Gastritis: A Pattern Based Approach

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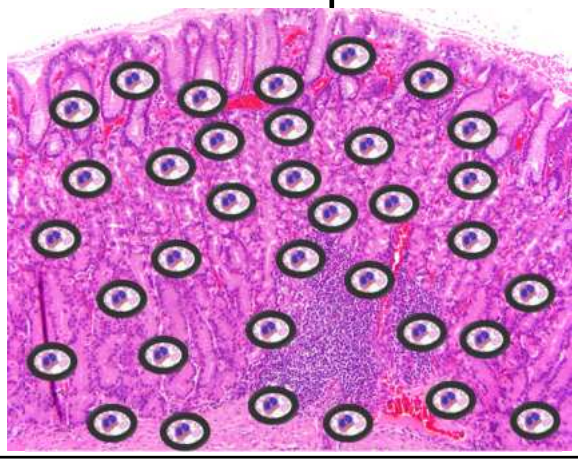
Patterns to be discussed

- The biopsy with prominent eosinophils
- The biopsy with "chronic inflammation"
  - "Top heavy"
  - "Bottom heavy"
    - Body
    - Antrum *and* body
- The biopsy with chronic active inflammation **without** *H. pylori*
- The biopsy with lymphocytic and collagenous gastritis patterns
- The biopsy with prominent Mott cells
- The biopsy with a prominent monocytic reaction

The biopsy with prominent eosinophils



Prominent eosinophils

- *H. pylori* infection
- Crohn disease
- Solid organ transplantation
- Parasitic infection
- Post-radiation
- Autoimmune metaplastic atrophic gastritis (AMAG, early and fully developed).
- Collagenous gastritis
- Medications
- Eosinophilic gastritis – absence of all causes of eosinophilia

Lee et al. The development of eosinophilic colitis after liver transplantation in children. Pediatr Transplant. 2007 Aug;11(5):518-23
Romero et al. Peripheral eosinophilia and eosinophilic gastroenteritis after pediatric liver transplantation. Pediatr Transplant. 2003 Dec;7(6):484-8
Muir et al. Severe Eosinophilic Gastroenteritis in a Crohn's Disease Patient Treated With Infliximab and Adalimumab. Am J Gastroenterol. 2016 Mar;111(3):437-8.

Eosinophilic gastritis

- No established # threshold for dx
- No consensus regarding diagnostic criteria
- "Prominent" gastric eosinophils
  - Normal gastric eosinophil count is variable.
    - Lwin et al. found less than 32/mm^2 in normal controls*
    - Proposed threshold of > or equal to 127 eos/mm^2 in patients with no known causes of eosinophilia*
- Eosinophils infiltrating surface foveolar epithelium, gland epithelium, glandular lumina, muscularis mucosae, and submucosa.* *

*Lwin et al. Eosinophilic gastritis: histopathological characterization and quantification of the normal eosinophil content. Mod Pathol. 2011 Apr;24(4):556-63
**Collins, M. Histopathology associated with eosinophilic gastrointestinal diseases. Immunol Allergy Clin N Am 29 (2009) 109–117

Eosinophilic gastritis

- Generally thought of as a pediatric disease but can also be seen in adults
- Antrum almost always affected +/- fundus
  - Limited to the fundus on occasion
- May be seen with eosinophil infiltration in other areas of the upper GI tract (esophagus, duodenum)
- Not associated with colonic eosinophilia in patients with concurrent colonic biopsies*,#

*Ko, H. et al. Eosinophilic gastritis in children: clinicopathological correlation, disease course, and response to therapy. *Am J Gastroenterol* 2014; 109:1277–1285
#Caldwell et al. Histologic eosinophilic gastritis is a systemic disorder associated with blood and extragastric eosinophilia, TH2 immunity, and a unique gastric transcriptome. J Allergy Clin Immunol. 2014 Nov;134(5):1114-24

Eosinophilic gastritis

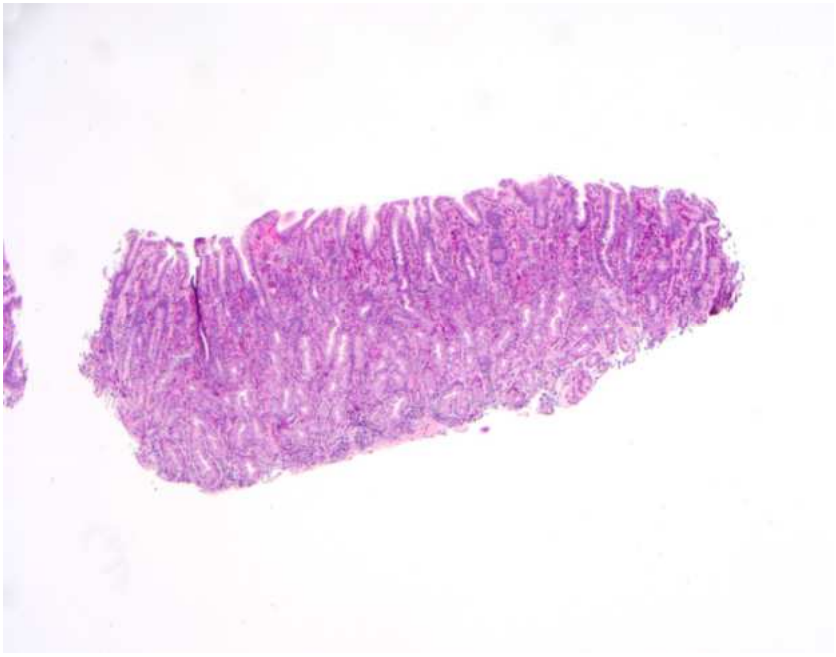
- In children:
  - Abdominal pain and vomiting
  - Atopy (asthma, allergic rhinitis, atopic dermatitis)
  - Food allergy (86%)
  - Protein losing enteropathy (22%)
  - Elevated peripheral eosinophil count
  - EoE (43%)
  - Duodenal eosinophilia (21%)

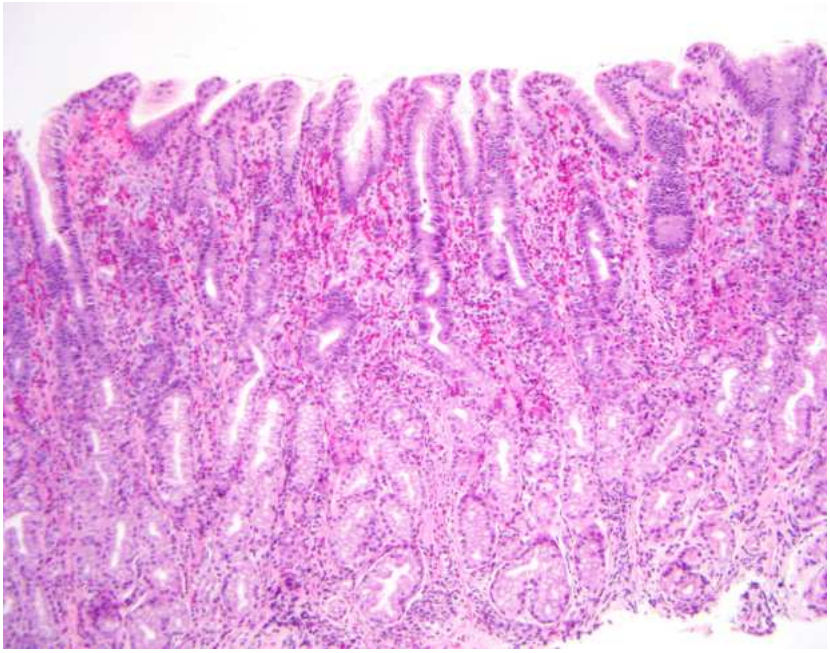
Ko, H. et al. Eosinophilic gastritis in children: clinicopathological correlation, disease course, and response to therapy. *Am J Gastroenterol* 2014; 109:1277–1285

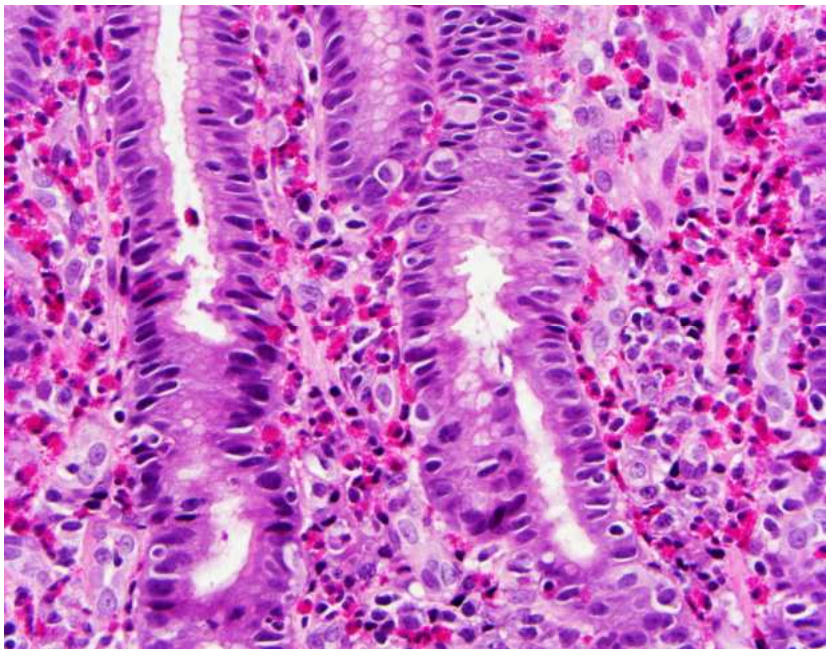
Eosinophilic gastritis

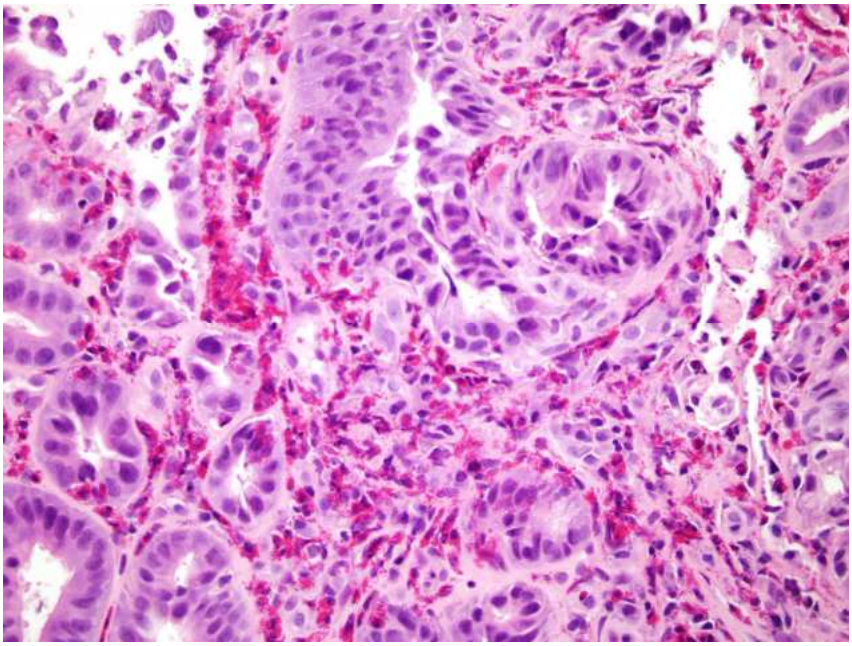
- Eosinophilic gastritis
  - Eosinophils are predominant cell type (minimal polys, plasma cells)
  - No architectural distortion/gland drop out
  - When present, muscularis mucosae is involved
  - Eosinophilic abscesses seen often
  - Eosinophilic degranulation
- Gastric eosinophilia associated with *H. pylori* infection and Crohn disease tends to be mild and admixed with neutrophils without eosinophilic microabscesses

Ko, H. et al. Eosinophilic gastritis in children: clinicopathological correlation, disease course, and response to therapy. *Am J Gastroenterol* 2014; 109:1277–1285









Eosinophilic gastritis

- Children may be treated with dietary restriction
  - Approximately 80% experience symptom resolution and histologic response, most with histologic response in the stomach
    - Associated EoE may or may not respond to dietary restriction
  - Peripheral eosinophil count remains elevated irrespective of histological response to tx
- Adults may be treated with steroids, cromolyn sodium, antihistamines, asthma drugs

Ko, H. et al. Eosinophilic gastritis in children: clinicopathological correlation, disease course, and response to therapy. *Am J Gastroenterol* 2014; 109:1277–1285

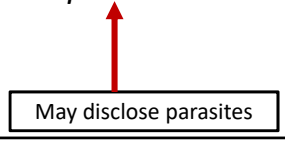
The biopsy with prominent eosinophils, sample report

- *Gastric mucosa with marked eosinophilia. See note.*

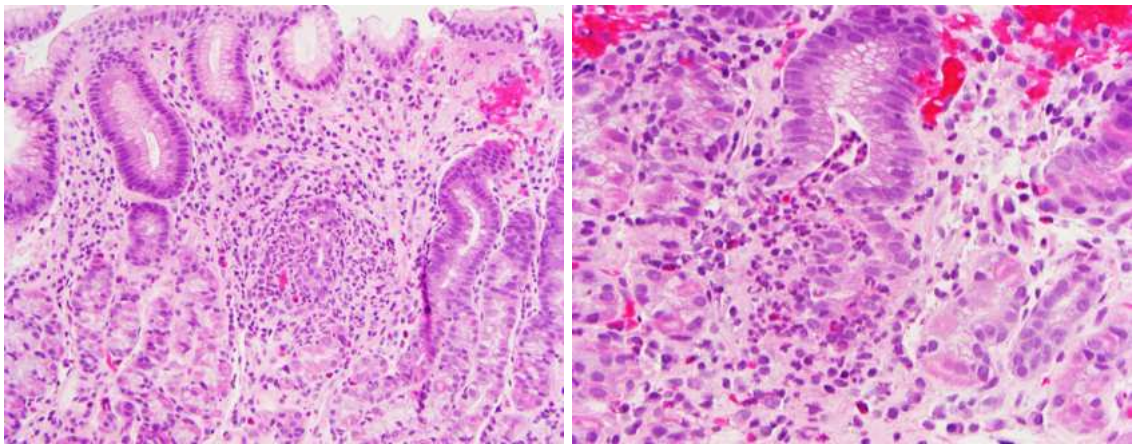
or

- *Eosinophilic gastritis pattern. See note.*

Note: Tissue eosinophilia may be seen in the settings of H. pylori infection, inflammatory bowel disease, solid organ transplantation, parasitic infection, or post-radiation. Eosinophilic gastritis should be considered in the absence of these known causes of eosinophilia. No Helicobacter organisms or parasites identified. Deeper levels have been examined.

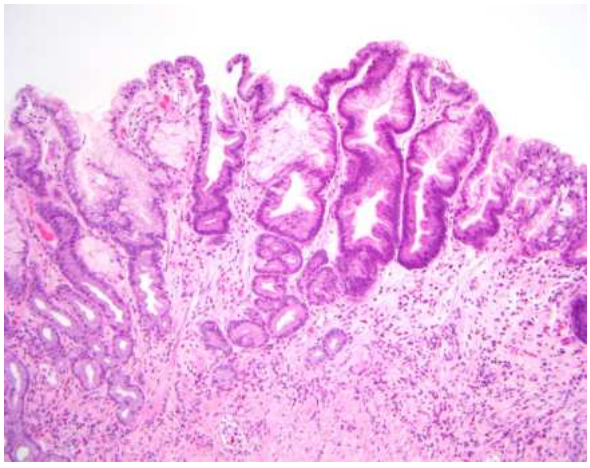


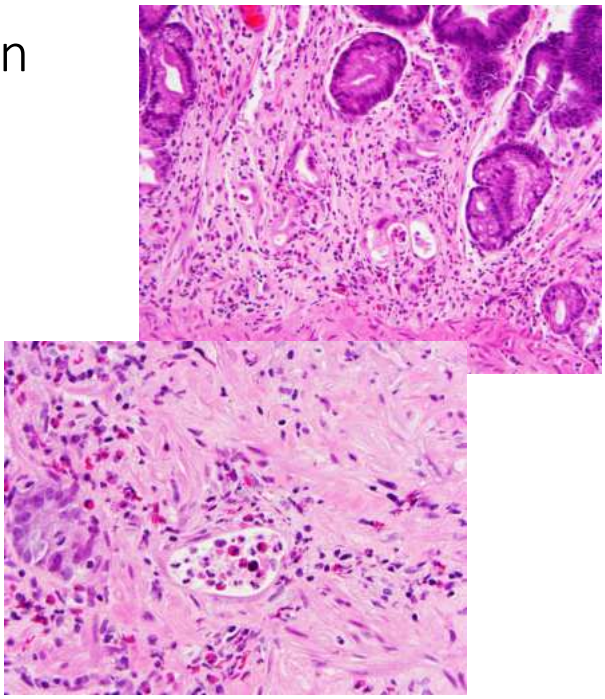
Eosinophils post-radiation



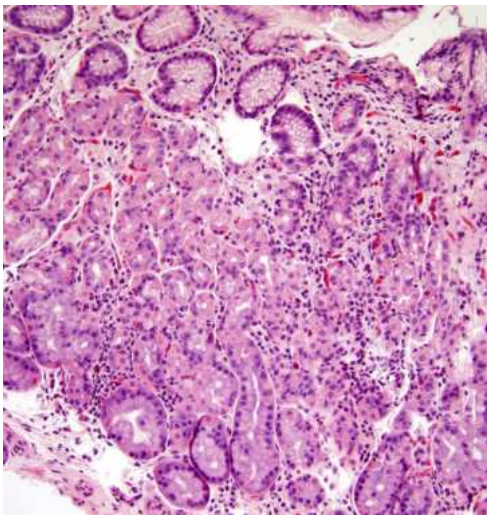
H. pylori negative MALT

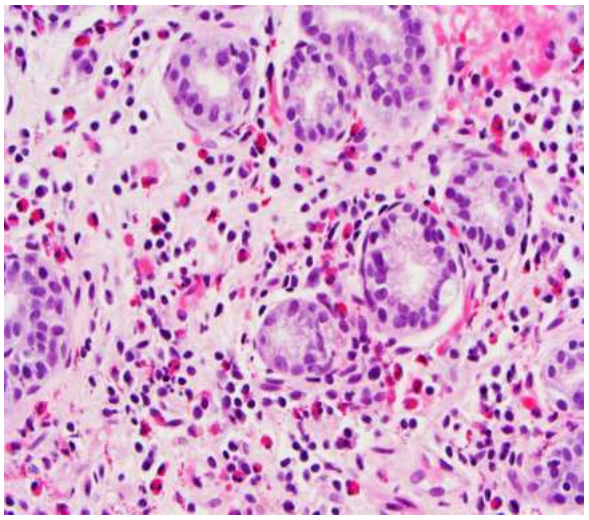
Eosinophils post-radiation





Eosinophils: Autoimmune Metaplastic Atrophic Gastritis (early and fully developed)



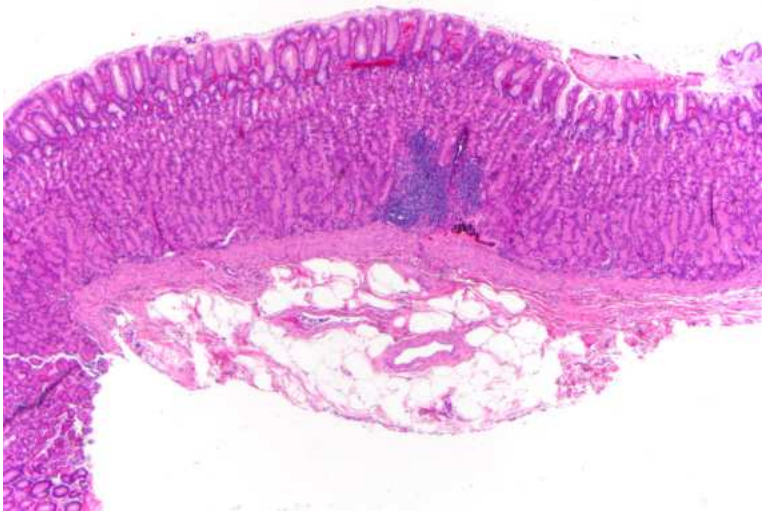


The biopsy with “chronic inflammation”

The biopsy with "chronic inflammation"

- Subjective – EVERYBODY has a different threshold for what constitutes chronic inflammation in the stomach
- My approach:
  - I diagnose chronic gastritis when I see it at 4x:
    - Increased dots (plasma cells, lymphocytes) separating glands
    - Corroborate at 40x that they are indeed chronic inflammatory cells

"Normal"



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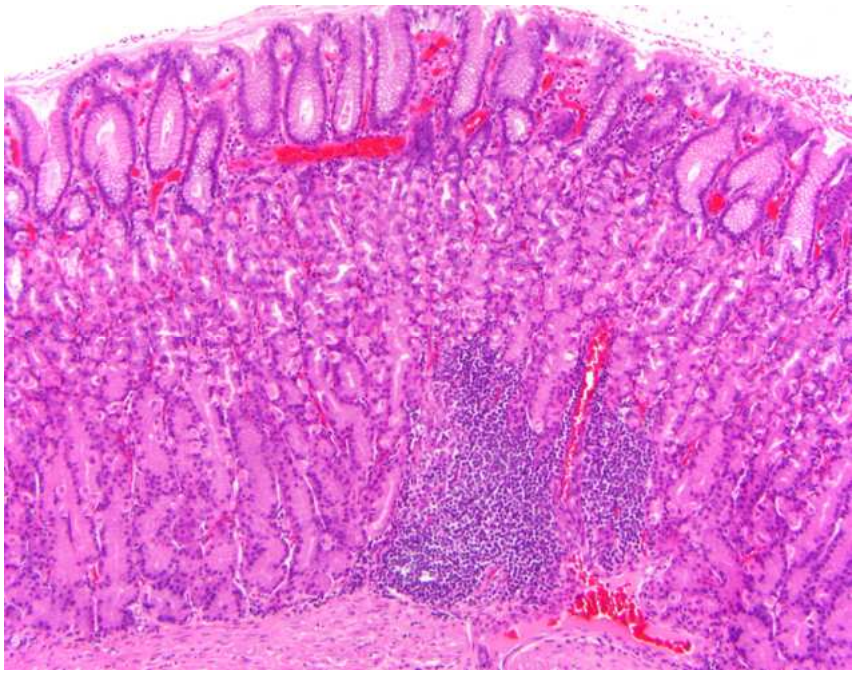

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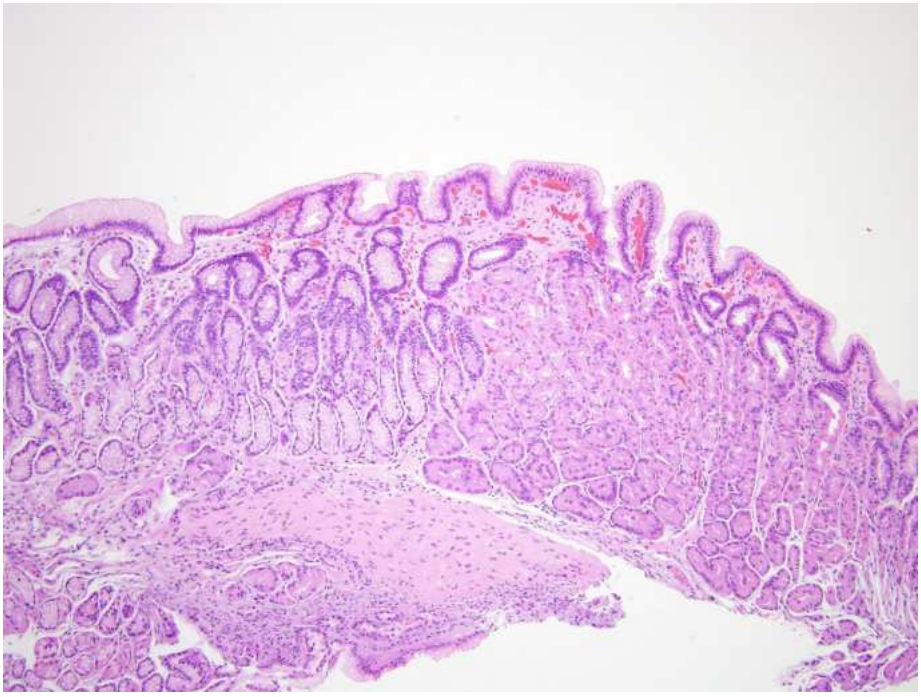


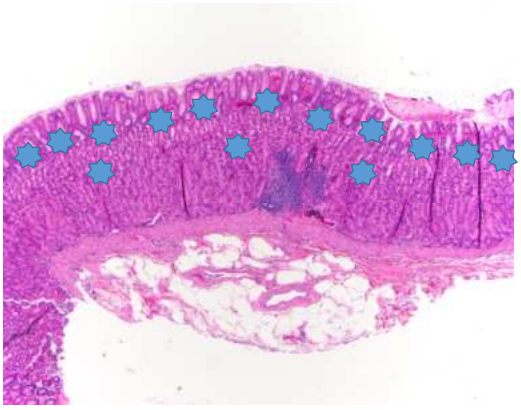
The biopsy with "chronic inflammation"

- Look at the ***distribution*** of the infiltrate
  - **Top** heavy: *H. pylori* infection
  - **Bottom** heavy, **body** only: autoimmune metaplastic atrophic gastritis (AMAG)
  - **Bottom** heavy, antrum **and** body: atrophic autoimmune pangastritis, autoimmune enteropathy, olmesartan
  - **Patchy**: think IBD

The biopsy with "chronic inflammation"

- Look at the distribution of the infiltrate (contd)
  - Lymphocytic gastritis pattern (prominent intraepithelial lymphocytes) with or without prominent irregular collagen table:
    - Celiac disease
    - *H. pylori*
    - Inflammatory bowel disease
    - Common variable immunodeficiency (CVID)
    - Olmesartan
    - Proton pump inhibitors (omeprazole [Prilosec], lansoprazole [Prevacid]).

