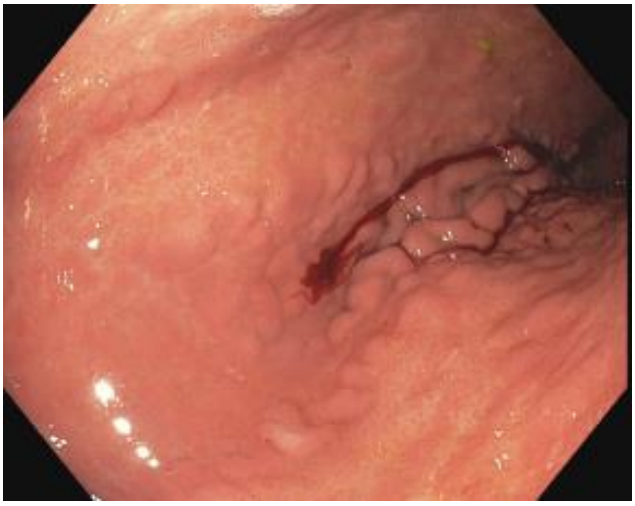
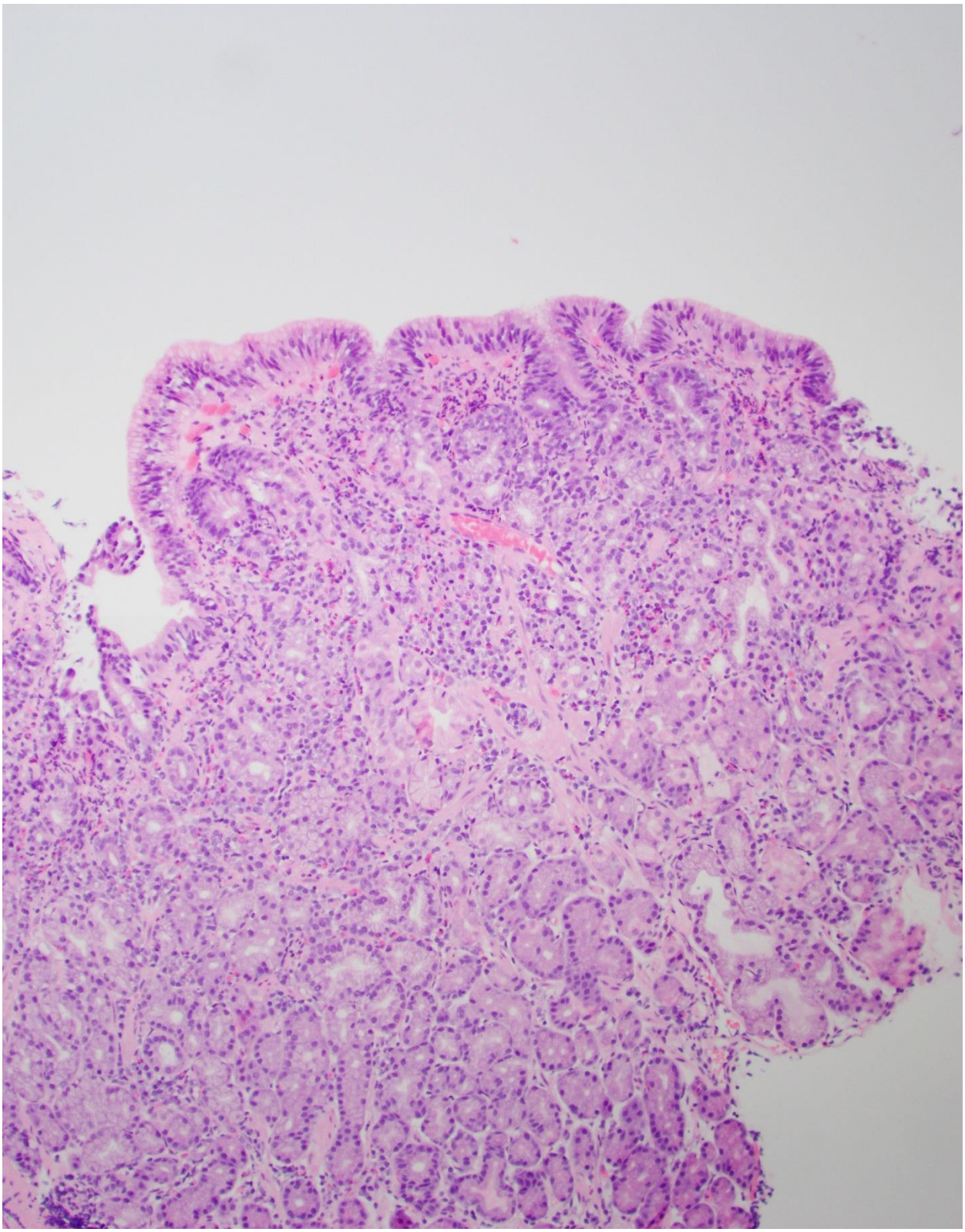
Case history

