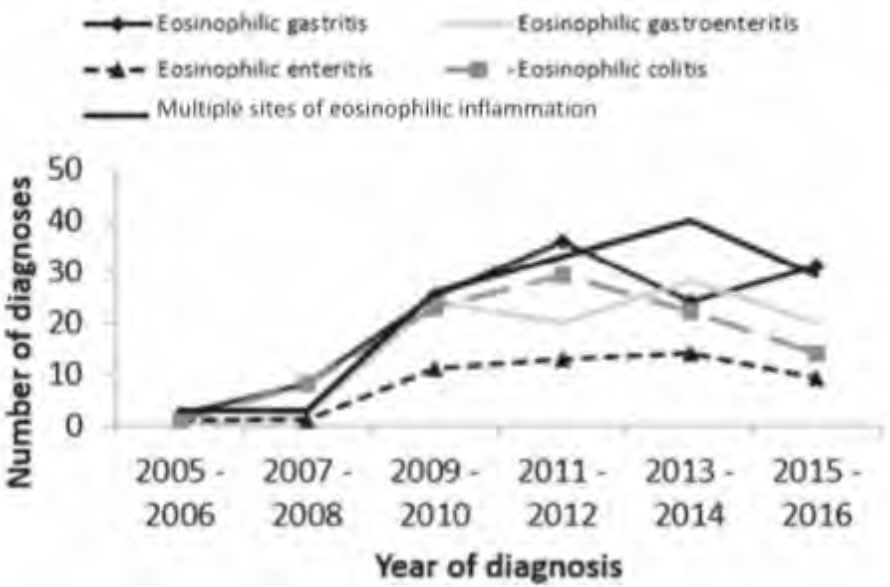




Lamina propria Eos

Increasing Rates of Diagnosis, Substantial Co-Occurrence, and Variable Treatment Patterns of Eosinophilic Gastritis, Gastroenteritis, and Colitis Based on 10-Year Data Across a Multicenter Consortium

Am J Gastroenterol 2019;114:984–994.



Primary Site (n)	PEC/HPF (IQR)	Symptoms
Small bowel and Stomach (n=123)	SB: 50 (42-75) Stomach: 50 (32-100)	Nausea/vomiting (52%) Abdominal pain (50%) Diarrhea (32%)
Stomach (n=142)	60 (32-100)	Nausea/vomiting (54%) Abdominal pain (48%)
Colon (n=108)	60 (45-85)	Abdominal pain (60%) Diarrhea (52%) Nausea/vomiting (38%) Bloody stools (24%)

Increasing Rates of Diagnosis, Substantial Co-Occurrence, and Variable Treatment Patterns of Eosinophilic Gastritis, Gastroenteritis, and Colitis Based on 10-Year Data Across a Multicenter Consortium

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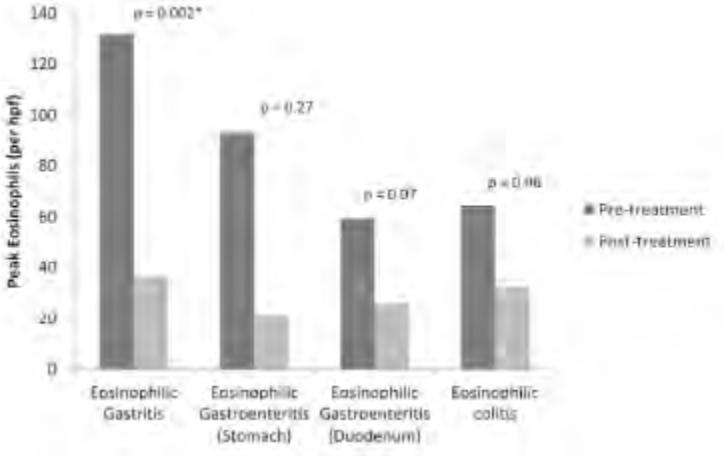
Table 6. Treatment responses by disease and measure of change

	EG, n = 124 (n, %)	EGE, n = 100 (n, %)	EC, n = 93 (n, %)	*P* value
Number with follow-up*	40 (32%)	42 (42%)	14 (15%)	<0.001
Symptom improvement	24/32 (75%)	24/37 (65%)	7/13 (54%)	0.36
Endoscopic improvement	16/30 (53%)	22/36 (61%)	6/13 (46%)	0.61
Histologic improvement	20/30 (67%)	28/41 (68%)	8/9 (89%)	0.42