The biopsy with "chronic inflammation", top heavy infiltrate: *H. pylori*



The biopsy with "chronic inflammation", top heavy infiltrate: *H. pylori*

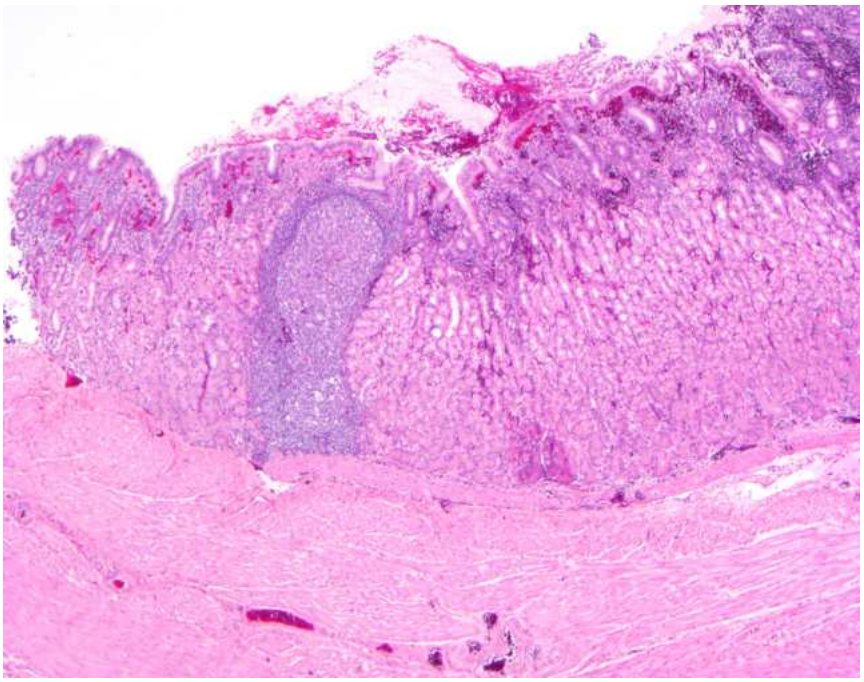
- Accompanied by active inflammation, at least focally
  - If activity is not present, it may represent treated *H. pylori* gastritis
- The presence of germinal center/s (a.k.a. follicular gastritis) is indicative of *H. pylori* infection
- At least one of the following are always seen in children:*
  - Germinal center formation (but may be seen in 51.3% of patients with *H.pylori*-negative gastritis***)
  - Active inflammation (but compared to adults kids are more likely to lack activity)
  - Oxyntic mucosa with moderate to severe chronic inflammation
  - Antral mucosa with any chronic inflammation, exclusive of mild and superficial chronic inflammation
  - Limit IHC to 30% of all gastric biopsy specimens and reduce costs by up to $55,306.90 per 1,000 biopsies
- May or may not see:
  - Atrophy
  - Intestinal metaplasia

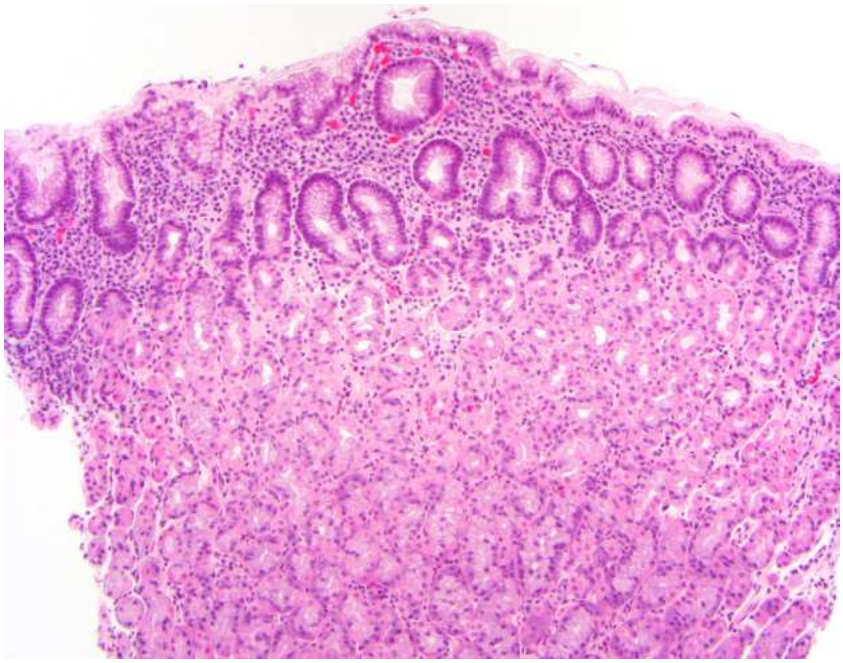
Infection eradication associated with regression of atrophy and IM**

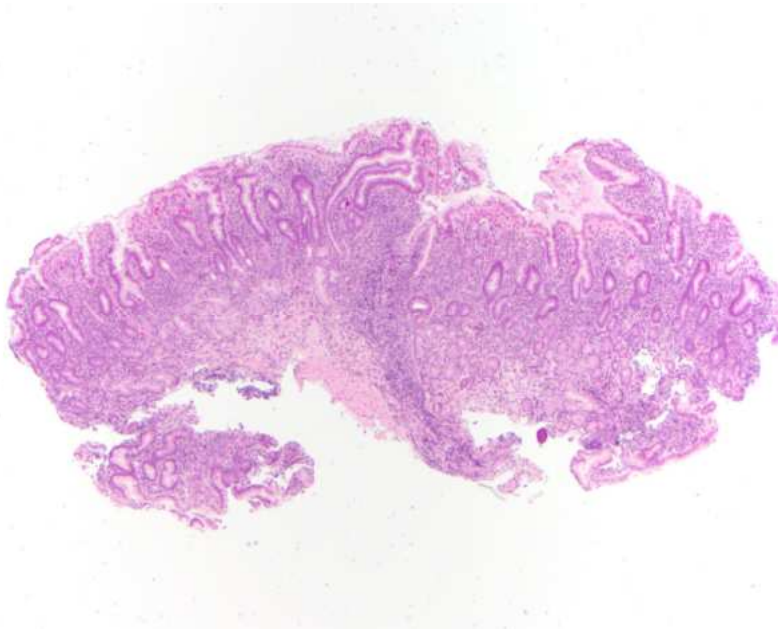
*Conces et al. A Strategy for Helicobacter Immunohistochemistry Utilization in Pediatric Practice: Insights From Morphologic and Cost-Benefit Analyses. *Am J Clin Pathol. 2016 Nov 1;146(5):611-617.*

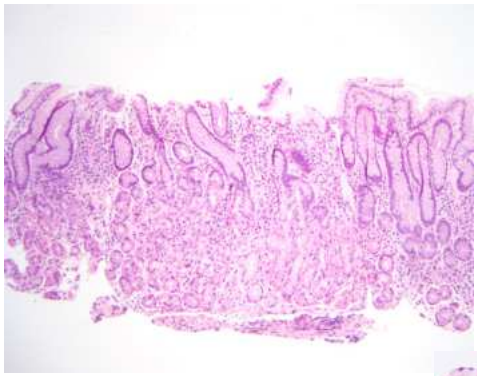
** Hwang et al. Reversibility of atrophic gastritis and intestinal metaplasia after Helicobacter pylori eradication - a prospective study for up to 10 years. Aliment Pharmacol Ther. 2018 Feb;47(3):380-390. doi: 10.1111/apt.14424. Epub 2017 Nov 29

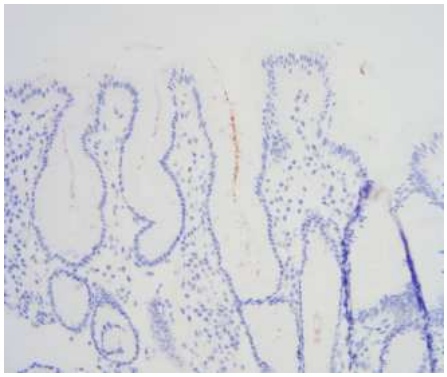
***Broide et al. Lymphoid follicles in children with Helicobacter pylori-negative gastritis. Clin Exp Gastroenterol. 2017 Aug 11;10:195-201

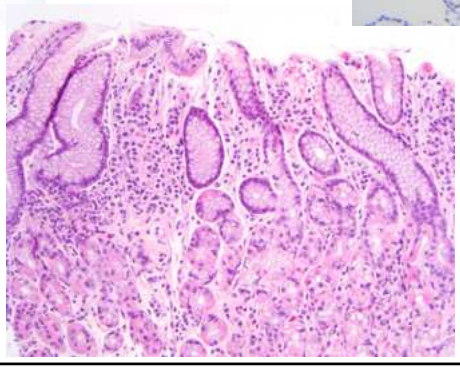


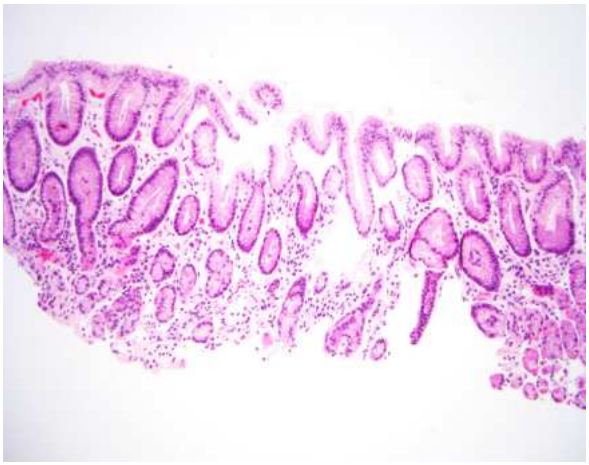




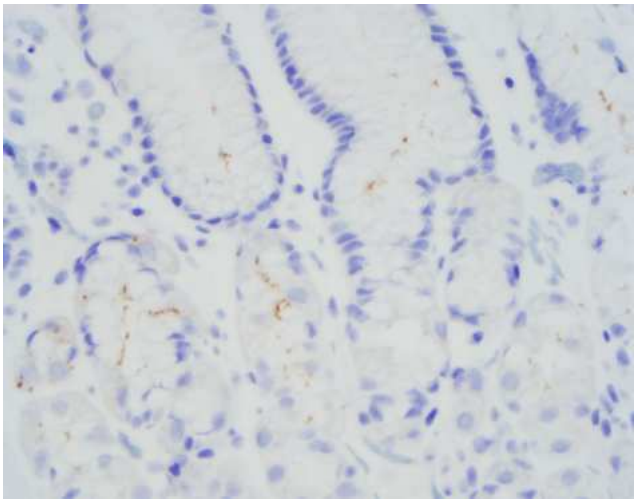




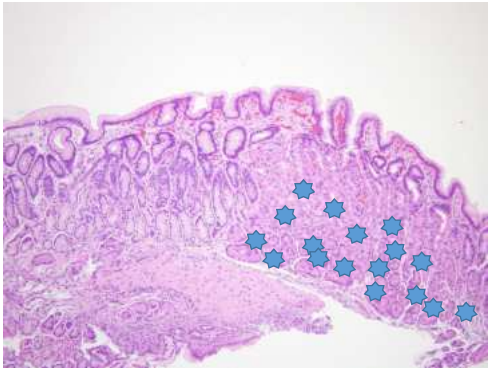


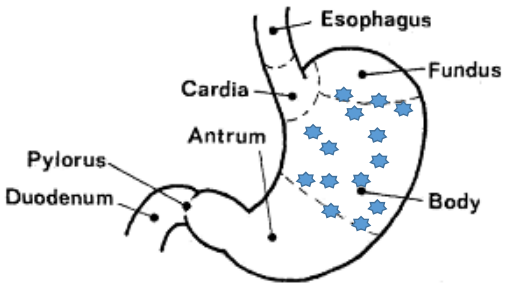


Not all cases read books or attend these lectures



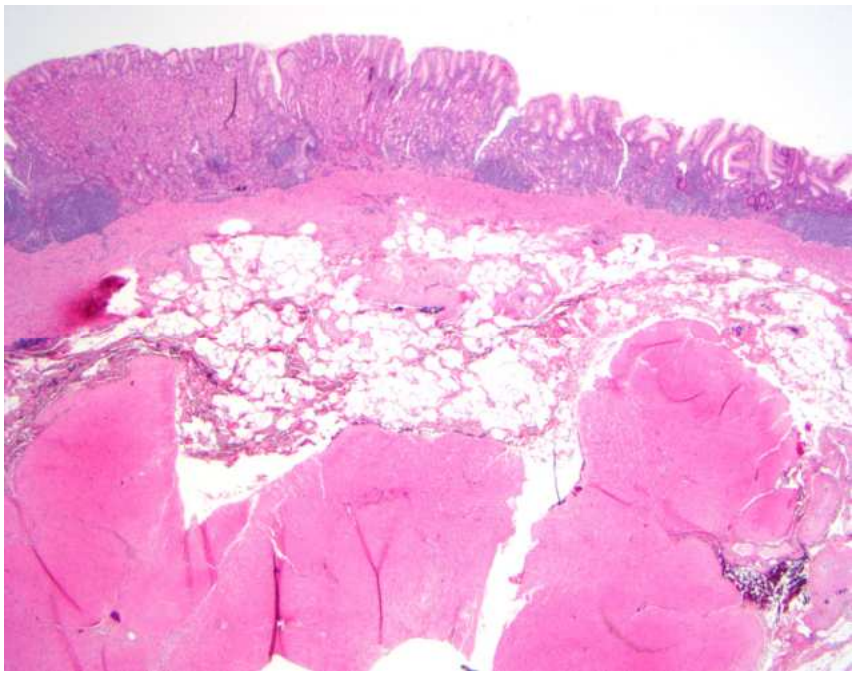
The biopsy with “chronic inflammation”, bottom heavy infiltrate, limited to the body: AMAG

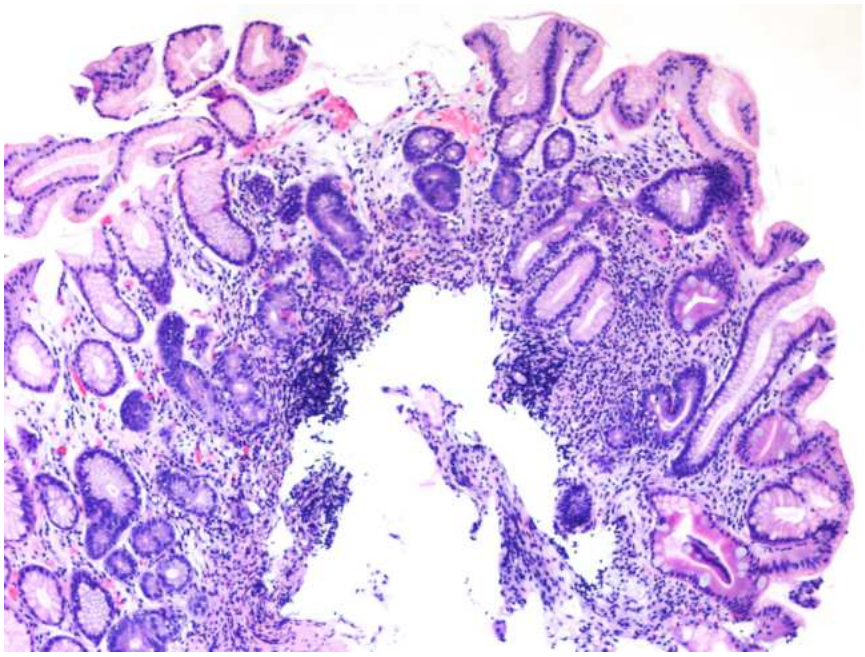


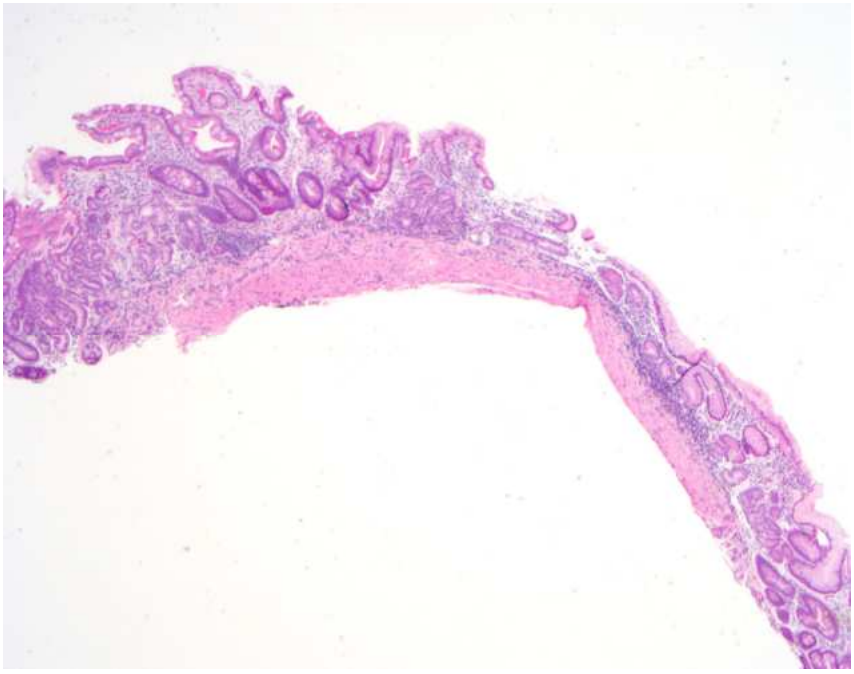


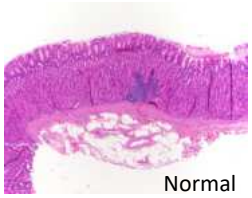
The biopsy with “chronic inflammation”, bottom heavy infiltrate, limited to the body: AMAG

- Normal antrum or may look like reactive gastropathy
- Body also shows:
  - Atrophy (decreased or absent parietal cells)
  - Intestinal metaplasia (present in most biopsies)
  - Pseudopyloric metaplasia
  - ECL cell hyperplasia (nodular or linear or both)
  - 50% cases show pancreatic metaplasia (rare in the stomach outside the context of AMAG)
  - Rare cases show striking eosinophils
  - Inflammation tends to decrease as atrophy develops (in contrast to atrophic autoimmune pangastritis)