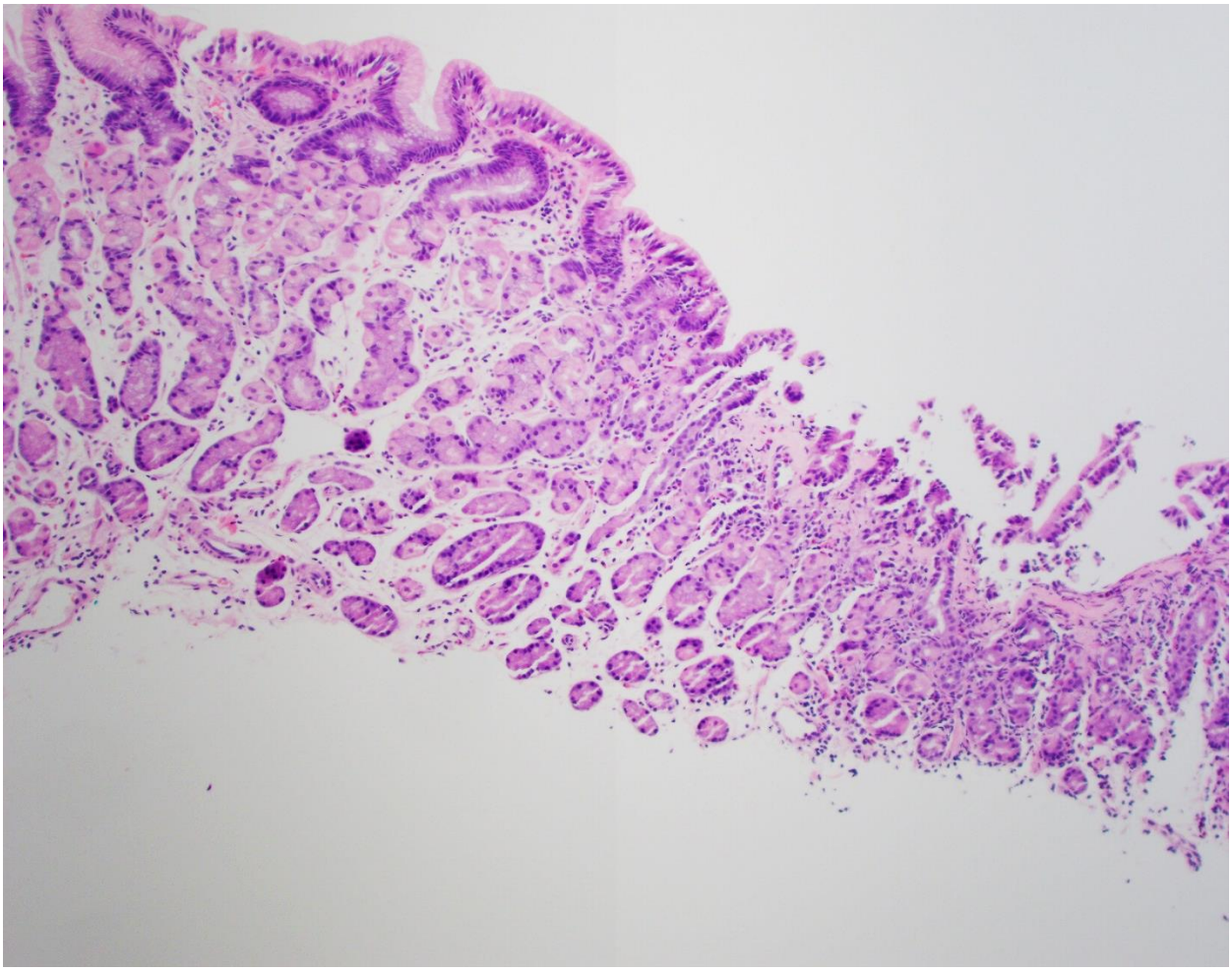
A 19-year-old woman presented to her gastroenterologist with a chief complaint of chronic abdominal pain. Her past medical history included allergic rhinitis, anxiety, gastroesophageal reflux disease, iron deficiency anemia, migraines, and an eating disorder. Her medications included amitriptyline, gabapentin, acetaminophen, esomeprazole magnesium, ferrous sulfate, fluticasone propionate nasal spray, hyoscyamine, melatonin, and omeprazole. Laboratory tests for tissue transglutaminase IgA and deaminated gliadin were negative. Serum IgA levels were normal. She underwent esophagogastroduodenoscopy which showed a normal-appearing esophagus, bilious-appearing fluid in the stomach, moderate erythema of the gastric antrum and body with significant nodularity of the gastric body, and a normal appearing duodenum. Biopsies were obtained of the esophagus, gastric antrum and body, and duodenum. The biopsies of the esophagus, antrum, and duodenum were normal. Endoscopic photos of the gastric body and photomicrographs of the H&E-stained slides of the gastric body are seen below. Immunohistochemical stains for gastrin and *H. pylori* and Congo red stain for amyloid on the biopsies of the gastric body were negative. Prior biopsies of her colon were normal.