Treatment	Change in peak eosinophils (/hpf)			
Topical steroids	Stomach: Pre: 145.4 Post: 50.8 *P* value: 0.03	Stomach: Pre: 22.3 Post: 6.5 *P* value: 0.06	Duodenum: Pre: 66 Post: 20 *P* value: 0.07	Colon: Pre: 56.5 Post: 15 *P* value: 0.054
Crushed steroids	Stomach: Pre: 238 Post: 12.5 *P* value: 0.43	Stomach: Pre: 262.5 Post: 16.5 *P* value: 0.5	Duodenum: Pre: 43.5 Post: 41.5 *P* value: 0.76	Colon: Pre: 72.5 Post: 50 *P* value: 0.5
Systemic steroids	Stomach: Pre: 182.5 Post: 56.3 *P* value: 0.26	Stomach: Pre: 24 Post: 0 *P* value: 0.03	Duodenum: Pre: 65 Post: 50 *P* value: 0.74	Colon: Not enough observations
Food elimination	Stomach: Pre: 183 Post: 53.1 *P* value: 0.03	Stomach: Pre: 45.8 Post: 25.3 *P* value: 0.01	Duodenum: Pre: 65 Post: 50 *P* value: 0.74	Colon: Not enough observations

Data shown as number (n) and % of specific population. Eosinophil numbers are reported per hpf. Symptom, endoscopic, and histologic improvements are based upon provider assessment of these variables during follow-up clinical visits and/or endoscopy. *P* value was considered significant if < 0.05.
EC, eosinophilic colitis; EG, eosinophilic gastritis; EGE, eosinophilic gastroenteritis; hpf, high powered field.
*Follow-up calculated for subjects from initial enrollment who had follow-up within 6 months of starting initial treatment(s).