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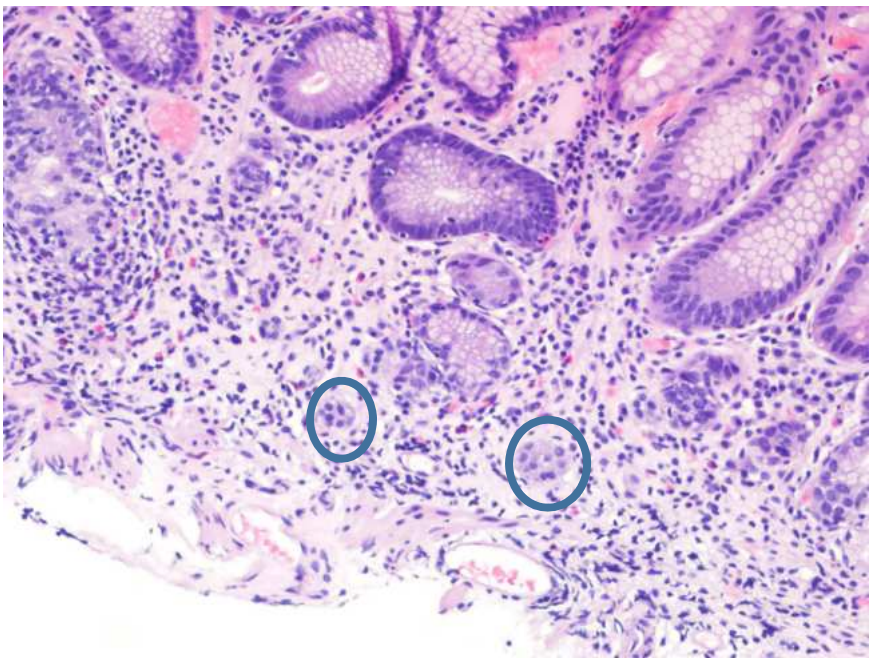
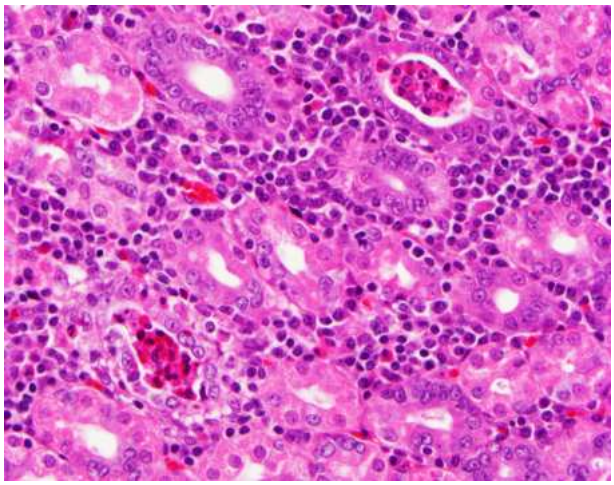
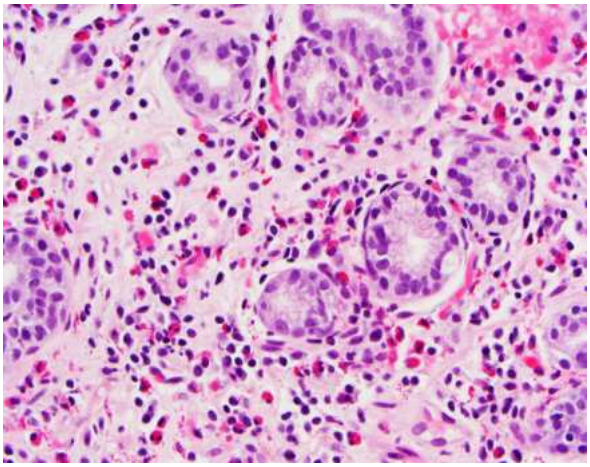
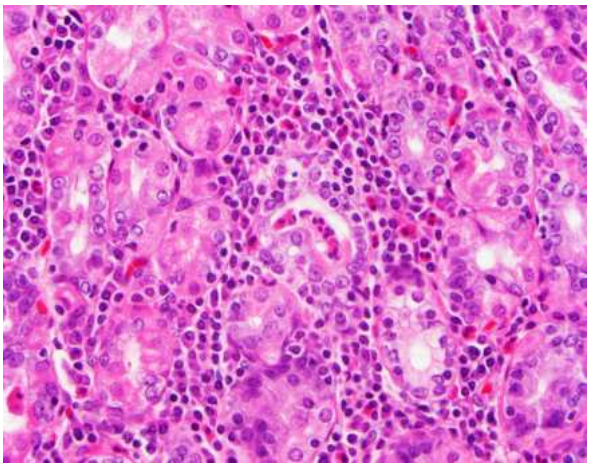
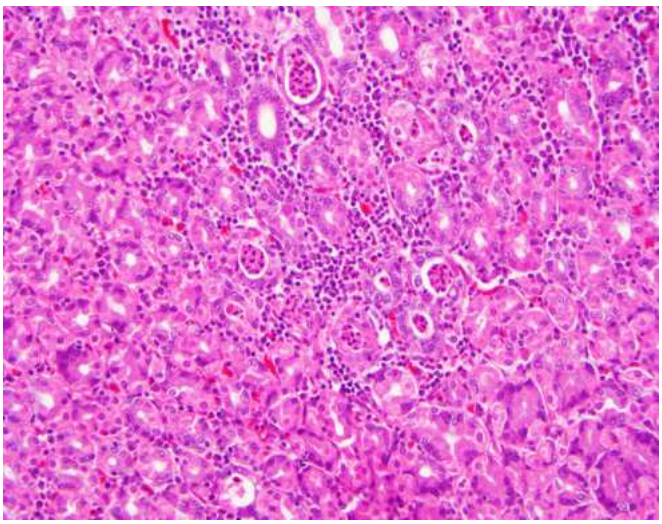


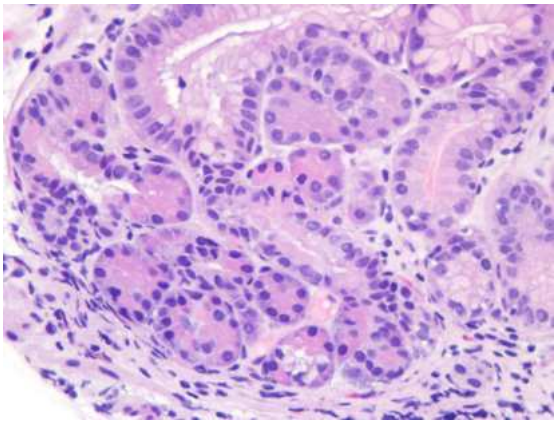
Eosinophils!



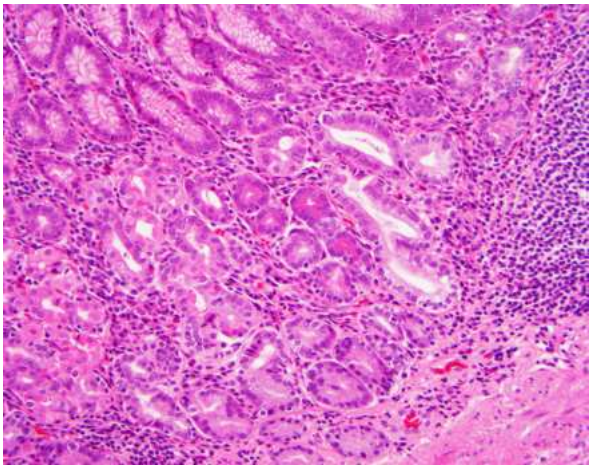


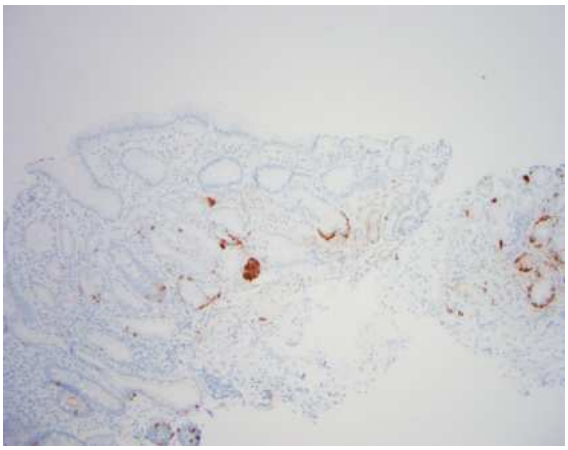


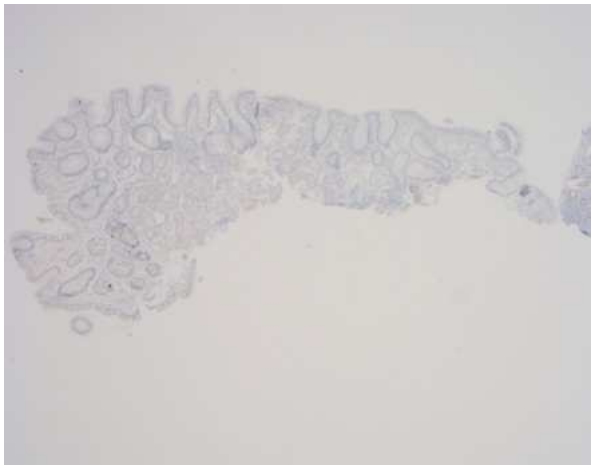


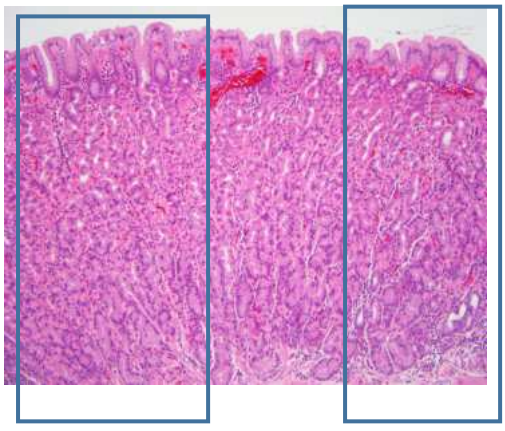


Pancreatic metaplasia





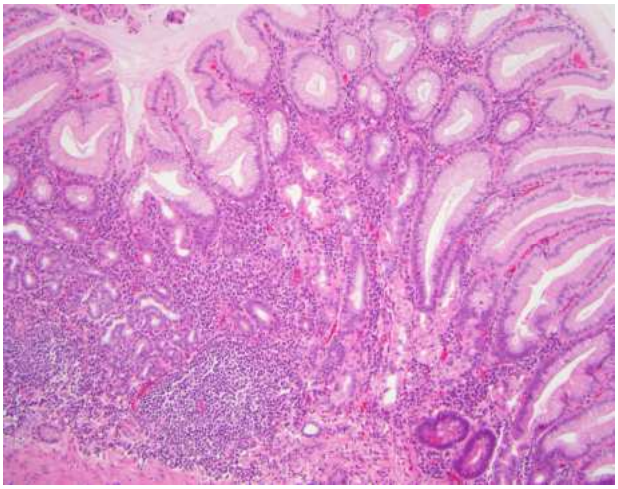


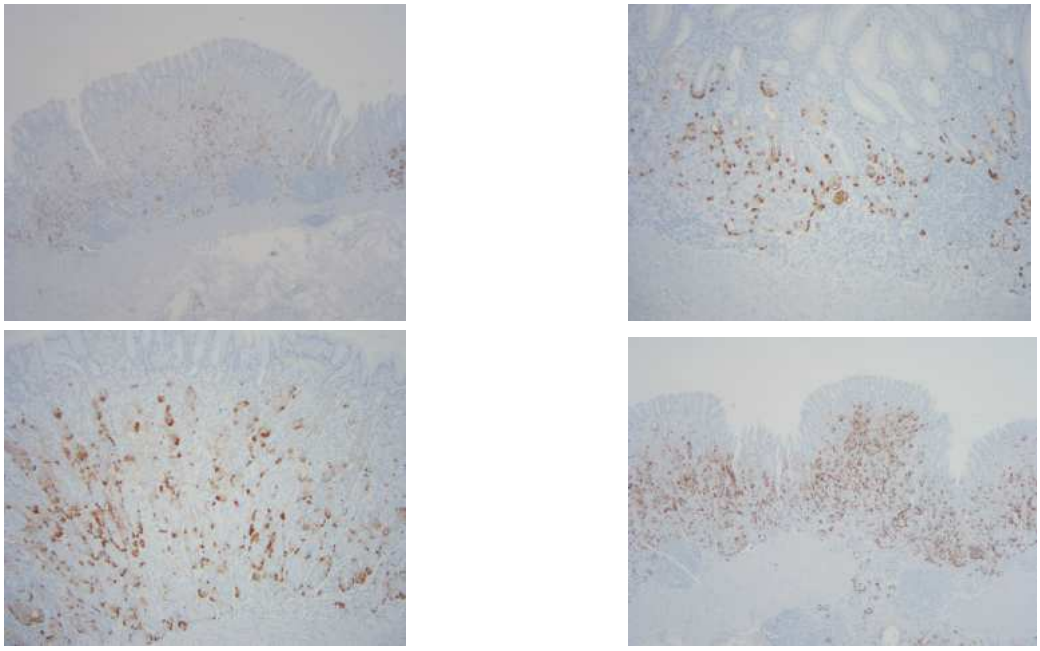


Normal

Early AMAG?

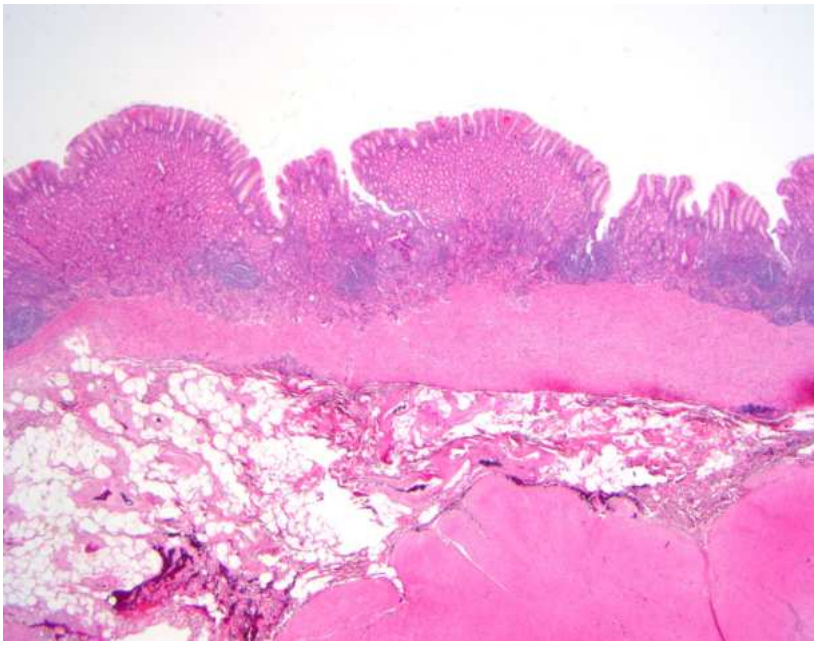
Pitfall: Patchy





The biopsy with “chronic inflammation”, bottom heavy infiltrate, limited to the body: AMAG

- Gastric polyps in the setting of AMAG
  - Hyperplastic polyps
  - NET (carcinoid tumor, G1 or G2)
  - Gastric adenoma (intestinal or pyloric gland types)
  - Residual, non atrophic mucosa in the background of severe atrophy



Krasinskas et al. Oxyntic Mucosa Pseudopolyps: A Presentation of Atrophic Autoimmune Gastritis. Am J Surg Pathol. 2003. February;27(2):236-41.

The biopsy with “chronic inflammation”, bottom heavy infiltrate, limited to the body: AMAG

- Important to diagnose:
  - Leads to pernicious anemia due to B12 deficiency
    - Pernicious anemia (25%)
    - Iron deficiency anemia (29.7%)
    - Hypothyroidism (23%)
    - Vitiligo (2.8%)
    - 65% patients have anti-parietal antibodies
  - Patients are at increased risk of gastric carcinoma (3x)

Villanacci et al. Autoimmune gastritis: relationships with anemia and Helicobacter pylori status. Scand J Gastroenterology. 2017 Jun-Jul;52(6-7):674-677

AMAG sample report

- *Autoimmune metaplastic atrophic gastritis (AMAG). See note.*

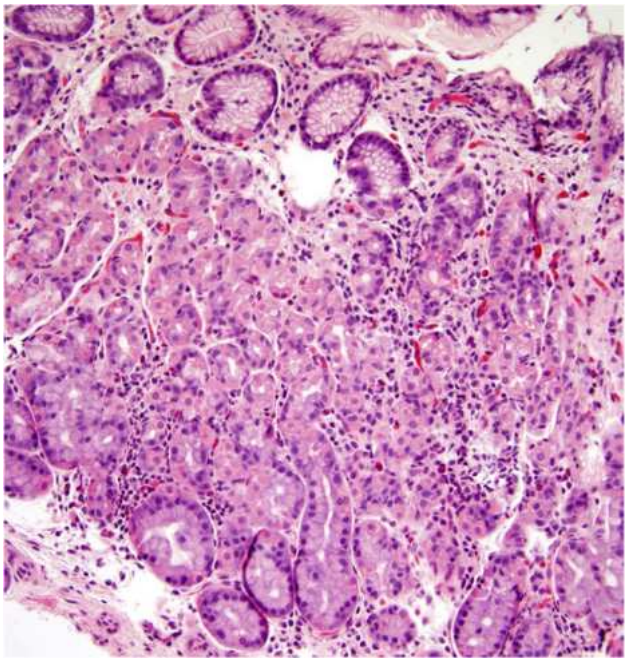
Note: A gastrin immunostain is negative, confirming tissue origin from the body. A chromogranin immunostain highlights nodular and linear ECL hyperplasia. ***The patient is at risk for pernicious anemia. Correlation with vitamin B12 levels is recommended.***

In our experience, after a diagnosis of AMAG only 43% of patients get laboratory tests for vitamin B12 levels.

Early AMAG

- Findings are subtle
  - Heavy full thickness or deep lamina propria chronic inflammation
  - Inflammatory destruction of oxyntic glands
  - Intestinal, pyloric, or pancreatic acinar metaplasia
  - Prominent lamina propria eosinophils
  - Parietal cell pseudohypertrophy
- At least two of these features were present in 72% of prior biopsies of patients who later were diagnosed with AMAG
- Most will show at least linear ECL cell hyperplasia on chromogranin

Torbenson et al. Autoimmune gastritis: distinct histological and immunohistochemical findings before complete loss of oxyntic glands. Mod Pathol. 2002 Feb;15(2):102-9
Pittman, M. et al. Autoimmune Metaplastic Atrophic Gastritis: Recognizing Precursor Lesions for Appropriate Patient Evaluation. *Am J Surg Pathol.* 2015 Dec;39(12):1611-20.

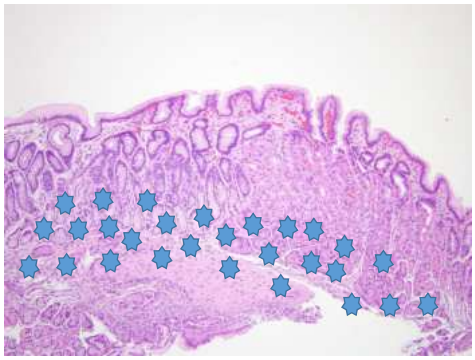


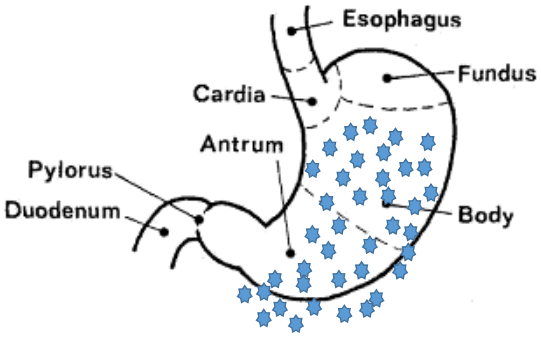
Early AMAG sample report

- *Mild chronic gastritis with focal oxyntic gland destruction and prominent eosinophils. See note.*

Note: Though non-specific, we have seen this pattern of inflammation in the setting of early autoimmune metaplastic atrophic gastritis (AMAG)/pernicious anemia. Correlation with serum serologic studies for anti-parietal and anti-intrinsic factor antibodies is recommended.

The biopsy with "chronic inflammation", bottom heavy (antrum ***and*** body): atrophic autoimmune pangastritis and gastric inflammation in patients with autoimmune enteropathy





The biopsy with "chronic inflammation", bottom heavy (antrum ***and*** body): atrophic autoimmune pangastritis

- Described in 2006 by Jevremovic *et al.**
- Histologic features:
  - Intense inflammation that persists even after severe atrophy develops (in contrast to AMAG)
    - Lymphocytes, plasma cells in entire mucosal thickness with deep predominance
    - Neutrophils present in variable proportions in all cases
  - Apoptotic bodies (GVHD-like)
  - Increased intraepithelial lymphocytes
  - Diffuse involvement of antrum ***and*** body
  - No *H. pylori*
  - No ECL cell hyperplasia
    - Decrease in overall neuroendocrine cells

Jevremovic D. Atrophic autoimmune pangastritis: a distinctive form of antral and fundic gastritis associated with systemic autoimmune disease. Am J Surg Pathol 2006;30:1412–1419

The biopsy with "chronic inflammation", bottom heavy (antrum ***and*** body): atrophic autoimmune pangastritis

- Associated with systemic autoimmune diseases (SLE, autoimmune enterocolitis, refractory sprue, autoimmune hemolytic anemia, fibromyalgia)
- Patients may be treated with immunosuppressive tx
- Neoplastic potential???
  - One of 8 patients in the study developed multifocal low grade dysplasia

Jevremovic D. Atrophic autoimmune pangastritis: a distinctive form of antral and fundic gastritis associated with systemic autoimmune disease. Am J Surg Pathol 2006;30:1412–1419

The biopsy with "chronic inflammation", bottom heavy (antrum ***and*** body): autoimmune enteropathy

- Patients present with intractable diarrhea
  - Severe villous atrophy, apoptosis, increased IELs, active inflammation. Not responsive to dietary restrictions
  - Gut autoantibodies (anti-goblet cell, anti-enterocyte) and/or associated autoimmune conditions
  - Lack of severe immunodeficiency
    - Immunodeficient states may be seen in pediatric patients*
- Children and adults
- Mucosal abnormalities seen outside the small bowel in nearly all pts**
  - Stomach (86% of cases)
  - Colon (64%)
  - Esophagus (28%)

*Singhi et al. Pediatric autoimmune enteropathy: an entity frequently associated with immunodeficiency disorders. Mod Pathol. 2014 Apr;27(4):543-53.
**Masia et al. Gastrointestinal biopsy findings of autoimmune enteropathy. A review of 25 cases. Am J Surg Pathol Volume 38, Number 10, October 2014

Autoimmune Enteropathy vs Refractory Celiac Disease (RCD)

AIE

- Higher proportion of men (60%)
- Younger (mean age, 44)
- Higher proportion present with chronic diarrhea (100%) and weight loss (90%)
- No differences in degree of villous atrophy
- 50% of cases have >40 lymphocytes/100 epithelial cells

RCD

- 29% males
- Mean age, 57
- Diarrhea (71%), weight loss (71%)
- Higher proportion has increased intraepithelial lymphocytes (>40/100 epithelial cells in 100%)

Sharma et al. Features of Adult Autoimmune Enteropathy Compared With Refractory Celiac Disease. Clin Gastroenterol Hepatol. 2018 Jan 4

The biopsy with "chronic inflammation", bottom heavy (antrum ***and*** body): autoimmune enteropathy