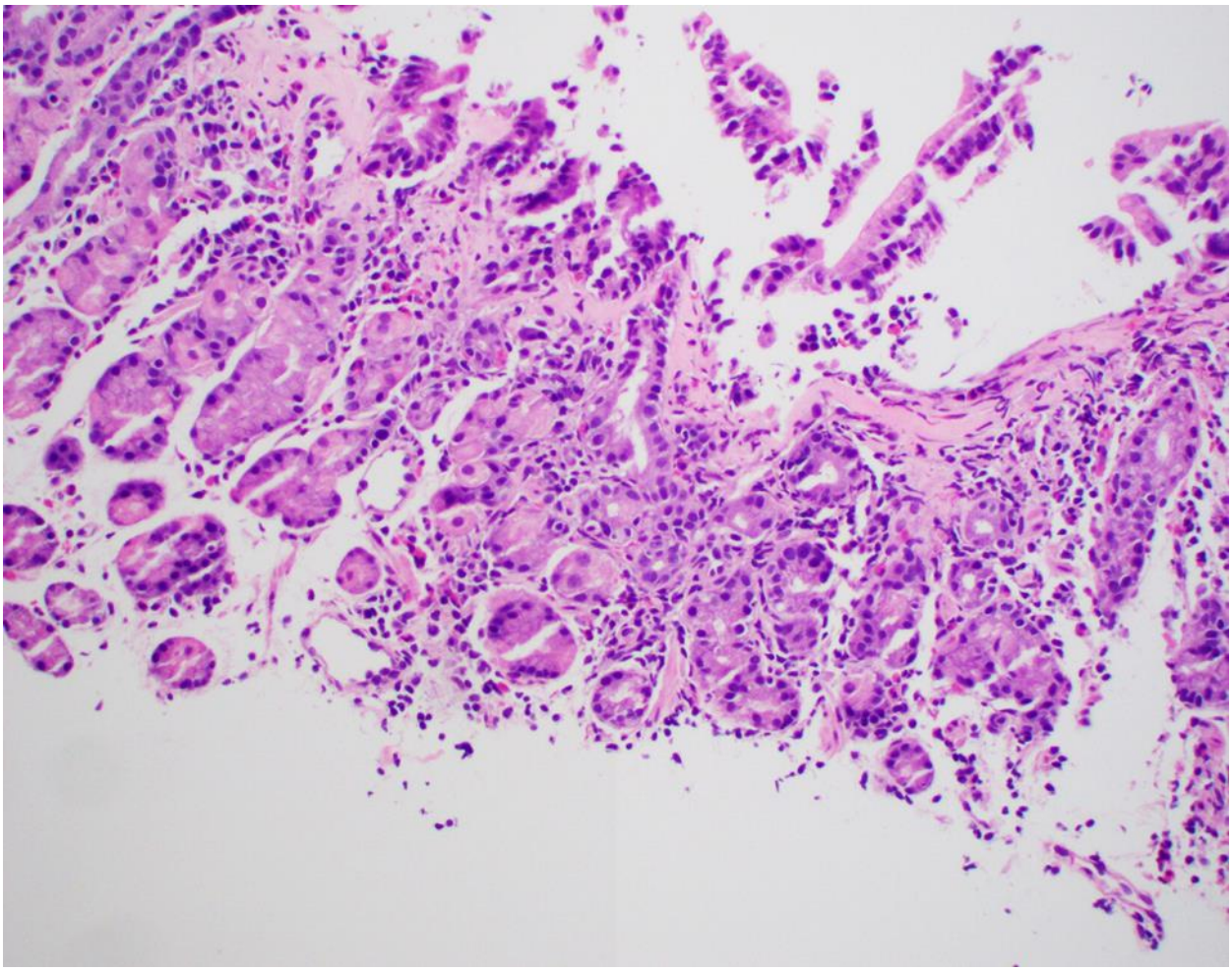
Endoscopic photo of the gastric body nodularity.