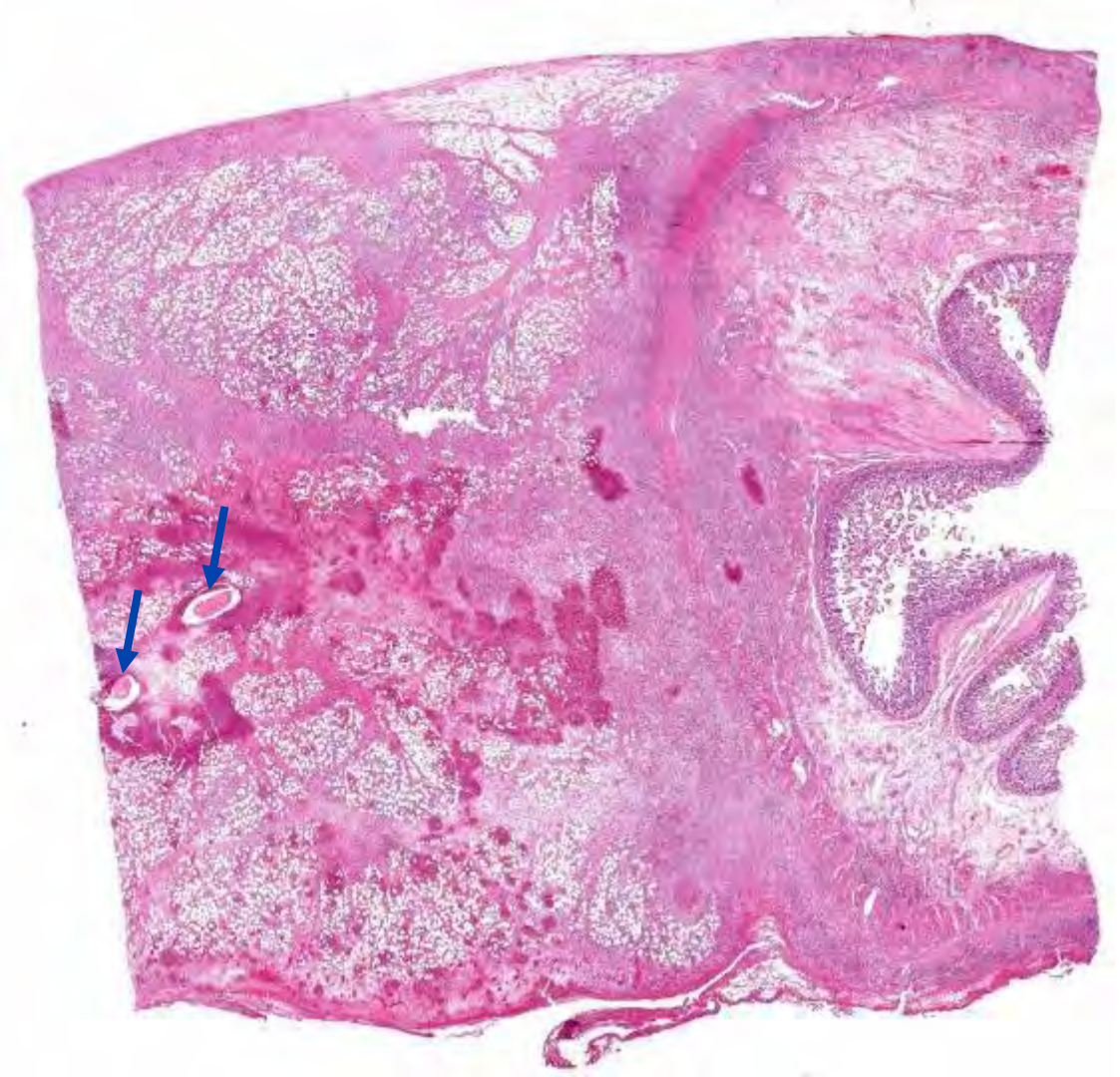


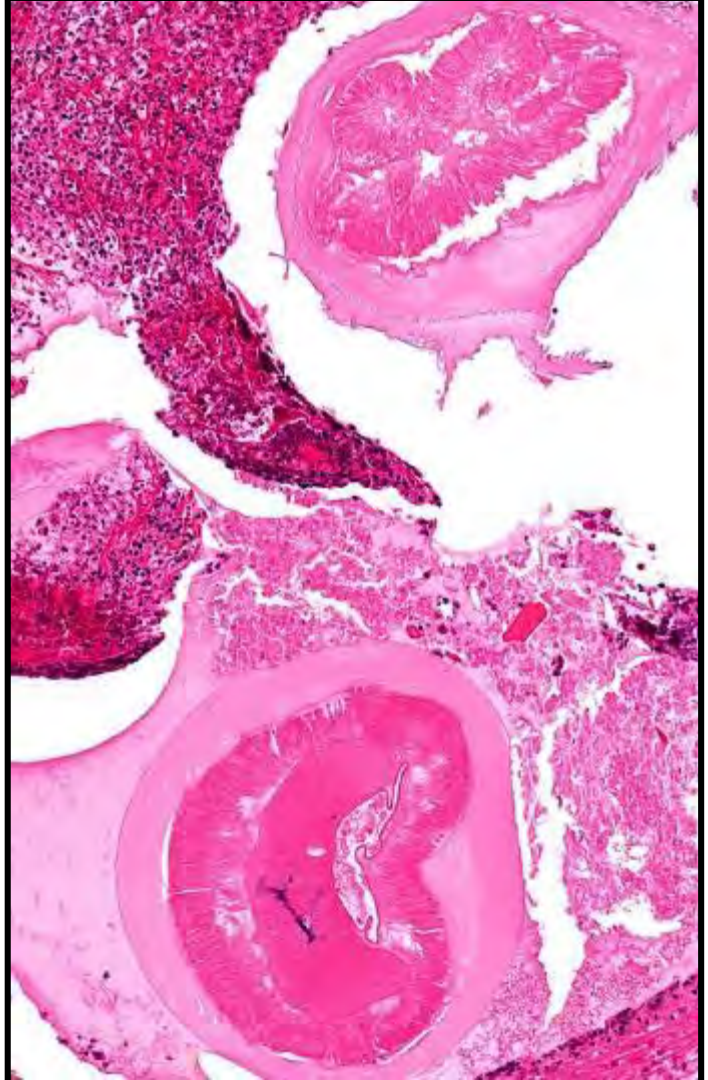
Back to the case

- No vasculitis
- No obvious neoplasm
- No known GIT disease that could explain the Eos
- Years of obstructive symptoms and abdominal pain that improved with dietary modification.
- Diagnosis?
  - Marked eosinophilic infiltrate of the small bowel extending from the mucosa to the serosa and resulting in a mesenteric mass, see comment
  - Comment: No organisms or neoplasm seen. Need to exclude secondary causes but could represent mural variant of EGE…