- Gastric biopsies
  - Atrophy
  - Dense lymphoplasmacytic inflammation
  - +/- intestinal metaplasia
  - +/- pyloric metaplasia
  - +/- intraepithelial lymphocytes
  - +/- neutrophils
  - Apoptotic bodies (GVHD-like)
  - Antrum equally affected as body
  - ECL cell hyperplasia often absent but may rarely be seen

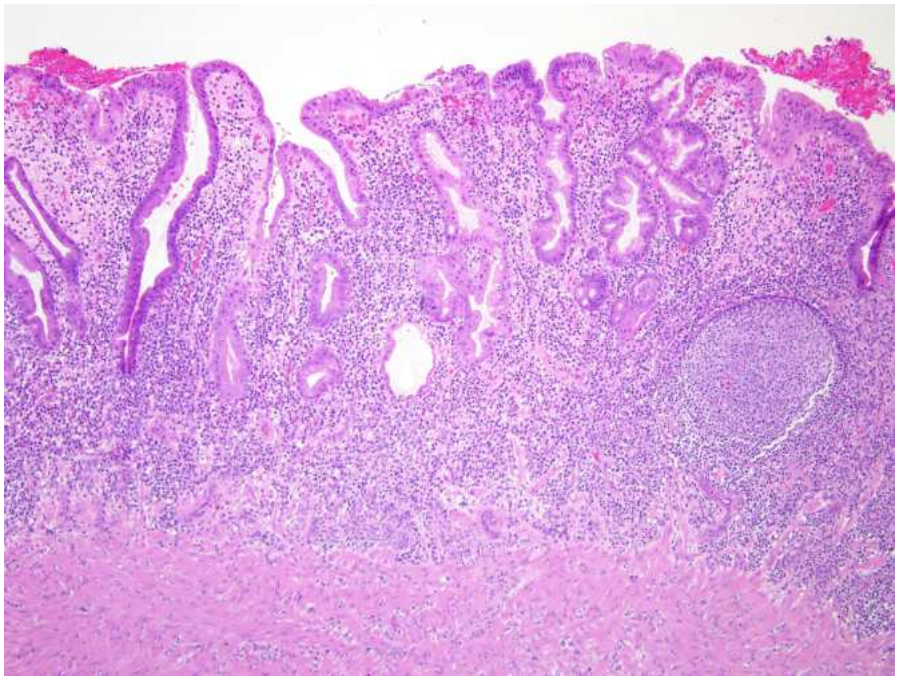
The biopsy with "chronic inflammation", bottom heavy (antrum *and* body): autoimmune enteropathy

- AIE may be seen as a component of certain genetic syndromes
- Mutations of the FOXP3 gene in X chromosome are associated with **IPEX** syndrome
  - Immune dysfunction
  - Polyendocrinopathy
  - Enteropathy
  - X-linked inheritance

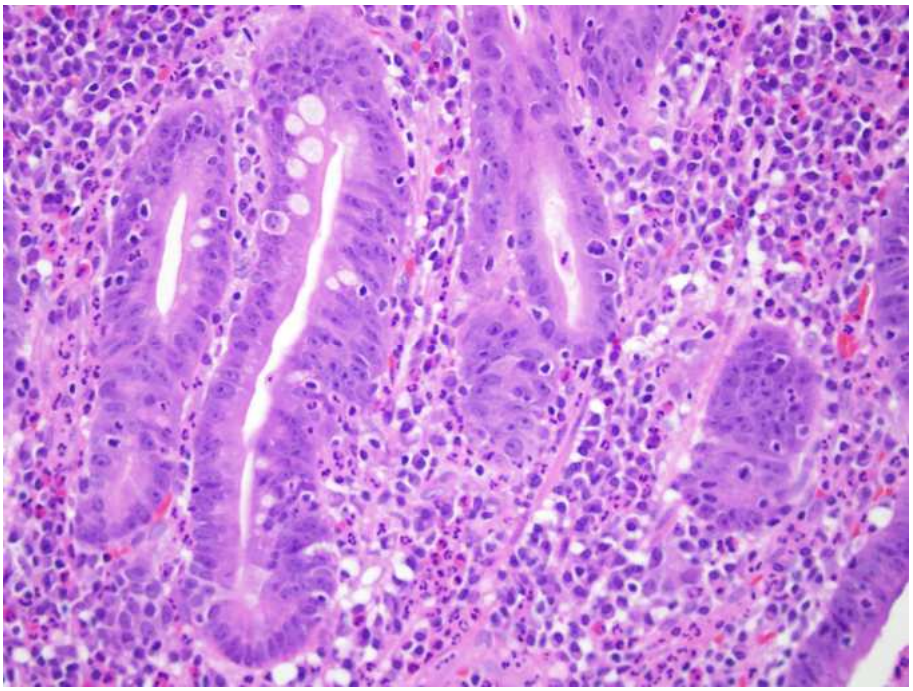
The biopsy with "chronic inflammation", bottom heavy (antrum *and* body): autoimmune enteropathy

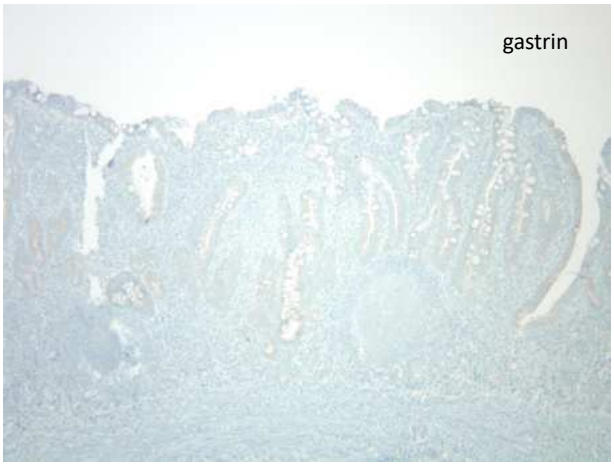
- **APECED** (= **APS**-1 autoimmune polyglandular syndrome 1) is autosomal recessive associated with mutations in the AIRE gene
  - Autoimmune polyendocrinopathy
  - Candidiasis
  - Ectodermal dysplasia
- Patients with AIE tx with immunosuppressive therapy and nutritional support

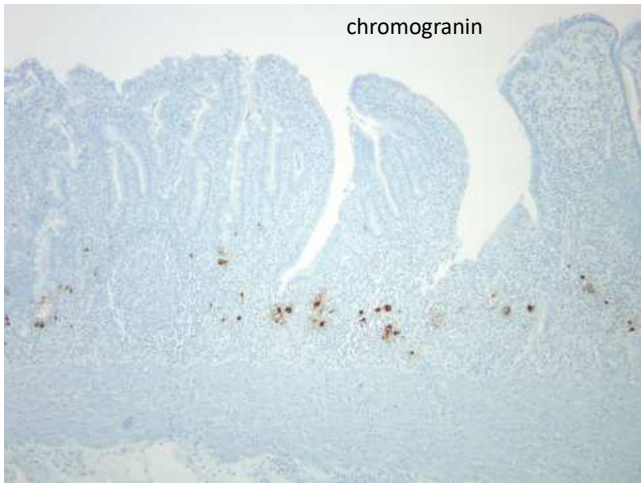
Atrophic autoimmune pangastritis



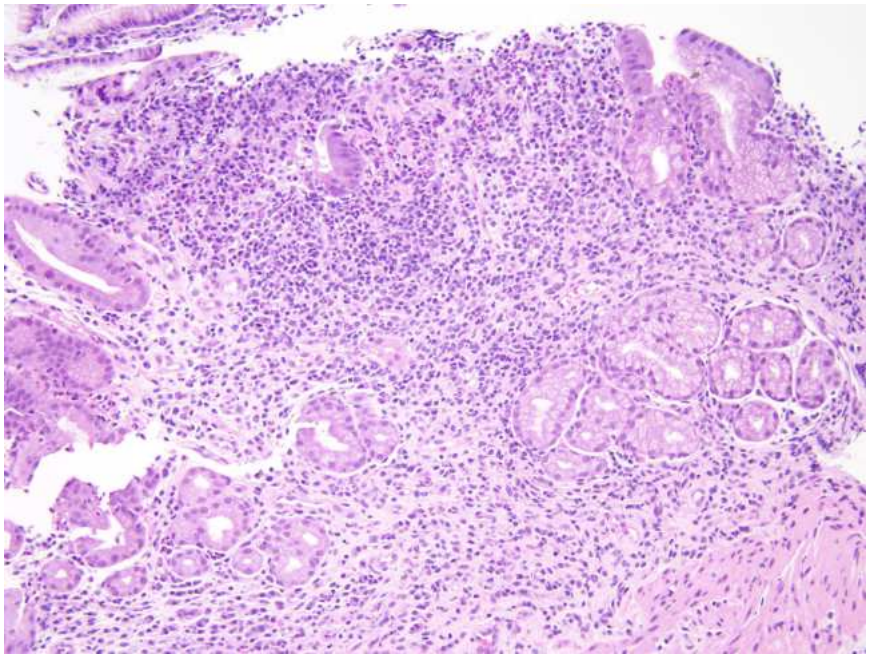
Atrophic autoimmune pangastritis



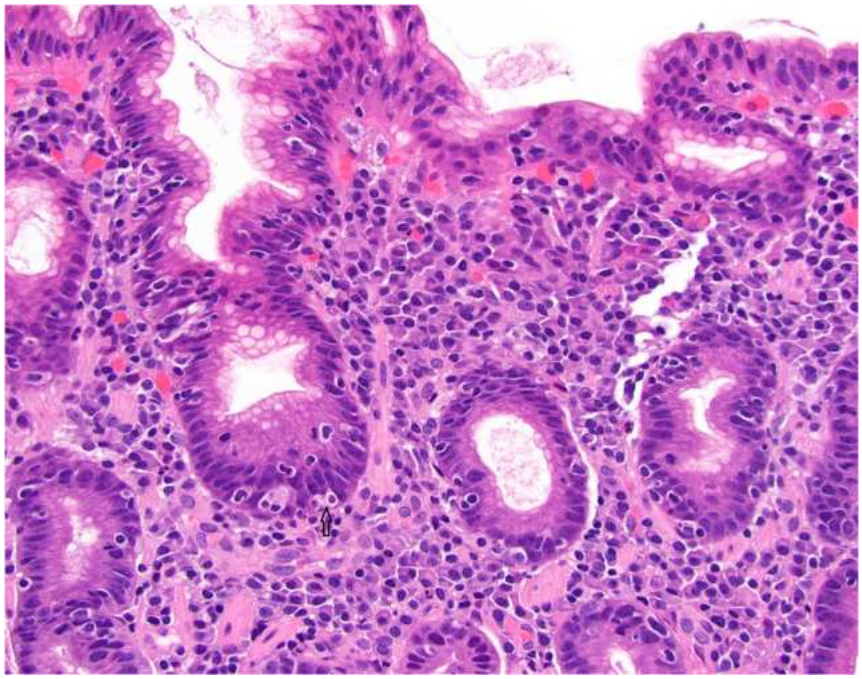




Autoimmune enteropathy



Autoimmune enteropathy



The biopsy with “chronic inflammation”, bottom heavy (antrum ***and*** body)

- Atrophic autoimmune pangastritis and AIE may be histologic manifestations of the same autoimmune disease spectrum
  - Identical histologic features
  - 4/8 patients in the initial description of atrophic autoimmune pangastritis also had autoimmune enterocolitis
- What to do when we encounter this pattern of inflammation????

The biopsy with “chronic inflammation”, bottom heavy (antrum ***and*** body)

- *Chronic active gastritis with severe atrophy and intestinal metaplasia. No H. pylori organisms identified on special stain. See note.*

Note: The process diffusely affects the antrum and body and a chromogranin immunostain demonstrates no ECL cell hyperplasia, arguing against a diagnosis of AMAG. These histologic findings are non-specific but may be seen in the settings of atrophic autoimmune pangastritis and autoimmune enteropathy. These two entities are described separately in the literature but are likely histologic manifestations of the same autoimmune disease spectrum and are managed in a similar fashion.

But don’t forget the great mimicker….

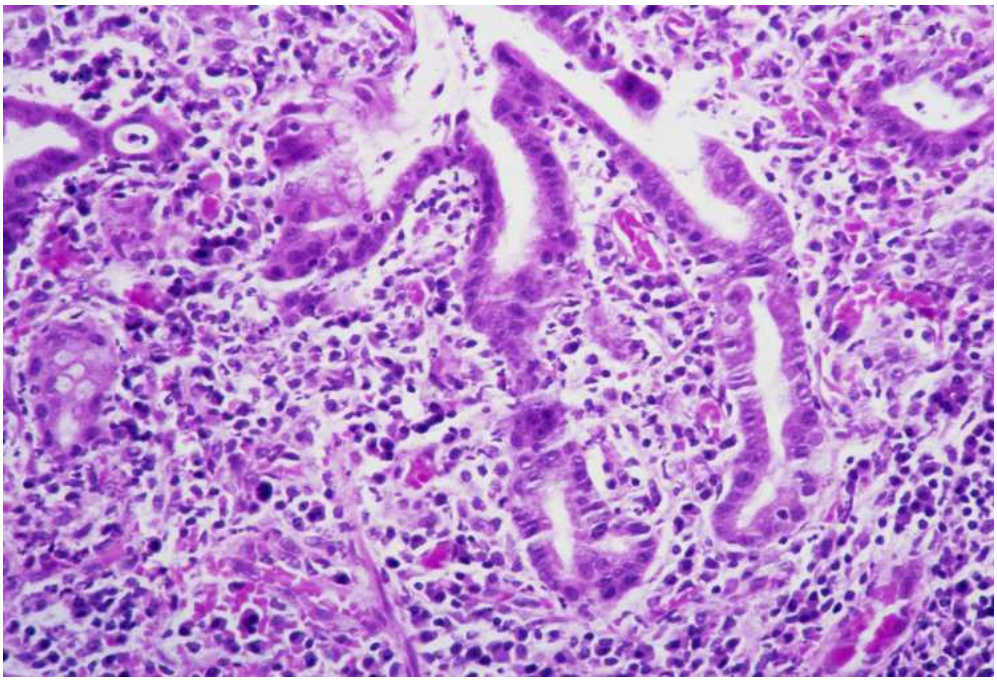
Syphilis

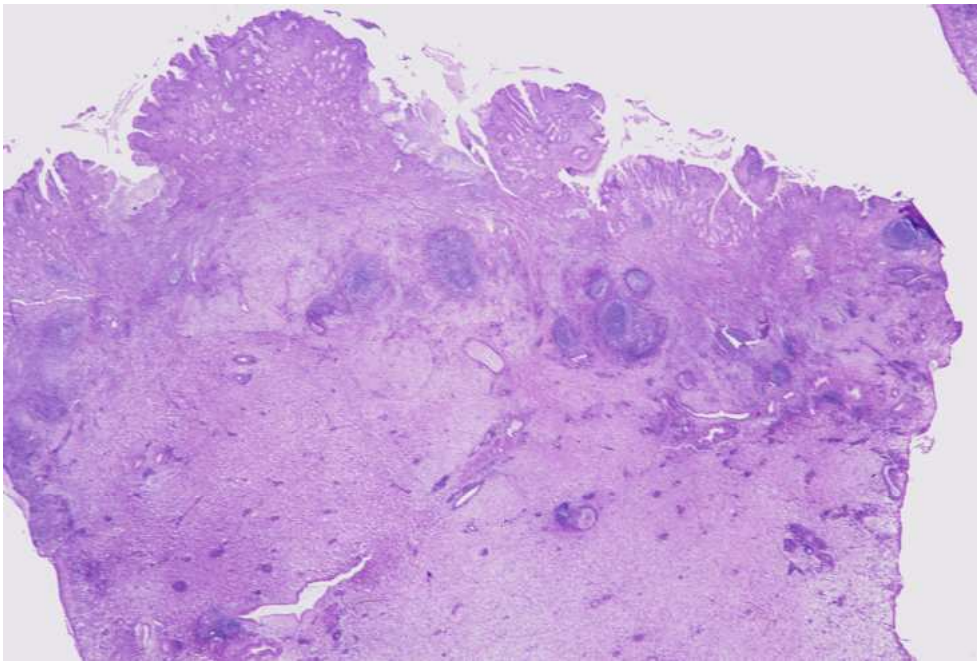
- Typically unsuspected
  - 13% of patients had a previous history of syphilis
- Epigastric pain/fullness, tenderness, upper GI bleed

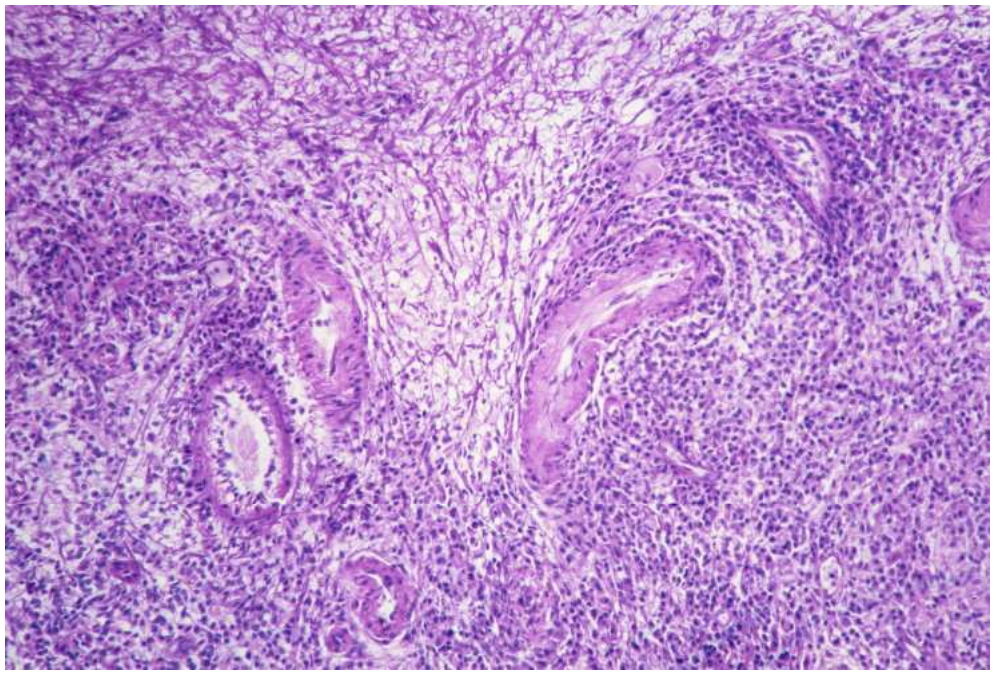
Yee et al. Pathologic features of Infectious Gastritis. Adv Anat Pathol. 2018 Feb 20. [Epub ahead of print]

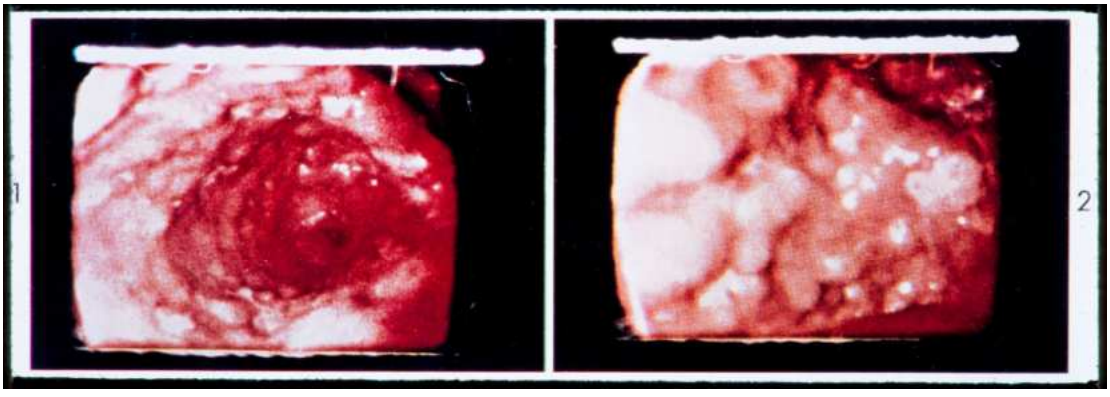
Syphilis gastritis

- Overwhelming inflammation
  - Glandular destruction
  - Crypt abscesses
  - Lymphoid aggregates
  - With or without granulomas
  - Perivascular lymphoplasmacytic cuffing
  - Associated vasculitis
  - Lymphoepithelial-like lesions