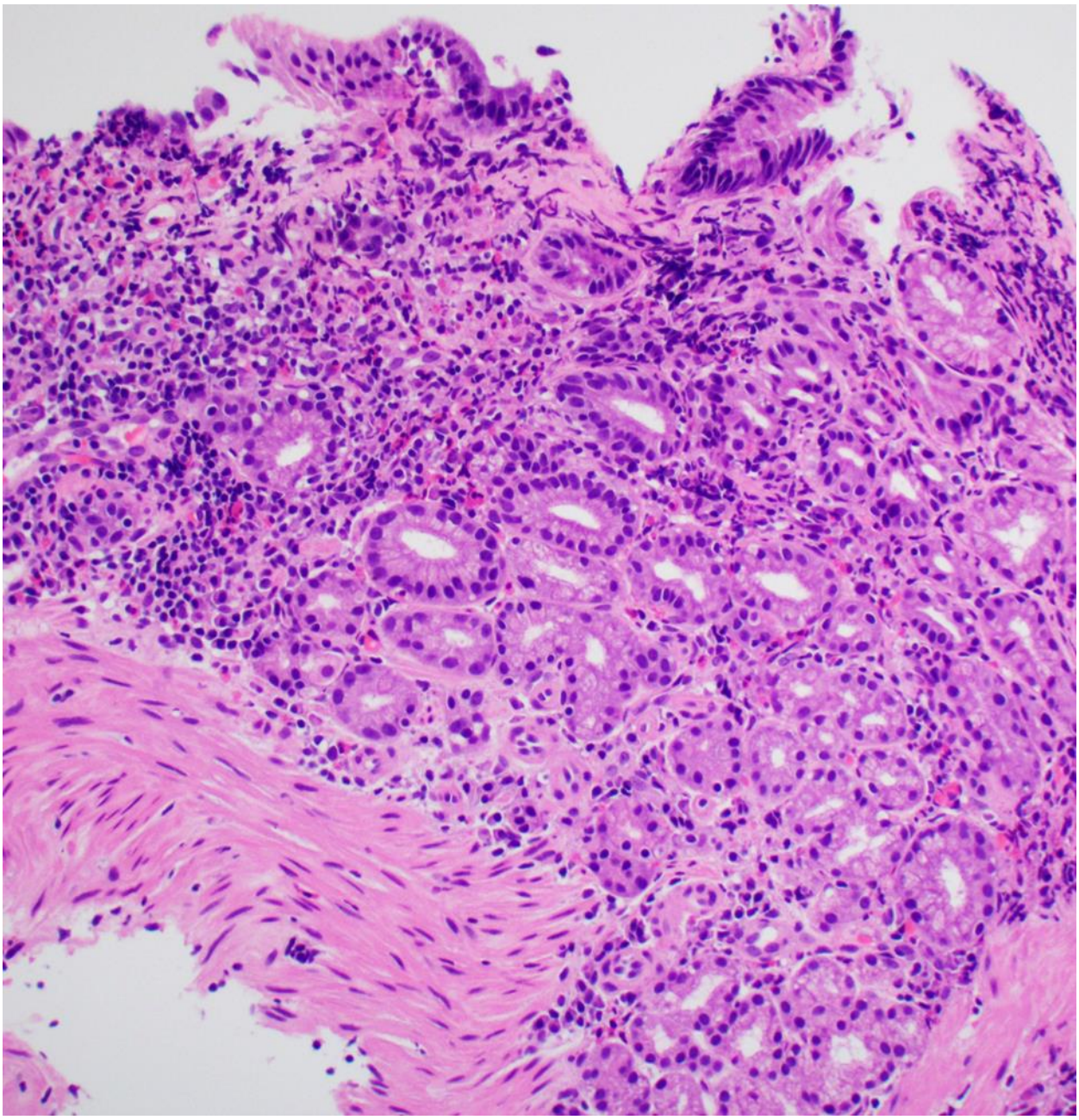
Gastric body, H&E 10x.