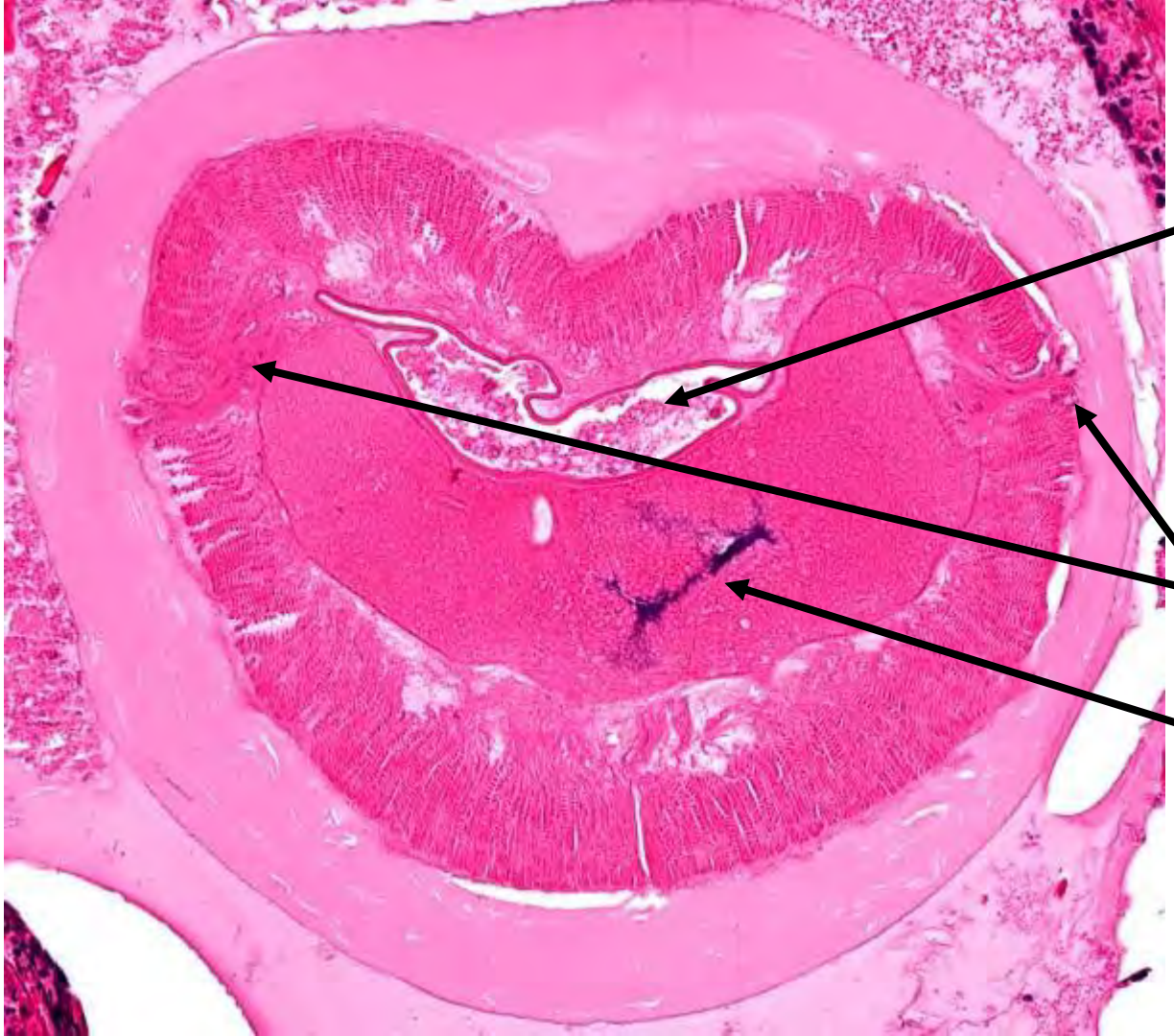
Back to the case

- Something didn't feel right.
- Such a rare diagnosis should give one pause
- Mesenteric mass seemed well sampled (4.8 cm and 4 sections were submitted)
- Still, submitted an additional 4 sections.