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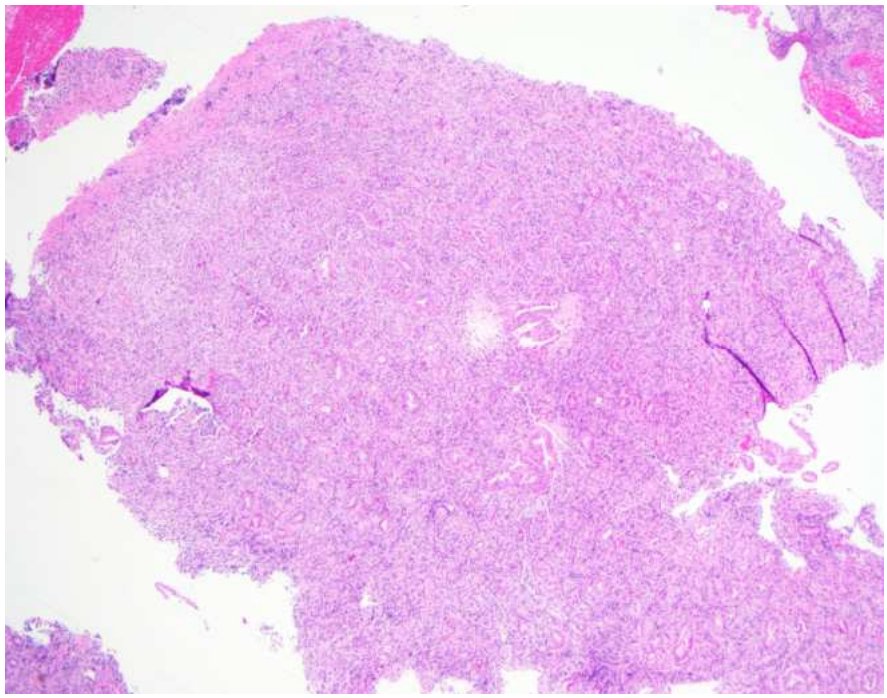
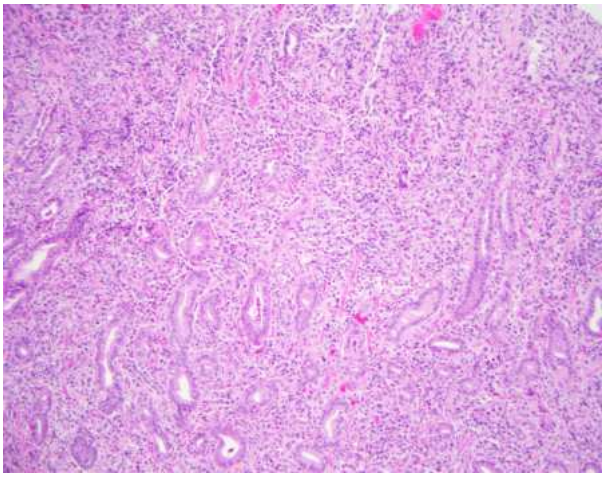
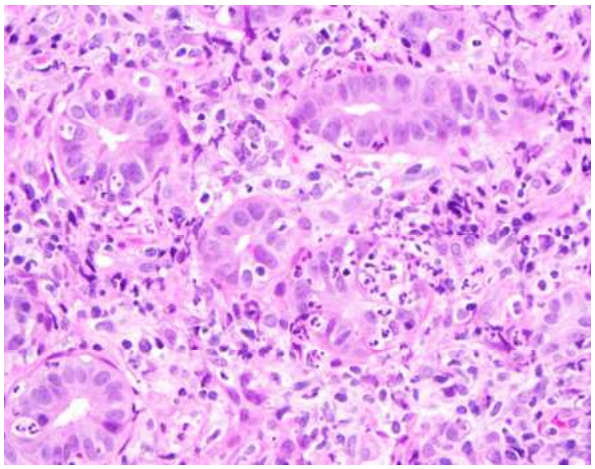
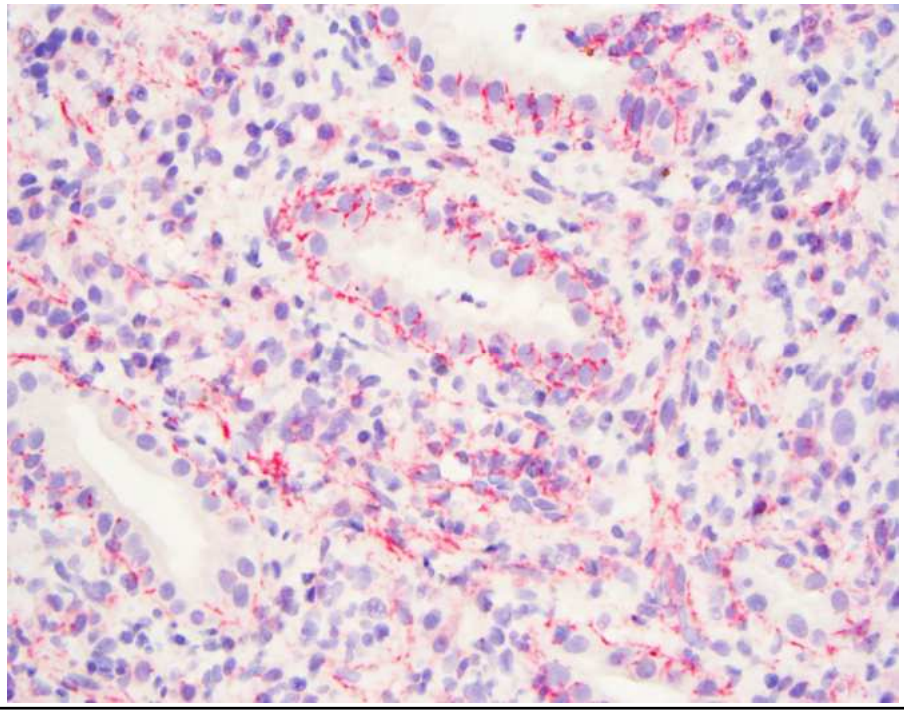
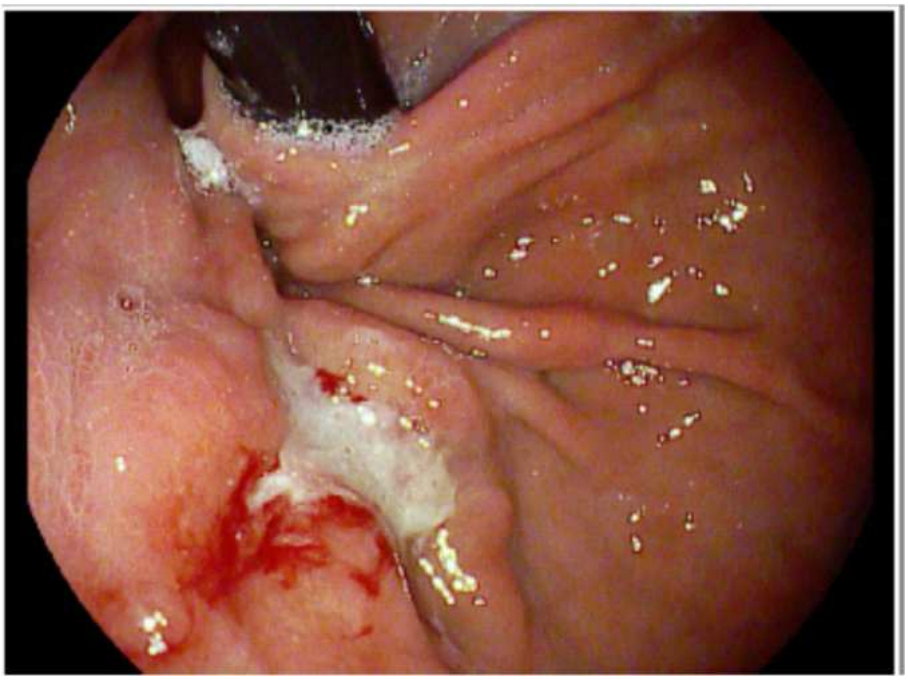










Complications

- Hemorrhage
- Gastric outlet obstruction
- Perforation

Diagnosis: Rests on Laboratory Tests

- Non-treponemal tests
  - Rapid plasma reagin (RPR), Venereal Disease Research Laboratory (VDRL) test, and the toluidine red unheated serum test (TRUST)
  - Reflect the activity of infusion and reported as titers
  - False positives with other inflammatory conditions
- Treponemal tests
  - Fluorescent treponemal antibody absorbed (FTA-ABS) test
  - Implies infection at some point
  - False positives with other inflammatory conditions
- PCR
  - Sensitive and specific
  - $$
  - Not widely available

Drs. Karen Hoover and Ina Park
https://www.cdc.gov/std/syphilis/syphilis-webinar-slides.pdf

The biopsy with chronic active gastritis ***without*** H. pylori

Chronic active gastritis **without** *H. pylori*

- In the setting of infection, organisms may be difficult to find:
  - Antibiotic therapy for unrelated reasons
  - Proton pump inhibitors
    - Migrate deep into the crypts
    - Coccoid or short bacillary forms

Chronic active gastritis without *H. pylori*

- Our practice is to describe the pattern of inflammation and provide a comment to correlate with other laboratory tests for *H. pylori.*
- After this dx, within a 6 month period **33%** of patients get tested by other means.
- **53%** of tested patients have positive *H. pylori* IgG or stool antigen test.
- Crohn patients made up **5%** of the overall study population and these patients had a significantly lower frequency of test positivity.

Robertson et al. The *H. pylori* Gastritis Pattern Without Identifiable Organisms: Correlation With Non-Invasive Laboratory Testing. USCAP 2015. Abstract 739.

Gastric histologic findings in patients with inflammatory bowel disease

- Upper GI involvement seen with UC and CD.
- Focally enhanced pattern
  - Pockets of glandular inflammation in a background of non-inflamed mucosa
  - Lymphocytes, neutrophils, histiocytes
  - +/- granulomas
- Initially reported as a common finding in patients with CD*
- Subsequent studies have found that this is an uncommon finding with low PPV and an association with other disease processes**

*Oberhuber et al. Focally enhanced gastritis: A frequent type of gastritis in patients with Crohn's disease. *Gastroenterology* 1997;112:698–706
**Xin and Greenson. The clinical significance of focally enhanced gastritis. *Am J Surg Pathol* 2004;28:1347–1351.

Gastric histologic findings in patients with inflammatory bowel disease

- This finding may be more specific for CD in the pediatric setting*,**.
- Ushiku *et al**.:
  - Looked at 119 consecutive newly dx IBD
  - FEG seen in 43% (55% CD, 30% UC, *P*=0.0092)
- In pediatric pts with CD, a focally enhanced pattern is associated with
  - Active ileitis
  - Granulomas elsewhere in the GI tract

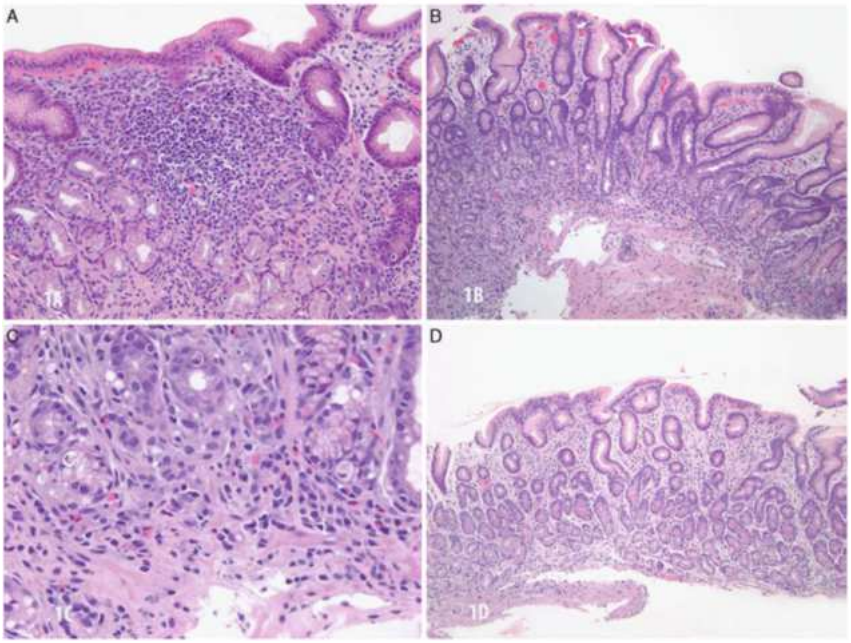
*Ushiku et al. Focally enhanced gastritis in newly diagnosed pediatric inflammatory bowel disease. Am J Surg Pathol 2013;37:1882–1888
**Sharif et al. Focally enhanced gastritis in children with Crohn's disease and ulcerative colitis. The American Journal of Gastroenterology. 2002;97:1415-1420.

Gastric histologic findings in patients with inflammatory bowel disease

- Gastric involvement is less common in UC but may be seen as*:
  - Focal intense gastritis
  - Diffuse superficial pattern rich in plasma cells
  - Patchy basal pattern

*Lin et al. Morphologic findings in upper gastrointestinal biopsies of patients with ulcerative colitis: A controlled study. *Am J Surg Pathol.* 2010;34:1672–1677.

Focal gastritis



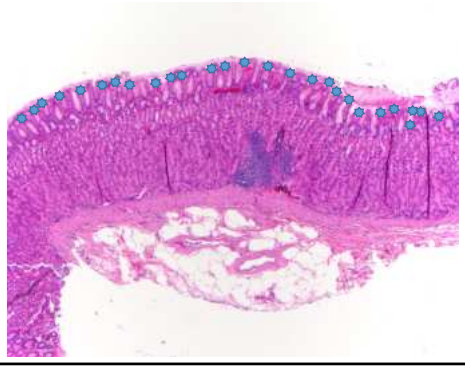
Basal mixed inflammation

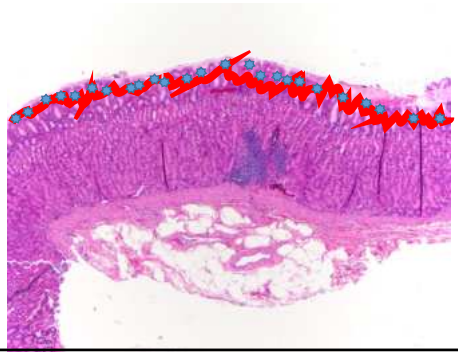
Basal mixed inflammation

Superficial plasmacytosis

*Lin et al. Morphologic findings in upper gastrointestinal biopsies of patients with ulcerative colitis: A controlled study. *Am J Surg Pathol.* 2010;34:1672–1677.

Lymphocytic and collagenous gastritis patterns

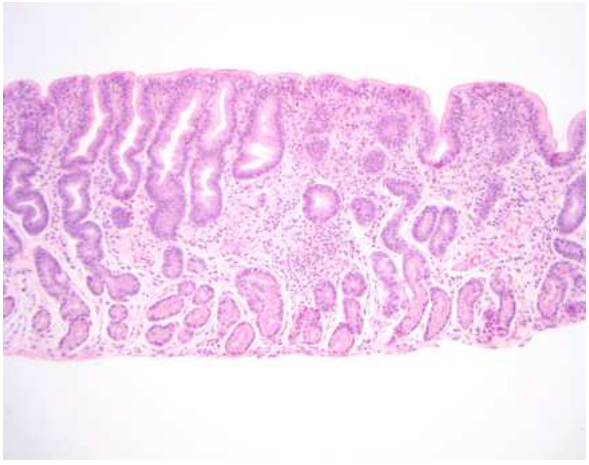


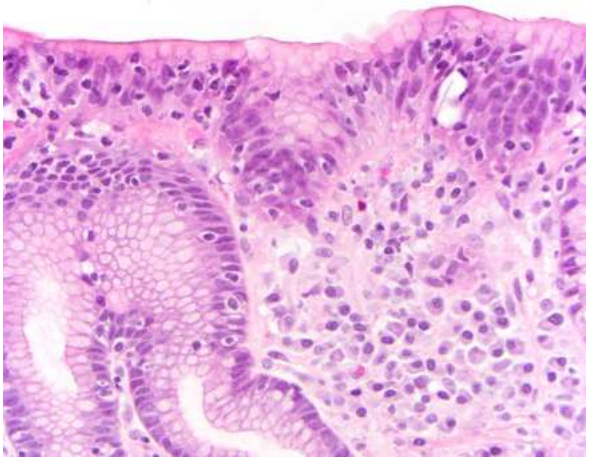


Lymphocytic gastritis pattern

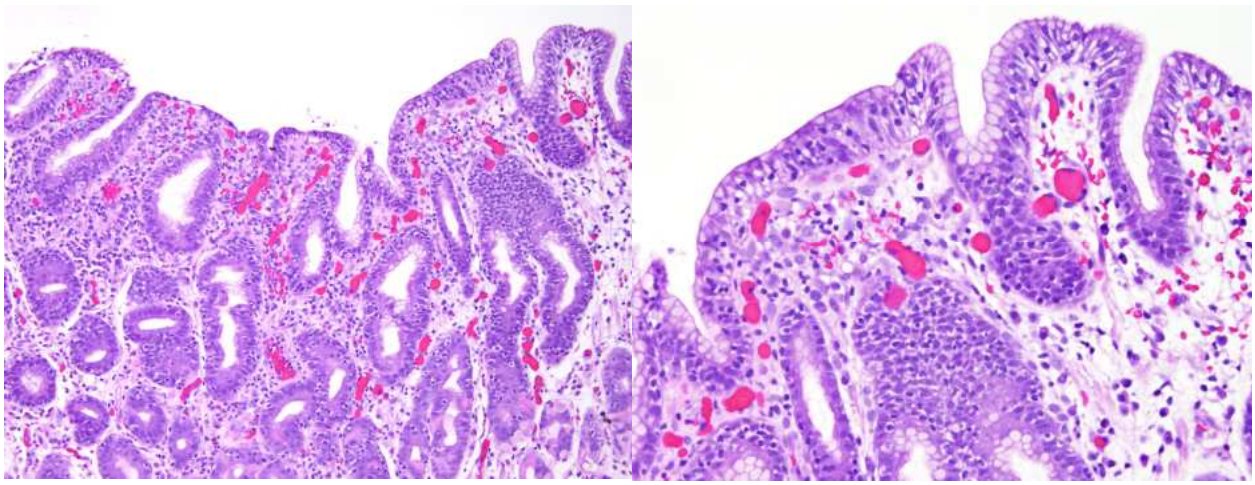
Dr. Maryam Kherad-Pezhouh

- Associated with a variety of etiologies:
  - *H. pylori*
    - 25%
    - Usually (though not always) accompanied by intra-epithelial or lamina propria neutrophils
    - Organisms may be few and far between
  - Celiac disease, 27%
  - Malignancy (adenoca or lymphoma), 7%
  - Crohn disease, 6%
  - Medications, 32%
    - NSAIDS, angiotensin II receptor antagonists, selective serotonin reuptake inhibitors, levothyroxine, statins, and certain proton pump inhibitors.





Lymphocytic gastritis



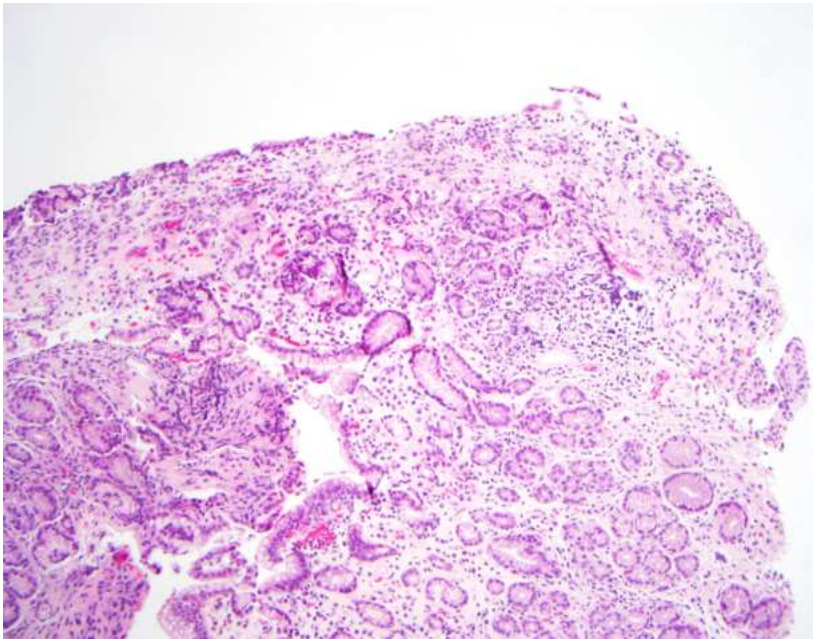
Collagenous gastritis pattern

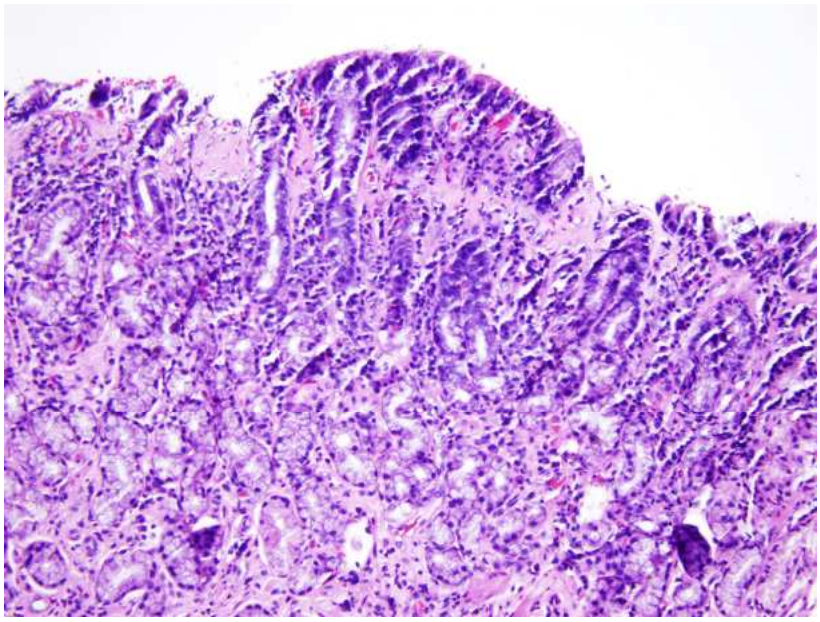
- Rare
- May be seen in children/young adults
  - Female predominance in adults
  - Equal sex distribution in children
- Associated systemic autoimmune conditions (14-20%)
- Anemia, epigastric/abdominal pain, n/v, diarrhea, rarely asymptomatic
- Endoscopy: atrophy or nodules

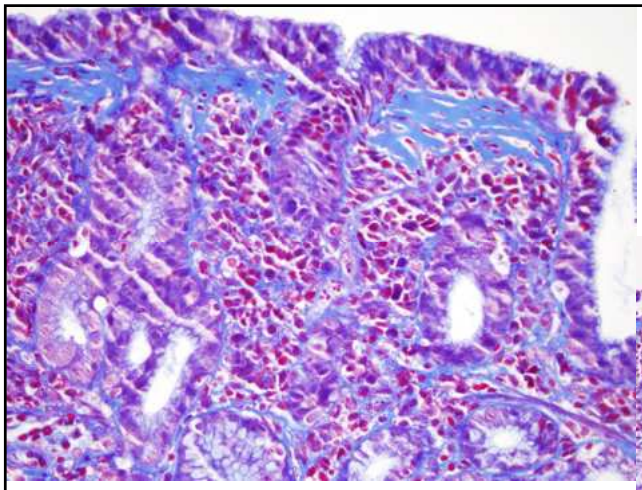
Collagenous gastritis pattern

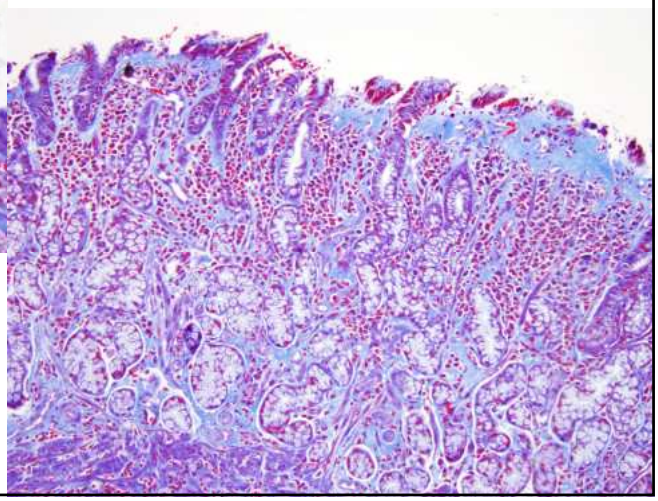
- Thick, irregular subepithelial surface collagen deposition that entraps inflammatory cells with or without
  - Prominent associated eosinophils
  - Atrophy of the body mucosa
  - Prominent intraepithelial lymphocytes
- Surface epithelial injury
  - Epithelial flattening and detachment

Arnason T, Brown IS, Goldsmith JD, Anderson W, O'Brien BH, Wilson C, et al. Collagenous gastritis: a morphologic and immunohistochemical study of 40 patients. *Modern pathology*. 2015;28(4):533-44.
Ma C, Park JY, Montgomery EA, Arnold CA, McDonald OG, Liu TC, et al. A Comparative Clinicopathologic Study of Collagenous Gastritis in Children and Adults: The Same Disorder With Associated Immune-mediated Diseases. *The American journal of surgical pathology*. 2015;39(6):802-12.