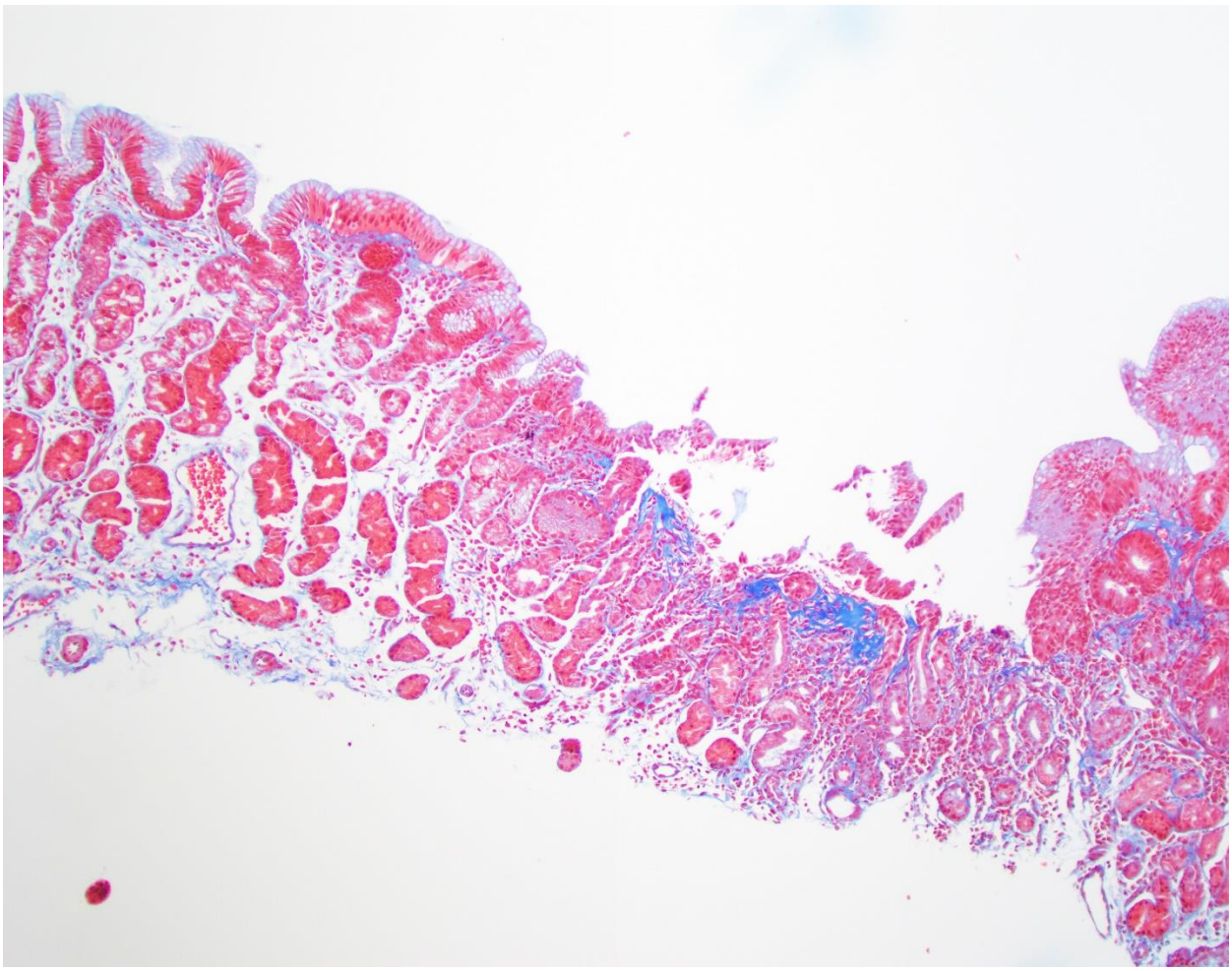
Gastric body, H&E 10x.