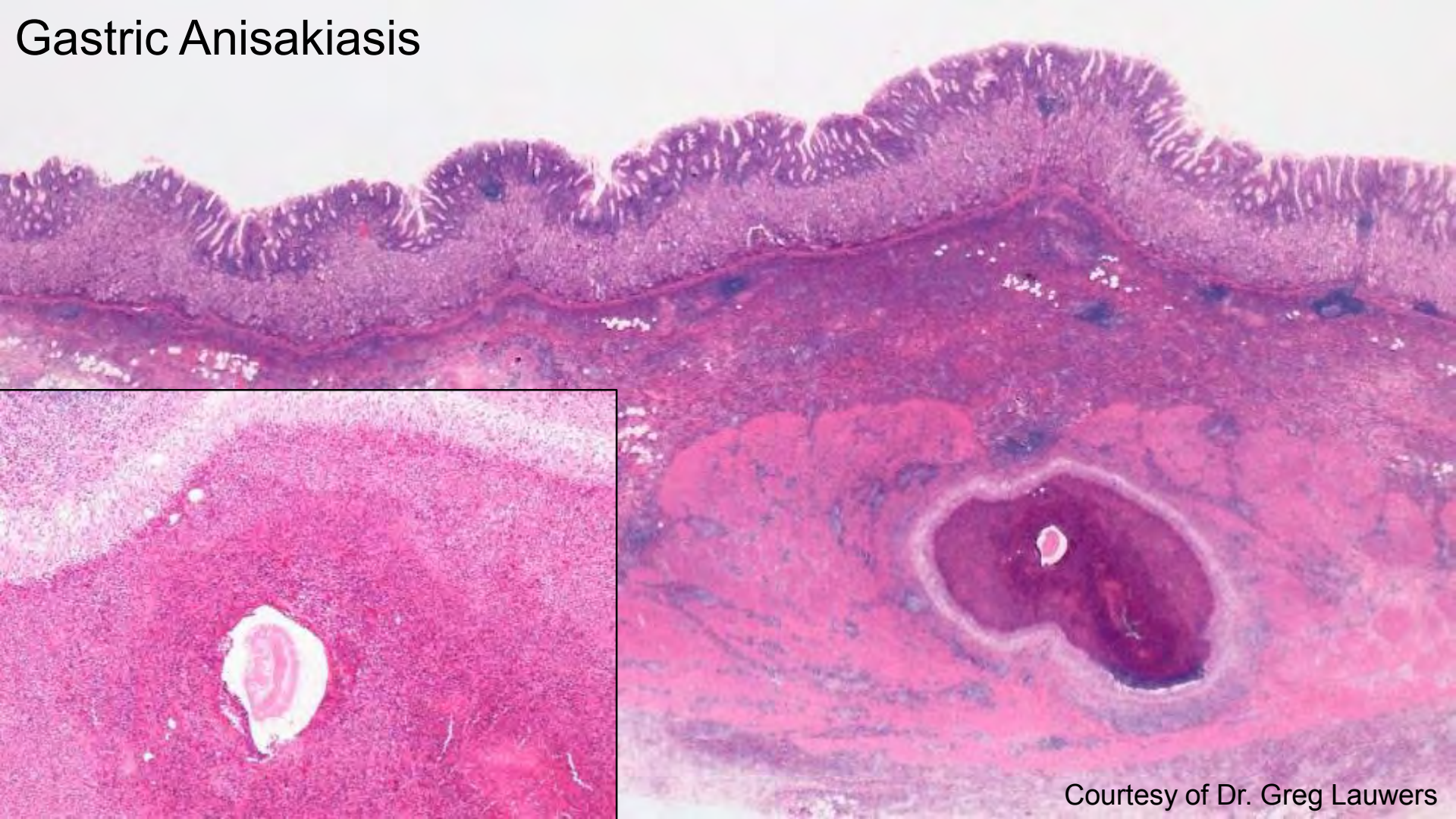




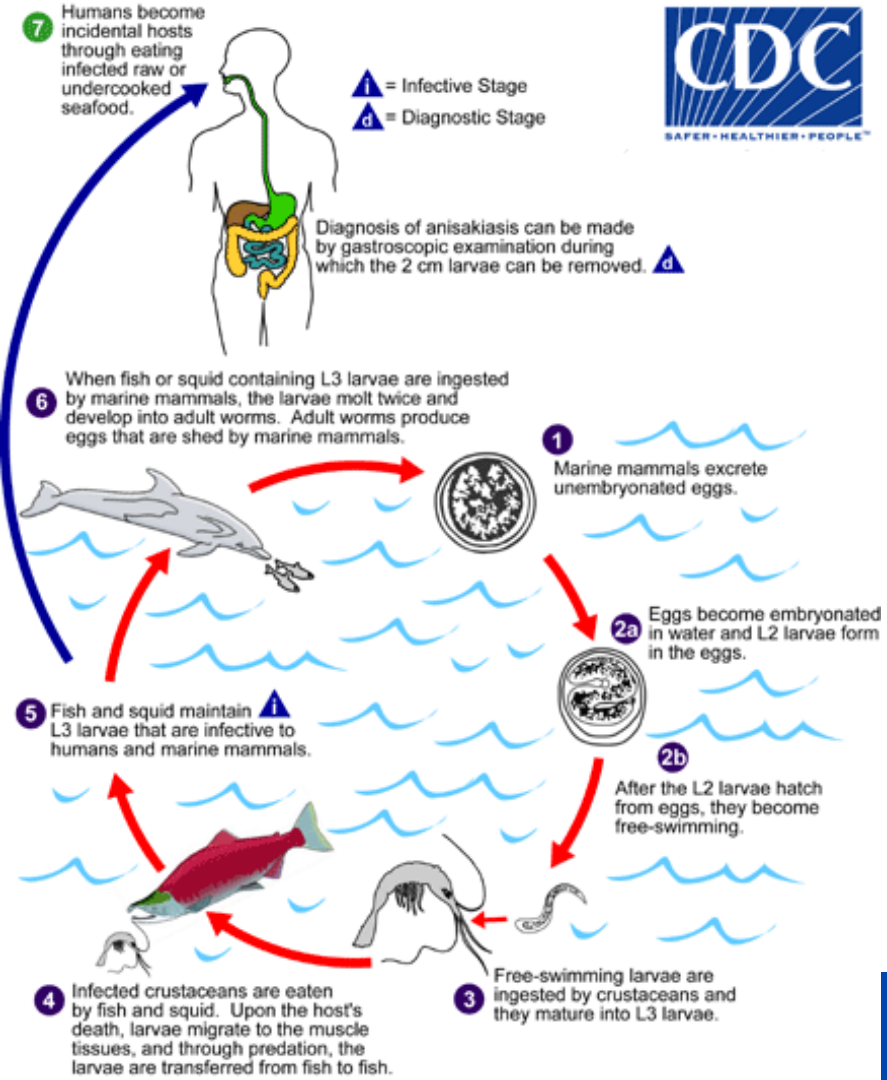
Anisakid larvae



Gastric Anisakiasis



Courtesy of Dr. Greg Lauwers



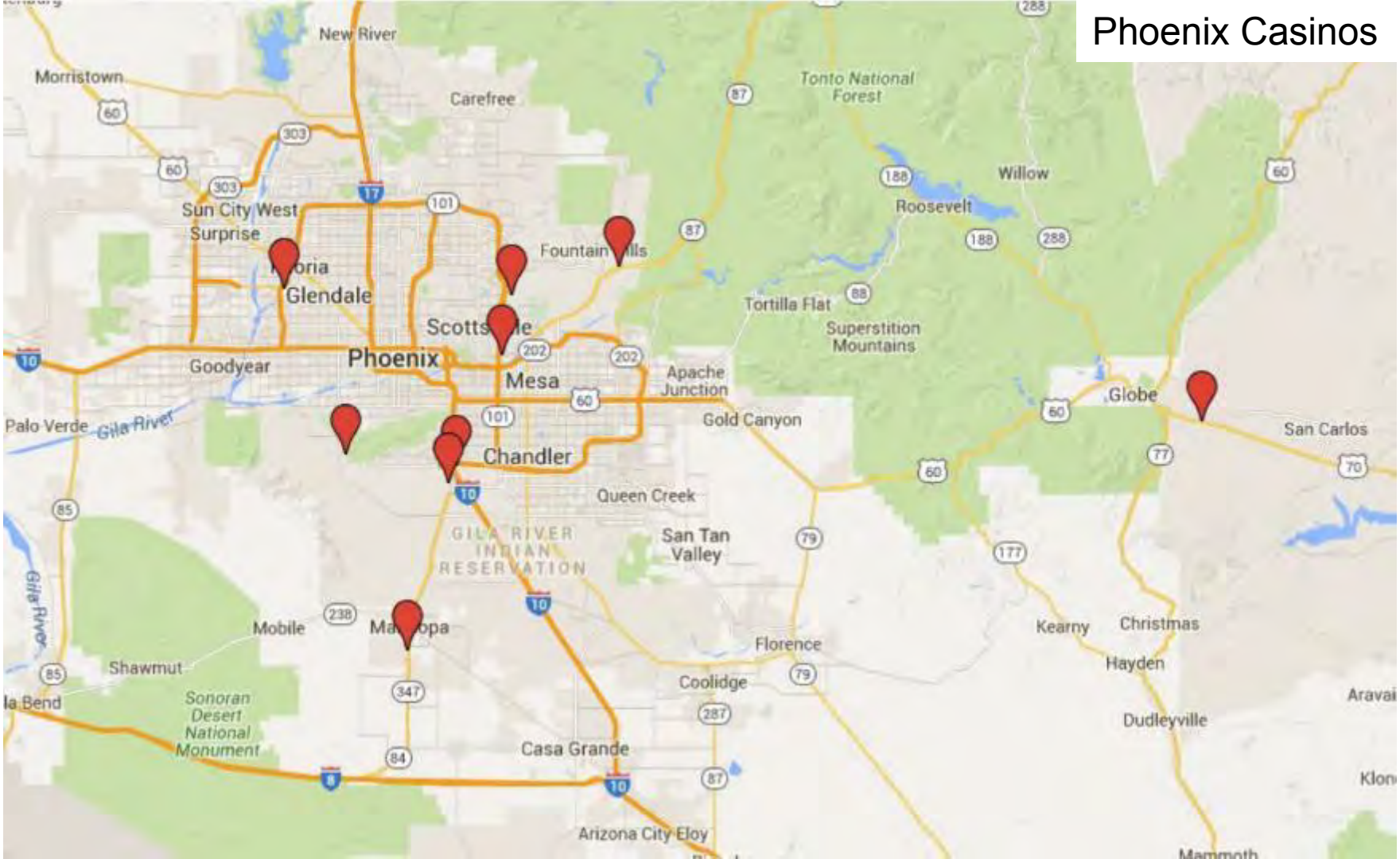
- Infected marine mammals excrete eggs
- Larvae are ingested by crustaceans which are then eaten by fish and squid
- Humans become incidental hosts through ingestion of uncooked seafood and larvae penetrate the bowel

Our patient:

- Works at a casino and LOVES sushi (eats sushi almost everyday).
- Almost all fish used for sushi are frozen, which kills the larvae
- Either she made homemade sushi from fish that was not frozen or the sushi at the casino where she works may not be properly prepared….

https://www.cdc.gov/parasites/anisakiasis/biology.html

Phoenix Casinos



What did we learn?

- Eosinophils often pose a diagnostic dilemma
  - Ignore them (normal component or obviously part of another disease process)
  - Obscure the true disease process
  - The primary mediators of the disease (EGIDs are increasing)
  - *Need help (and sometimes luck) to sort out these possibilities*
- When in doubt, take a break from the case, ask for help, submit more sections, get deeper levels, etc..
- **If you come to Phoenix, don't eat the sushi at casinos.**