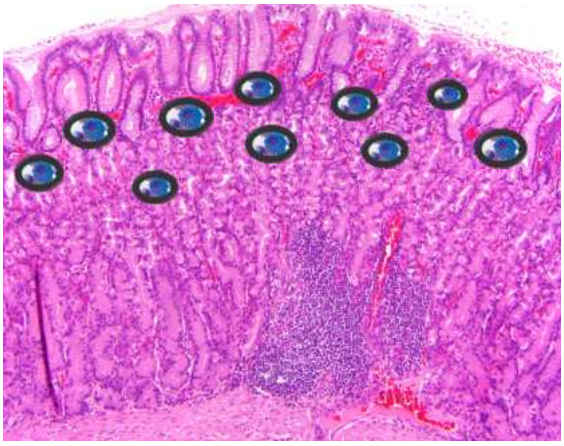
Collagenous gastritis

- Management is difficult
  - Gluten free diet
  - Budesonide
  - Carafate
  - Steroids
- Olmesartan associated injury may show a lymphocytic or collagenous pattern of injury

- ***Collagenous/lymphocytic gastritis pattern. See note.***

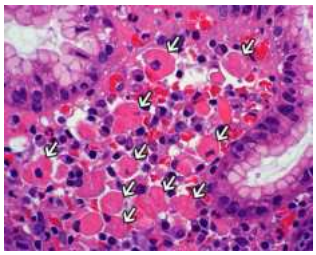
Note: This pattern of inflammation may be idiopathic or may be associated the use of certain medications (e.g. NSAIDs, certain proton pump inhibitors [lansoprazole, omeprazole], olmesartan). The possibility of medication associated injury should be explored prior to attempting immunosuppressive therapy since patients usually improve after removal of the offending agent.

The biopsy with prominent Mott cells



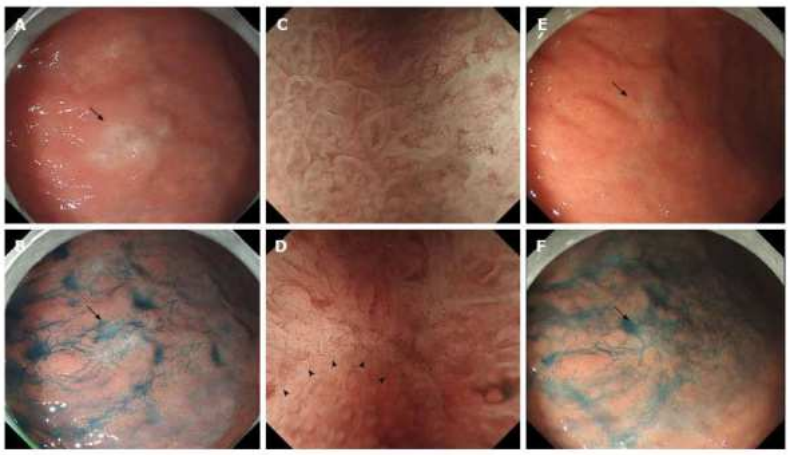
Russell body gastritis

- Benign and typically incidental
- Mucosal accumulation of plasma cells with intracytoplasmic, eosinophilic globules (a.k.a. Mott cells) composed of immunoglobulins (Russell bodies)
- Chronic inflammation
- *H. pylori* infection is a common though not universal association
- Significance:
  - Do not confuse with signet ring cell gastric carcinoma

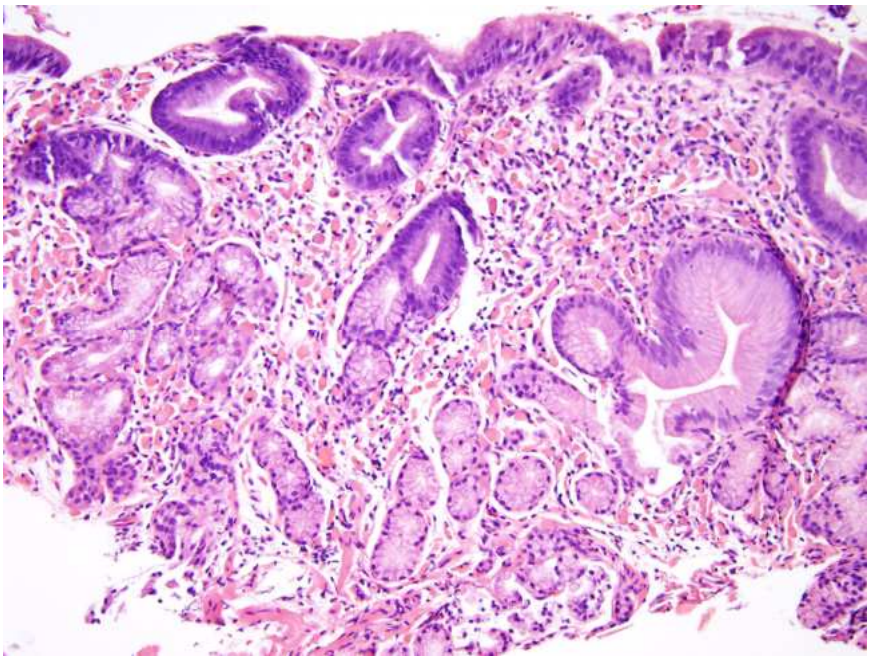


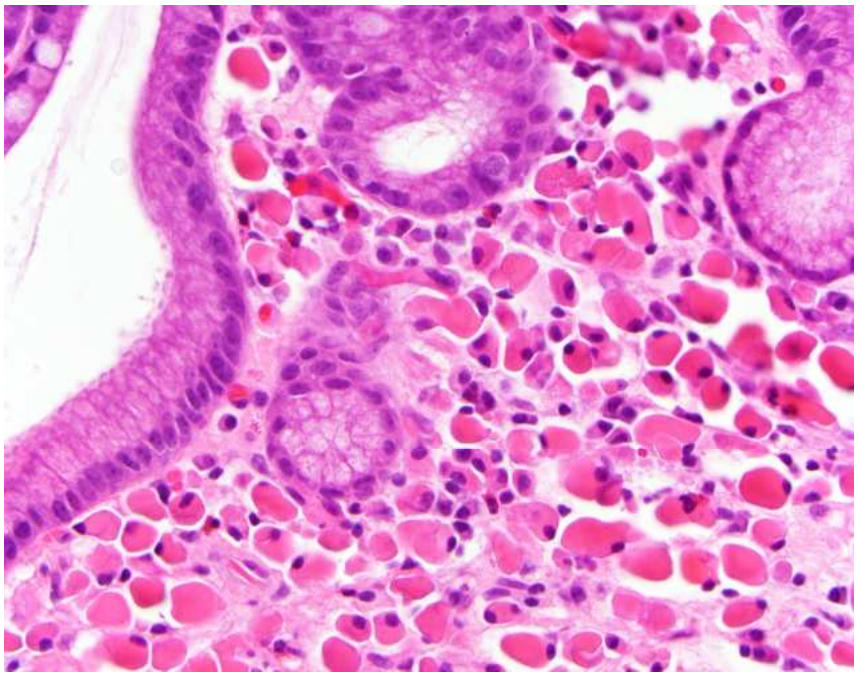
http://niigata-cp.org/?page_id=1342

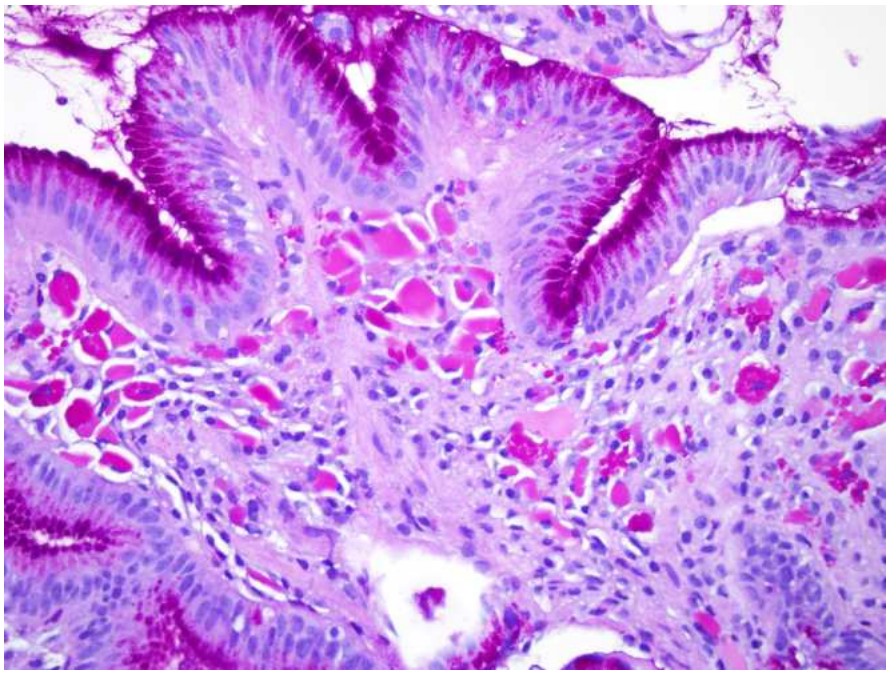
Russell body gastritis



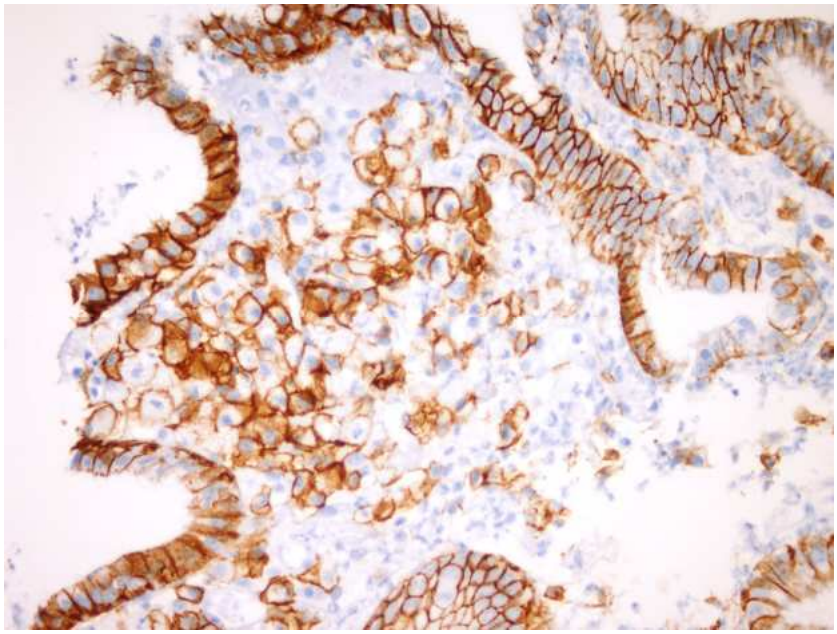
Yorita K, Iwasaki T, Uchita K, Kuroda N, Kojima K, Iwamura S, Tsutsumi Y, Ohno A, Kataoka H. Russell body gastritis with Dutcher bodies evaluated using magnification endoscopy. World J Gastrointest Endosc 2017; 9(8): 417-424







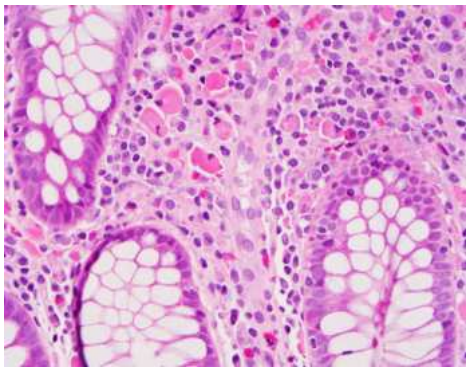
CD138 +
CD79a +
CK-
Kappa and lambda IHC not useful[+]

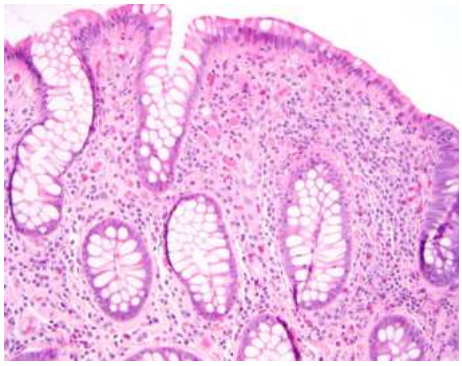


[+]Zhang H, Jin Z, Cui R. Russell body gastritis/duodenitis: a case series and description of immunoglobulin light chain restriction. Clinics and research in hepatology and gastroenterology. 2014;38(5):e89-97.

Russell body gastritis

- Russell body "esophagogastroenteritis"?
  - Esophagus
  - Small bowel
  - Colon





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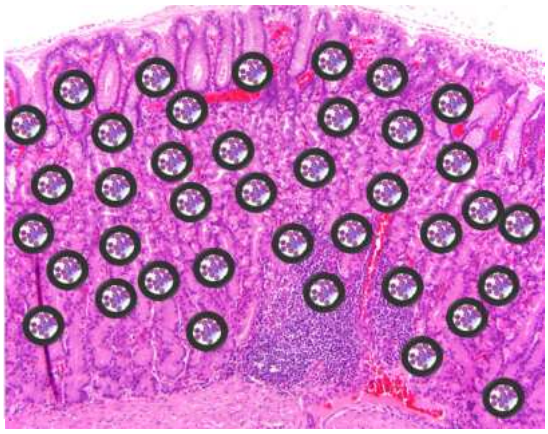
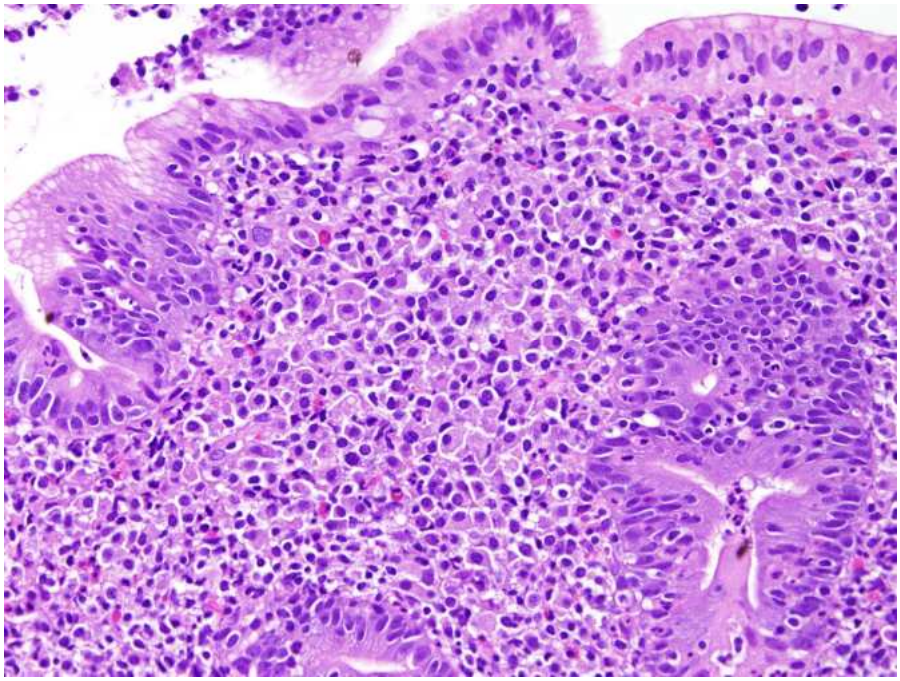
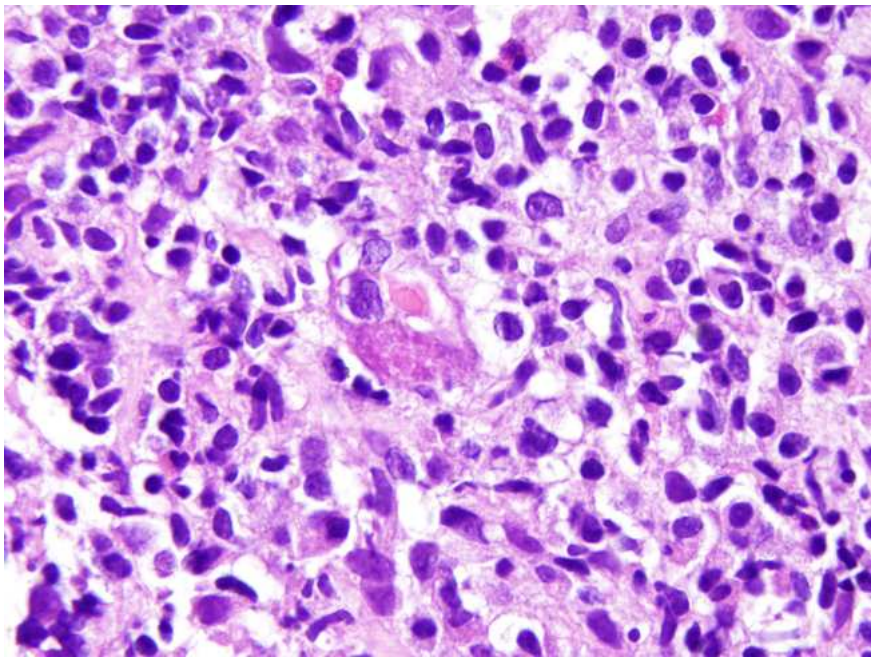
The biopsy with a prominent monocytic reaction

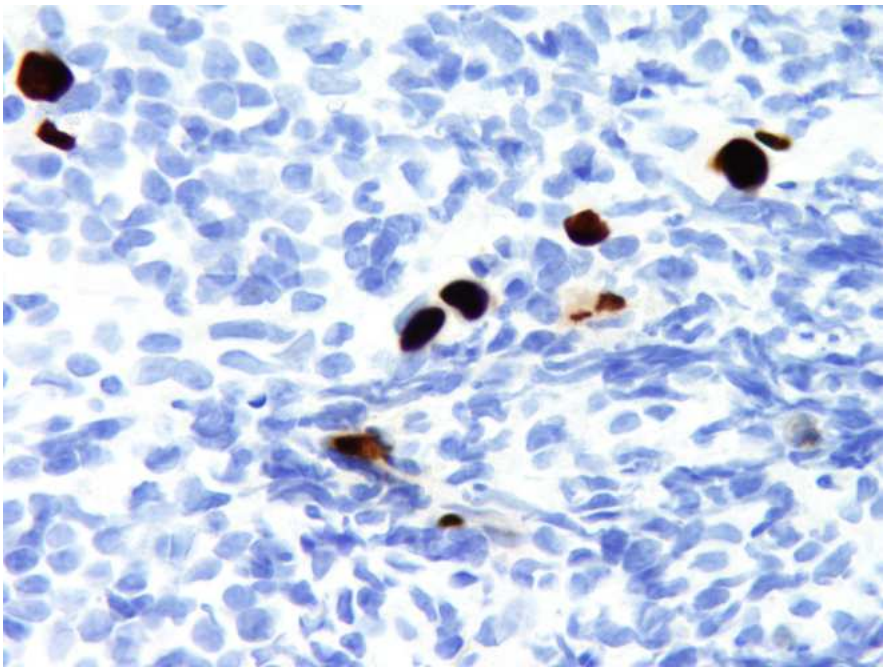


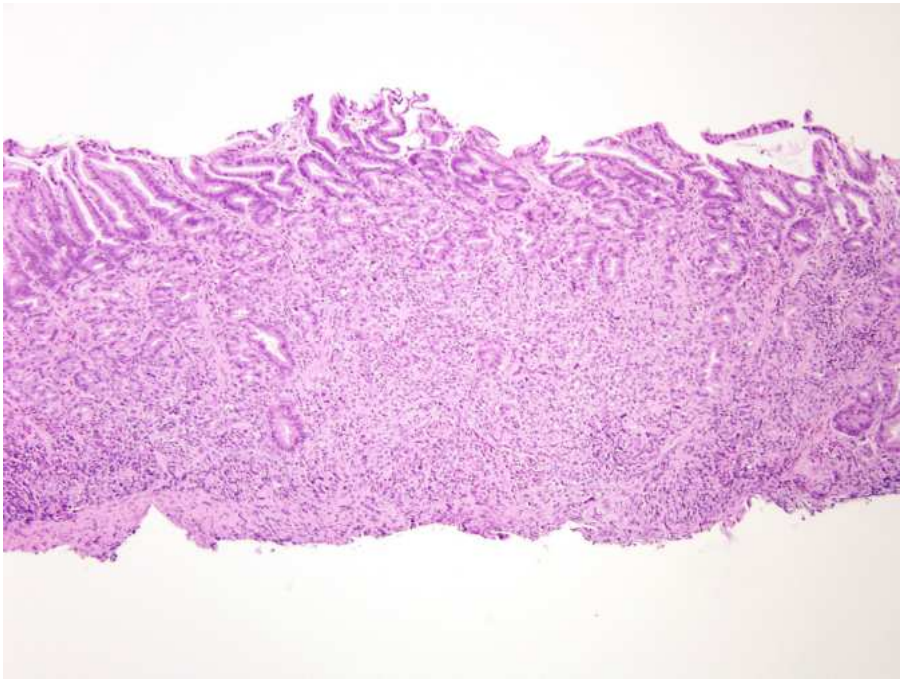
CMV and EBV gastritis

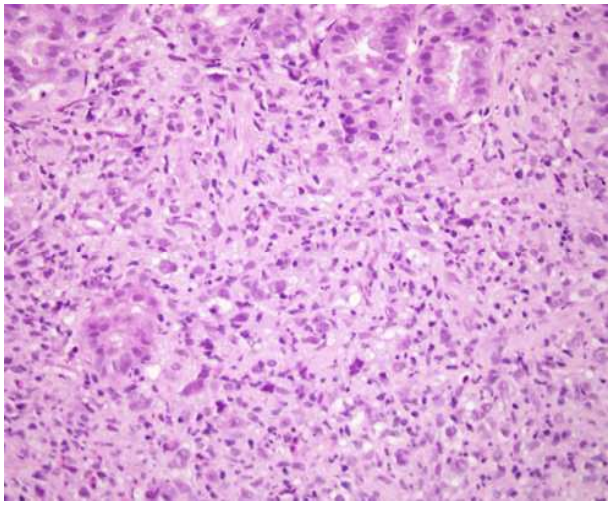
- Both may provoke a brisk monocytic response
- May simulate lymphoma

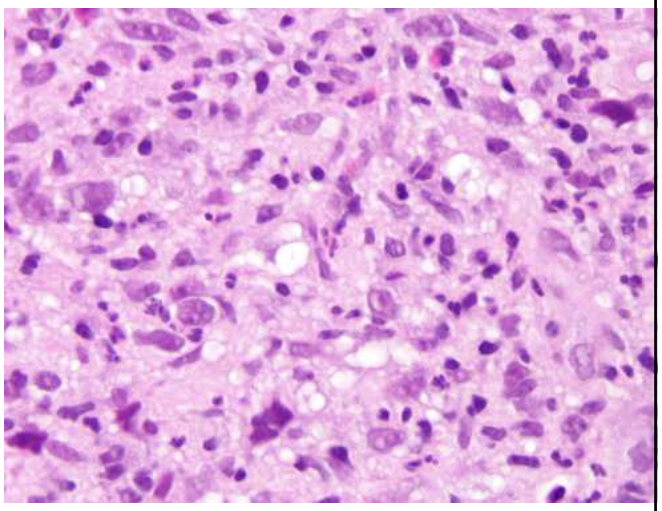


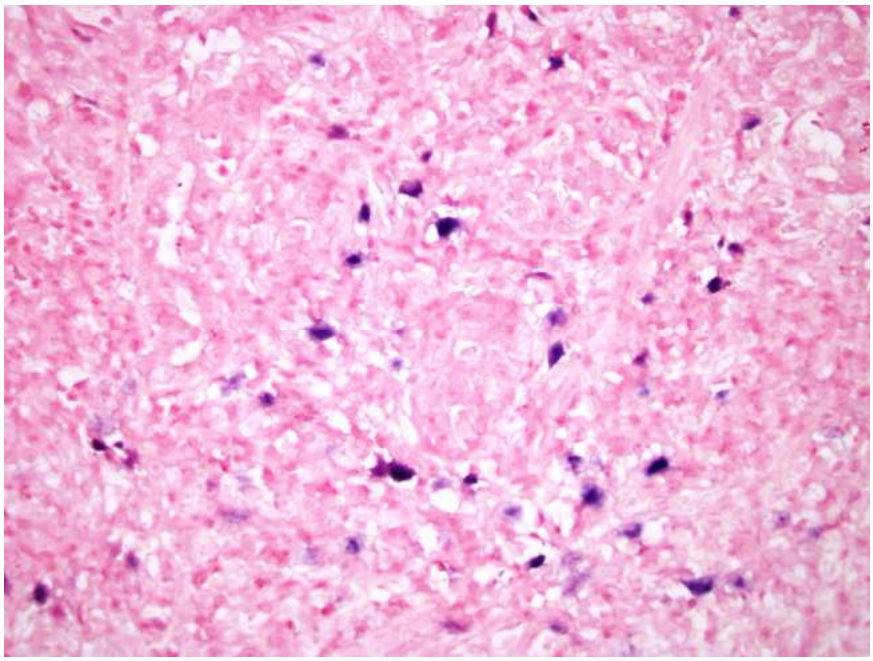












EBER

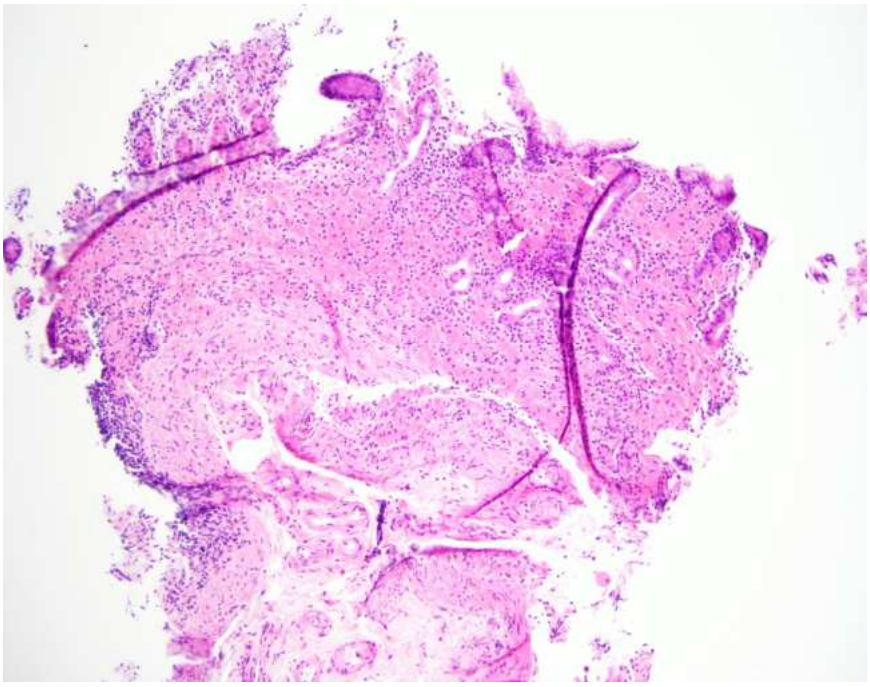
Take home message

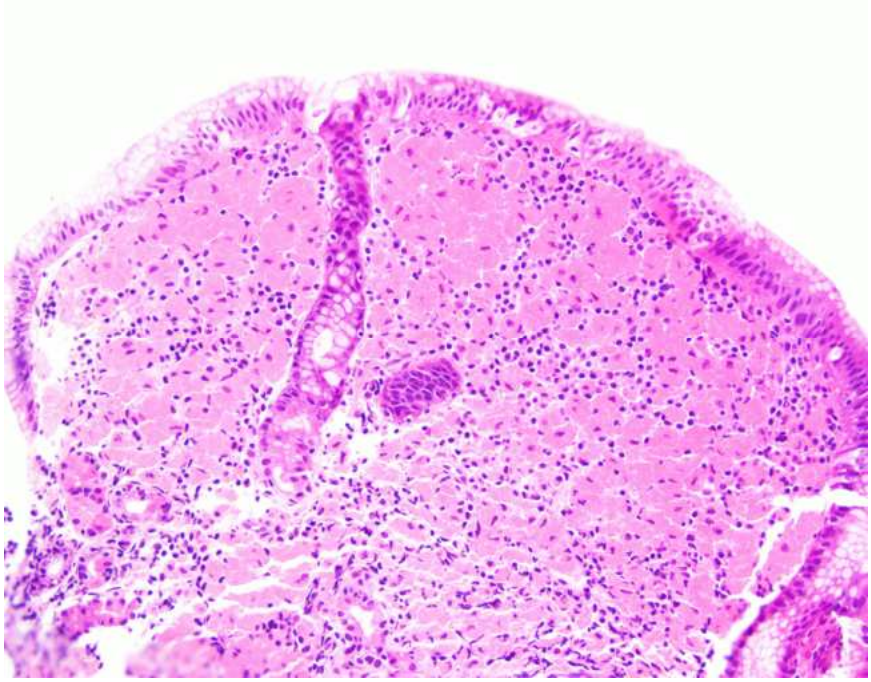
When entertaining a diagnosis of large cell lymphoma in the setting of an active inflammatory backdrop, it is worthwhile to add EBV and CMV ancillary studies.

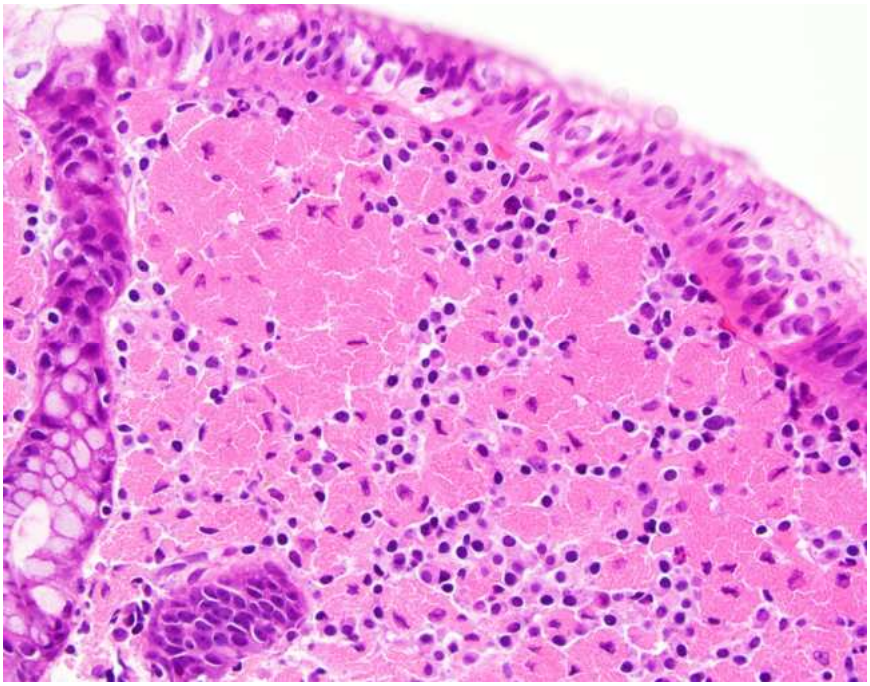
Case presentation

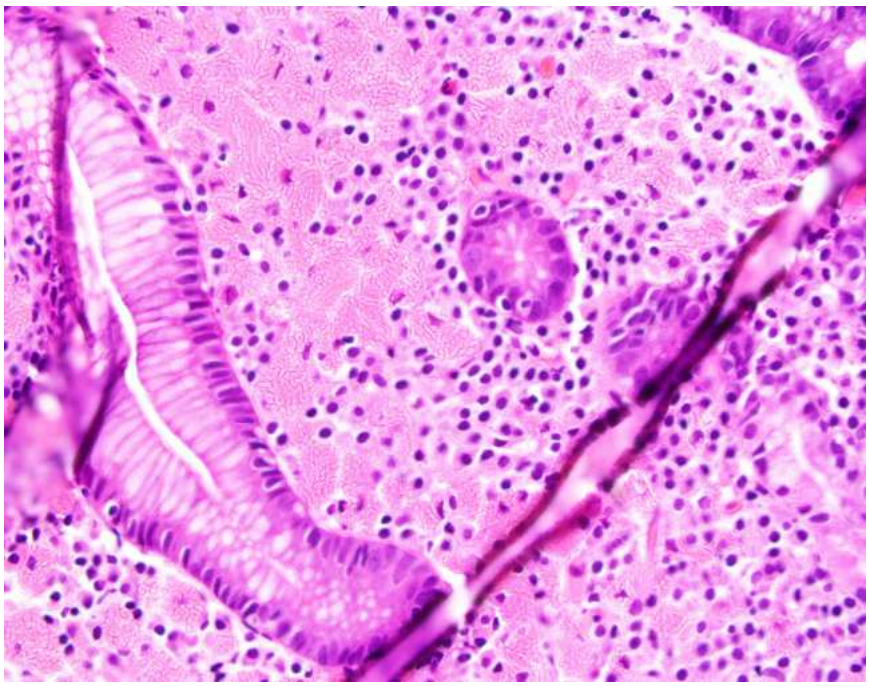
Case 1

- 80 y/o female
- Dysphagia
- Granular mucosa in fundus





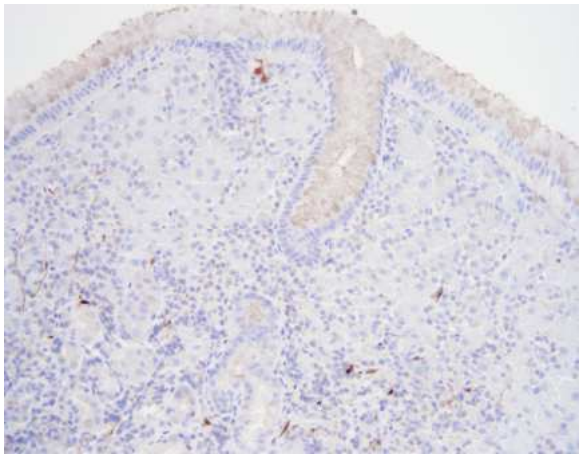




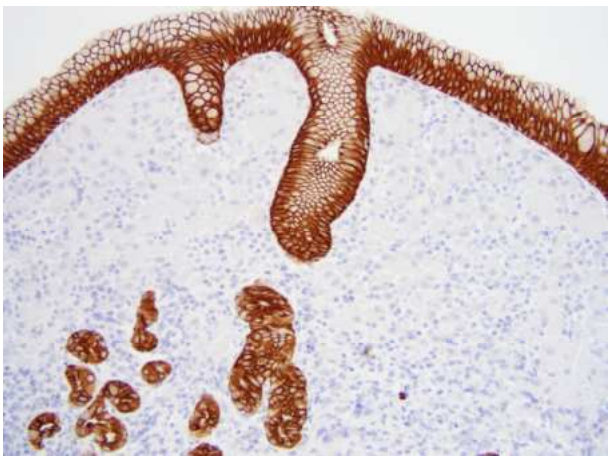
DDX

- Russell body gastritis
- Xanthoma
- Granular cell tumor
- Diffuse-type adenocarcinoma

S100



AE1/3



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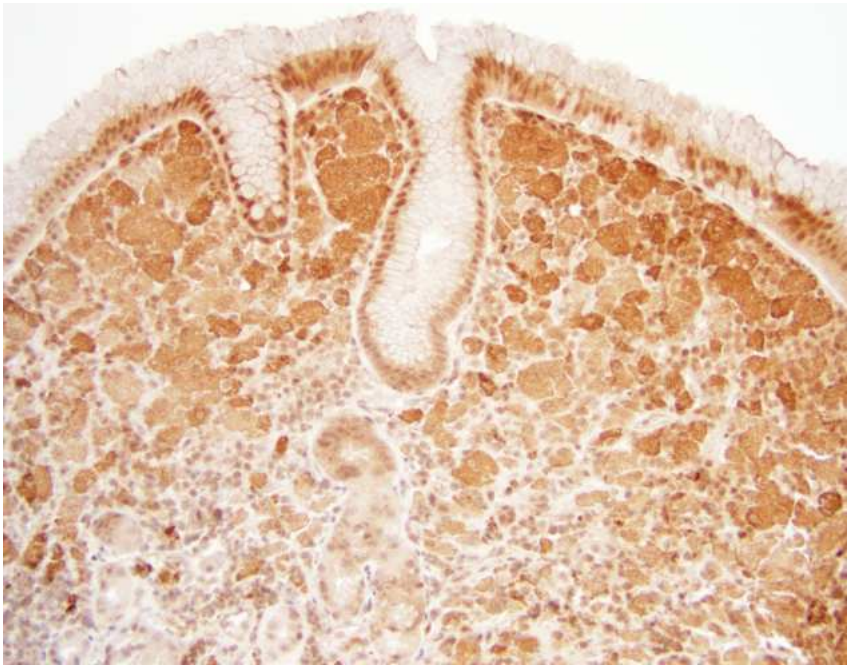
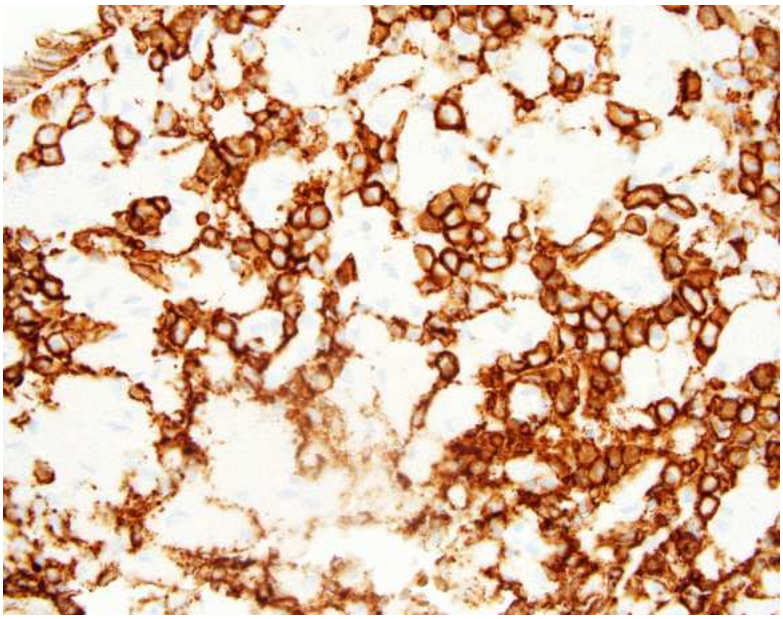


CD138



Crystal-storing Histiocytosis in the Stomach

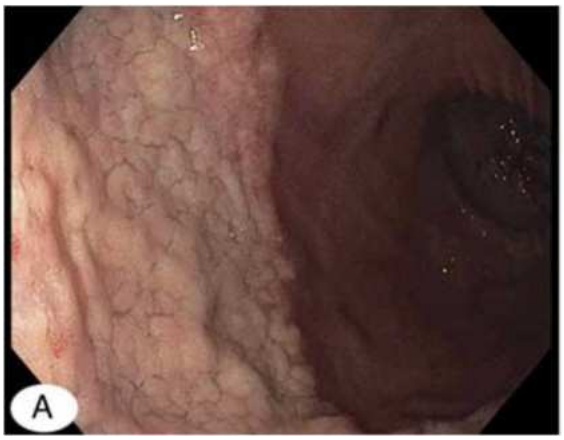
A Clue to Subtle Hematolymphoid Malignancies

Christina A. Arnold, MD, Wendy L. Frankel, MD,* Ling Guo, MD, PhD,* Chandra Krishnan, MD,† Sheryl Pfeil, MD,‡ Melinda Schumacher, MD,* Lysandra Voltaggio, MD,§ Martha M. Yearsley, MD,* and Wei Chen, MD, PhD**

Am J Surg Pathol 2018;42:1317–1324

CSH

- Nodularity, white discoloration, mass

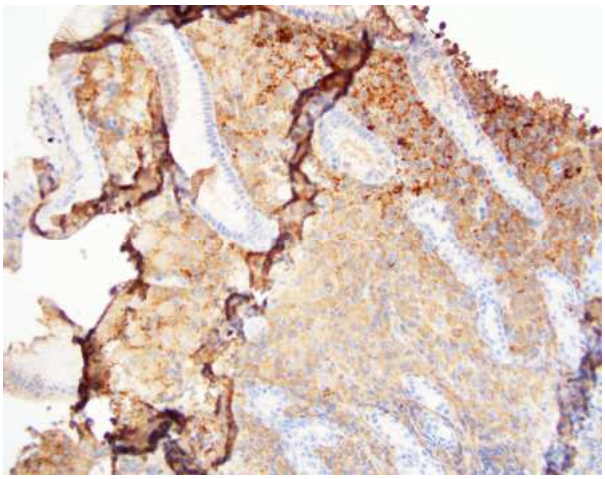


Arnold et al. Am J Surg Pathol 2018;42:1317–1324

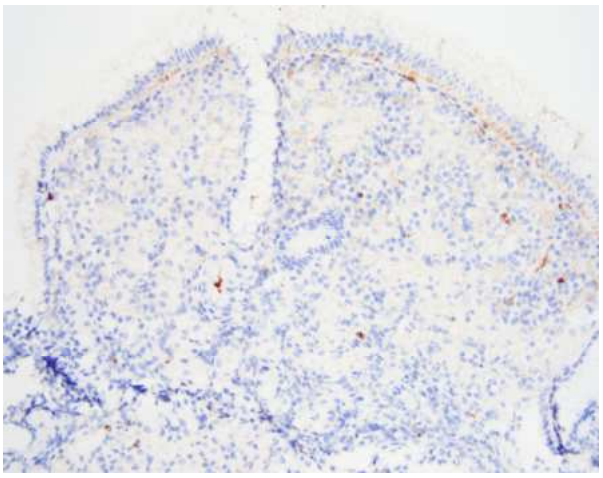
CSH

- Lymphohistiocytic infiltrate expanding lamina propria
  - Macrophages with abundant eosinophilic cytoplasm containing non-refractile, non-polarizable, fibrillary cytoplasmic inclusions
    - Intralysosomal monoclonal immunoglobulin light chains
- Associated with Kappa-restricted lymphoma (rarely lambda-restricted)
- May be misdiagnosed as xanthoma
- May be so florid as to obscure the lymphoma

Kappa



Lambda



Crystal storing histiocytosis with kappa restriction has been reported in association with monoclonal gammopathy, multiple myeloma, and low-grade B-cell lymphoma. Clinical correlation is needed to evaluate for the presence of any of these conditions.

References:
1. Arnold et al. Crystal-storing Histiocytosis in the Stomach: A Clue to Subtle Hematolymphoid Malignancies.Am J Surg Pathol. 2018 Oct;42(10):1317-1324. doi: 10.1097/PAS.0000000000001097.
2. Jones et al. Crystal-storing histiocytosis: a disorder occurring in plasmacytic tumors expressing immunoglobulin kappa light chain. Hum Pathol. 1999. Dec;30(12):1441-8.
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TABLE 1. Crystal-Storing Histiocytosis: Summary of Clinical and Pathological Features

Case	A/S	Presenting Symptom(s)	Dx	Ig Type (IHC)	Paraprotein (g/dL)	Sites of Deposition	Clinical Course
1.	48/M	Paraproteinemia	MM	IgAκ	S = 4.5/IgAκ	BM	Recur S/P BMT
2.	53/M	Bone pain, anemia	MM	IgAκ	S	BM	Lost to follow-up
3.	50/M	Bone pain	MM	IgGκ	S = 0.2	BM, skull, LN	BMT DOD at 10 mos
4.	77/F	Anemia Renal failure	MM	κ only	S	BM	Recur S/P CTX
5.	66/M	Bone pain Hypercalcemia	MGUS	IgAκ	S = 1.0/IgAκ	BM	Recur S/P BMT
6.	66/M	Splenomegaly Cold agglutinin	LPL	IgMκ	S = 0.04/biclonal U = 2.0/biclonal	BM, spleen (3860g)	DOD at 8 mos
7.	68/F	Nausea/hyponatremia Renal failure Hypercalcemia systemic amyloid	LPL	IgMκ	S = 4.0/triclonal IgM − > Gκ, two κ U = κ	LN	Persistent S/P CTX (cyclophosphamide)
8.	53/F	Hyerviscosity	LPL	IgMκ	S = 3.6/IgMκ +/−biclonal κ	BM	Persistent S/P CTX (2-CDA, CVP, Rx)
9.	70/M	Splenomegaly	LPL	IgMκ	Nd	BM, LN	Transformed to LCL at 24 mos
10.	70/M	Abdominal pain Splenomegaly	LPL	IgMλ	S = 4.5/biclonal	LN, BM spleen	CTX (C-MOP, ara-C) DOD at 4 mos
11.	35/F	Gastric pain Hyperviscosity	CSH	IgA > IgG, κ > λ	S = 4.7/IgGλ Polyclonal IgA	Stomach,	Polyclonal CSH Persistent S/P CTX
			LPL	IgGλ		Thymus, BM	(Chlor/Flud)
12.	54/F	Incidental	PCG	polyclonal	Nd	Lung	Surgery only Recurred at 10 yr

Abbreviations: MM, multiple myeloma; LPL, lymphoplasmacytic lymphoma; PCG, plasma cell granuloma; S, serum M-spike; U, urine M-spike; BM, bone marrow; LN, lymph node; (a)BMT, (autologous) bone marrow transplant; DOD, died of disease; LCL, large cell lymphoma; CTX, chemotherapy; Chlor, chlorambucil; Flud, fludarabine; ND, not done; CVP, cyclophosphamide/vincristine/prednisone; Rx, Rituxan (anti-CD20 antibody).

1442

Jones et al. Crystal-storing histiocytosis: a disorder occurring in plasmacytic tumors expressing immunoglobulin kappa light chain. Hum Pathol. 1999. Dec;30(12):1441-8.

Patterns we discussed

- The biopsy with prominent eosinophils
- The biopsy with "chronic inflammation"
  - "Top heavy"
  - "Bottom heavy"
    - Body
    - Antrum *and* body
- The biopsy with chronic active inflammation **without** *H. pylori*
- The biopsy with lymphocytic and collagenous gastritis patterns
- The biopsy with prominent Mott cells
- The biopsy with a prominent monocytic reaction
- BUT!.....

Patterns are just patterns

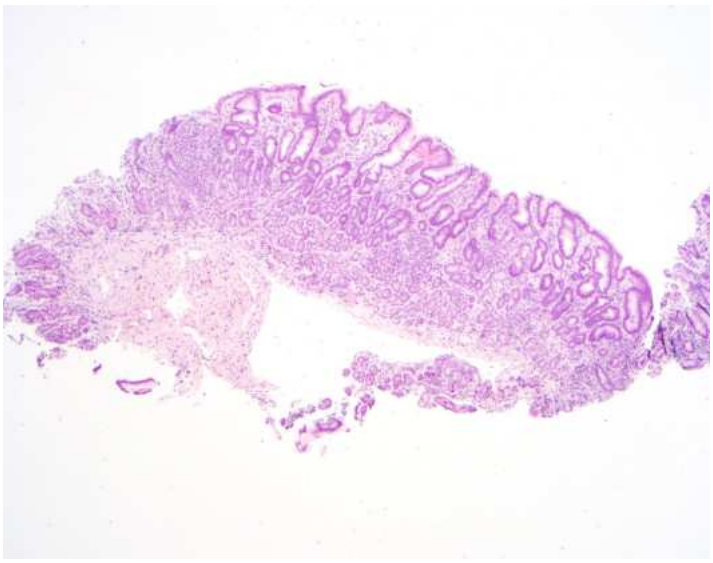
- Very little help when identified and reported in isolation.

- Chart review/conversation with the clinician is always helpful to:
  - Correlate a familiar pattern with a pertinent piece of clinical information
  - Identify new patterns and their associations

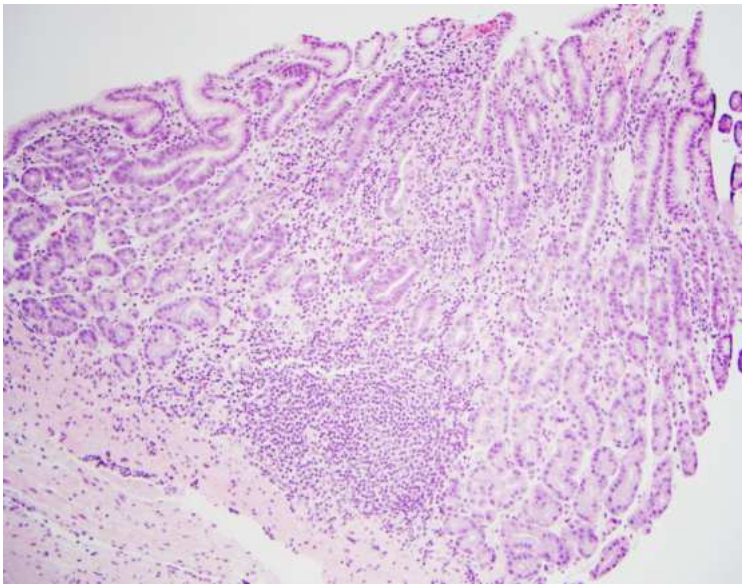
Case 1

- 13 y/o male with intermittent mouth sores, “gas build-up”.
- Fever
- Night sweats
- Anemia, hypoproteinemia, iron deficiency
- “Falling off the growth chart” for weight
- Daily bowel movements. Non mucous, non bloody. No diarrhea.

Case 1



Case 1



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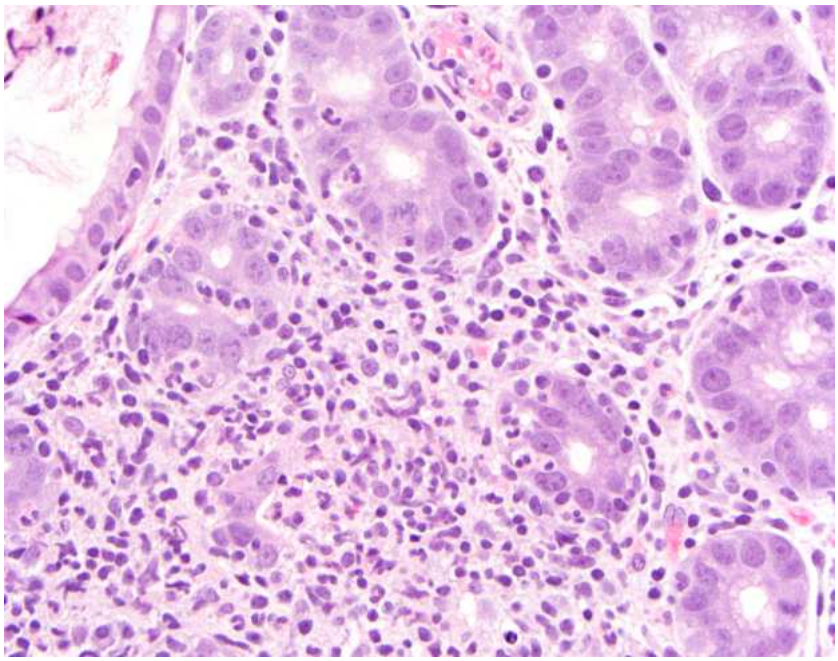

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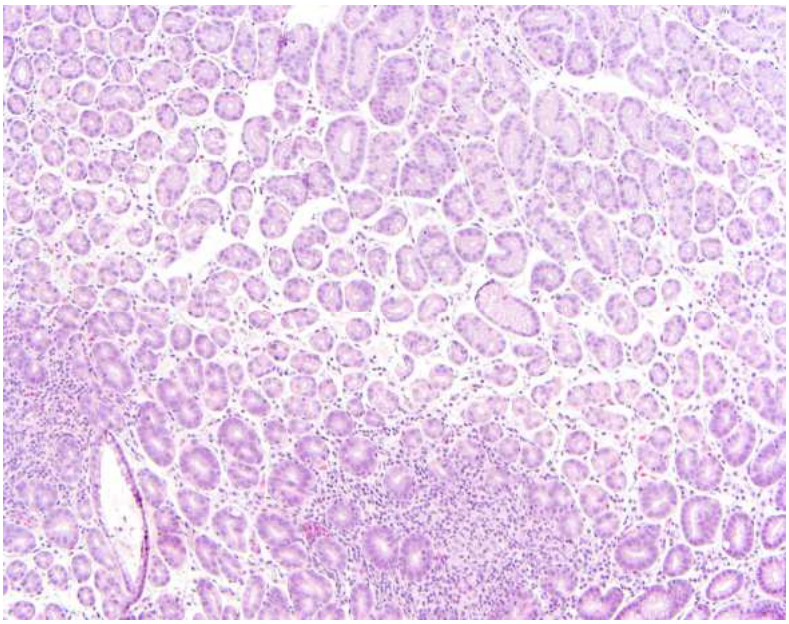

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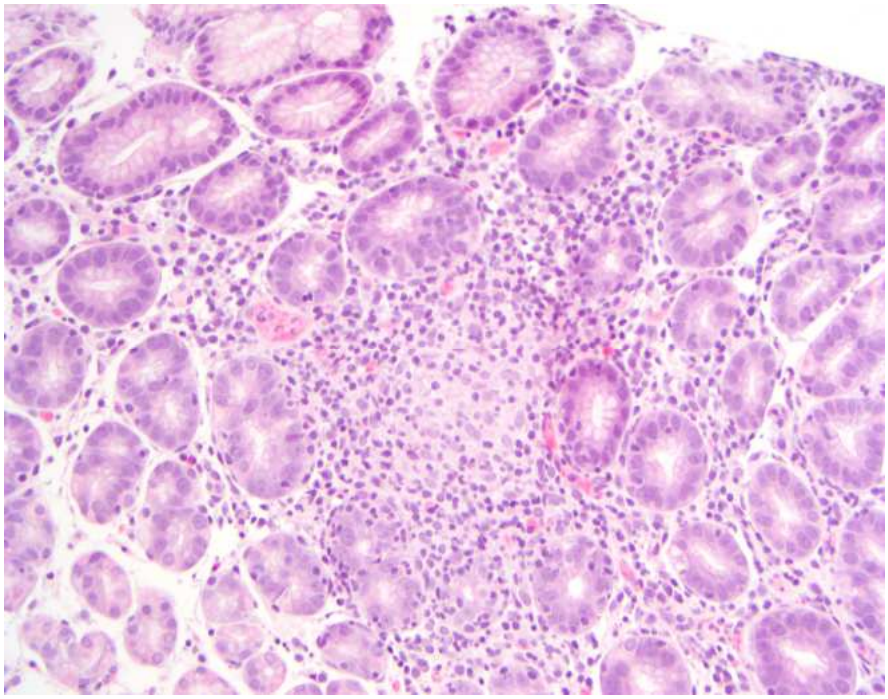
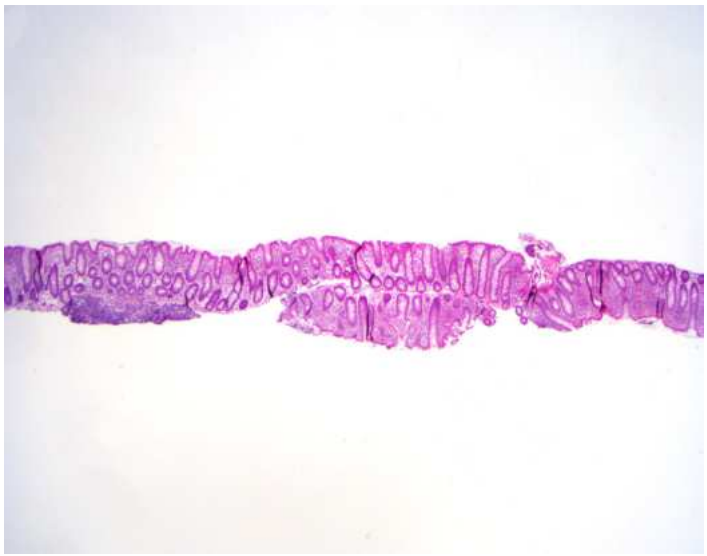


No *H.pylori* on immunostain

Case 1 Descending colon



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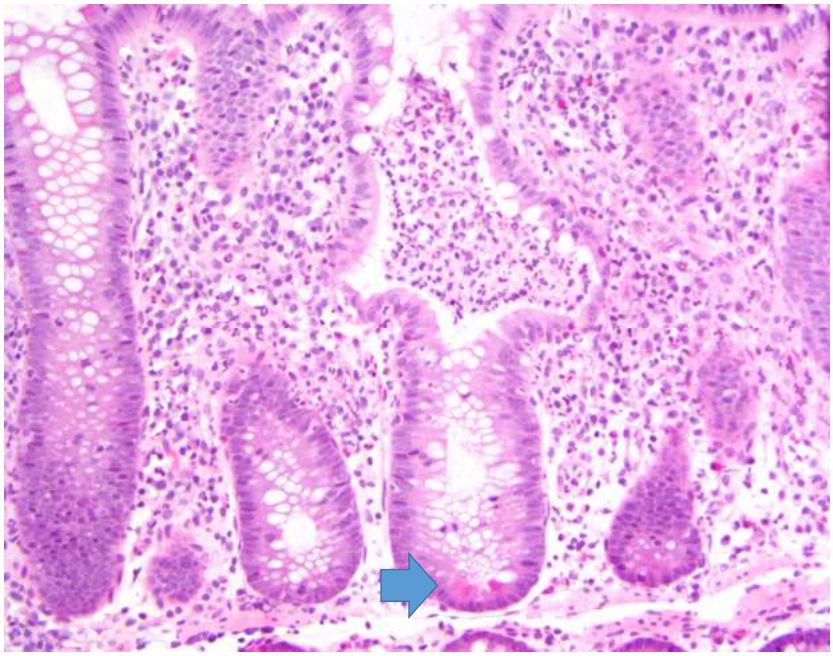

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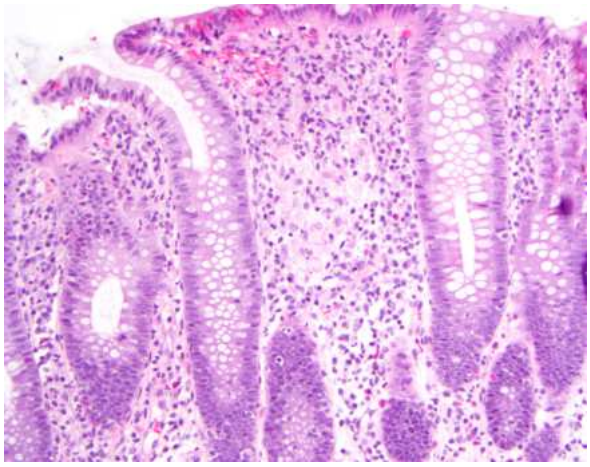
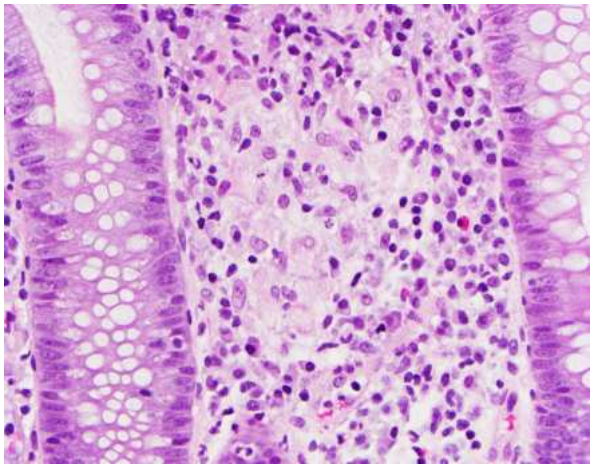
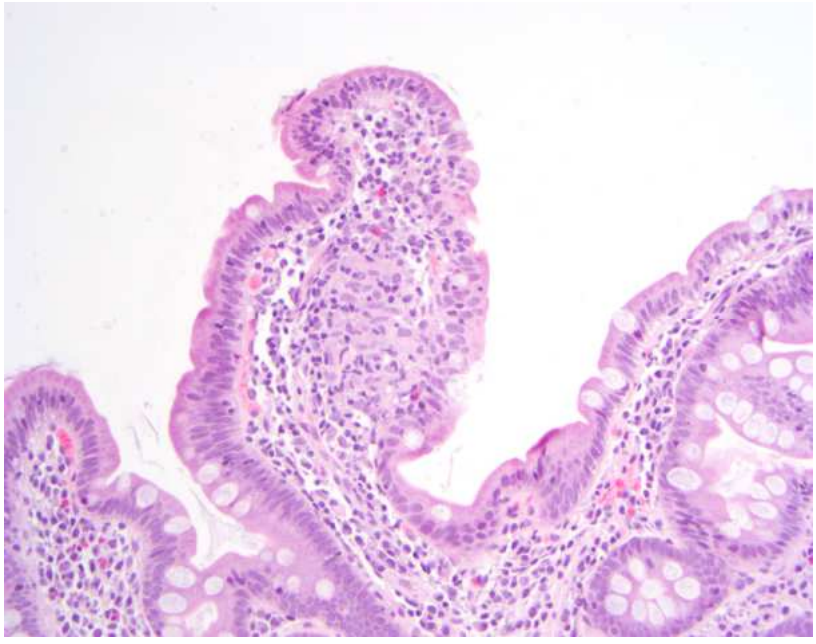




Case 1



Case 1

- Negative microbiological studies
- Diagnosis for stomach:

Antral and oxyntic mucosa with acute and chronic inflammation and focal non-necrotizing granuloma. *H. pylori* immunostain is negative. See note.

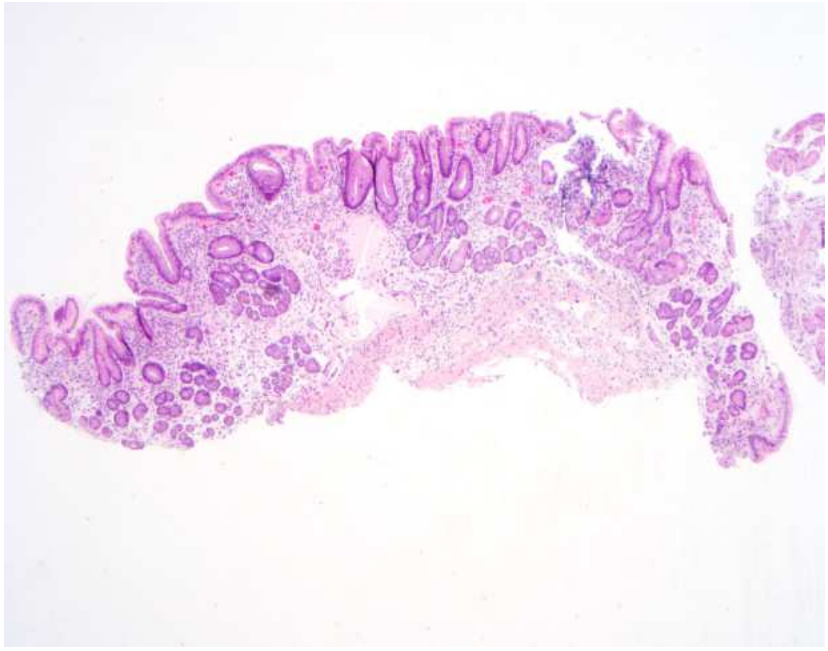
Note: In the absence of infection, the findings are in keeping with Crohn disease. See concurrent lower GI tract biopsies.

Case 2

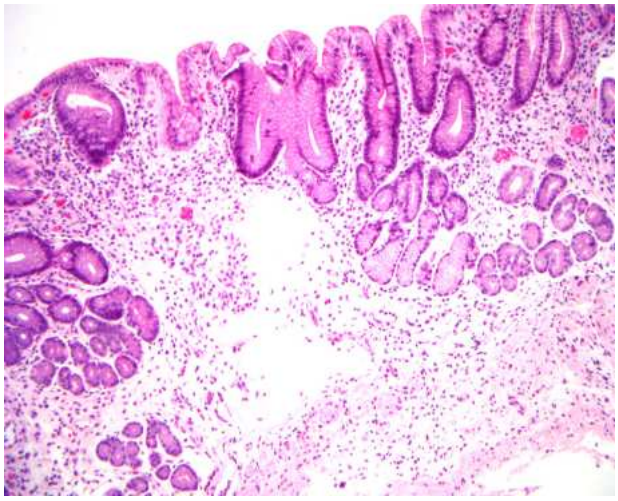
- 49 y/o male
- No prior material at JHH
- No history provided on requisition form

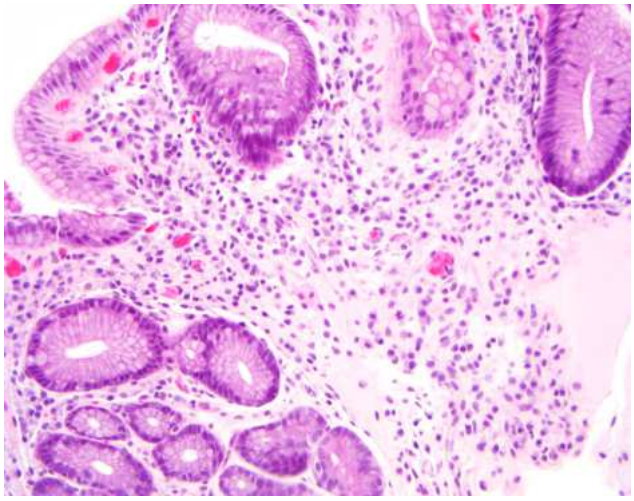
Case 2

Antrum



Case 2

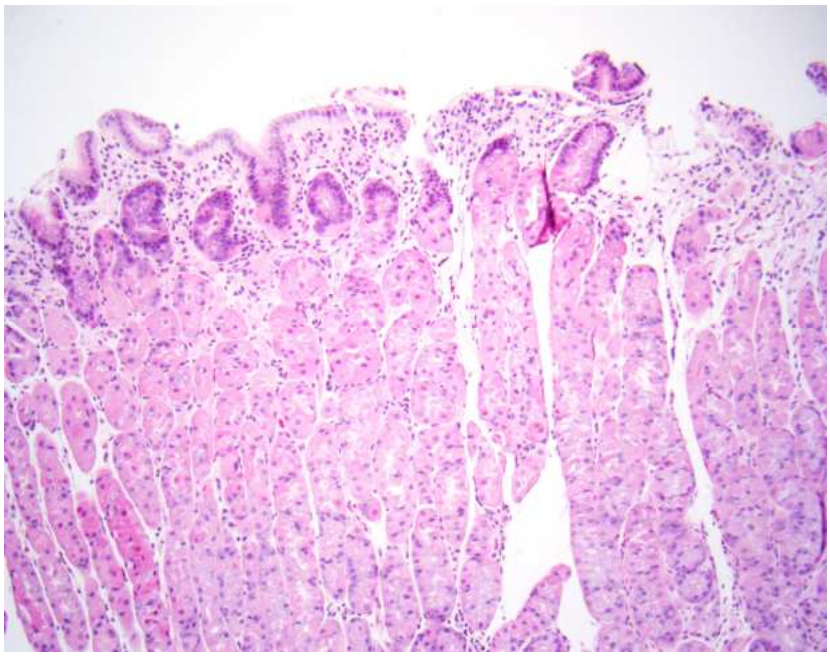




Antrum

Case 2

Negative *H.pylori* immunostain



Case 2

- Chart review at the time of sign out:
  - Treated a few months before for *H.pylori* infection

Chronic inactive antral and oxyntic gastritis. No Helicobacter organisms are seen on immunostain. See note.

Note: The patient's treatment for *Helicobacter pylori* infection is noted. The changes are in keeping with that history.