Gastric body, H&E 20x.



Gastric body, H&E 20x.



Trichrome stain 10x

What is the most likely diagnosis?

1) Collagenous Gastritis
2) Lymphocytic Gastritis
3) Eosinophilic Gastritis
4) Autoimmune Gastritis or Multifocal H. Pylori Atrophic Gastritis
5) Gastric Amyloidosis

The correct answer is 1) Collagenous Gastritis

Histologic sections of the gastric body biopsies demonstrate discontinuous foci of subepithelial collagen deposition > 10 µm in thickness with focal sloughing of the surface epithelium. The biopsies show a mild inflammatory infiltrate in the lamina propria composed of plasma cells, lymphocytes, and focally prominent eosinophils. Some of the fragments show atrophic changes consisting of a loss of specialized gastric (oxyntic) glands. No intestinal metaplasia or neutrophilic inflammation is seen. There is no increase in intraepithelial lymphocytes. An immunohistochemical stain for gastrin was negative, confirming location in the gastric body. An immunohistochemical stain for *H. pylori* was negative as well as Congo red stain for amyloid. Biopsies of the gastric antrum, esophagus and duodenum were normal.

Collagenous gastroenteritides include collagenous gastritis, collagenous sprue, and collagenous colitis. The exact etiology and pathogenesis of this disorder remain unclear. Collagenous colitis is the most common in this disease category, with collagenous gastritis and collagenous sprue being rarer. A significant portion of cases of collagenous gastritis described in the literature are in children and young adults that show a female predominance. The most common presenting symptoms and signs are abdominal pain,anemia and nodular appearance of the gastric body mucosa on endoscopic exam. The histologic findings of collagenous gastritis are characterized by a mild to moderate infiltrate of chronic inflammatory cells in the lamina propria and usually patchy deposition of subepithelial collagen thicker than 10 µm. The inflammatory cells may include lymphocytes, plasma cells, and eosinophils. Collagen deposition can be confirmed with Masson trichrome staining; amyloid stains like Congo red or Thioflavin are negative.

Approximately 100 cases of collagenous gastritis (CG) have been reported in the literature. In a series of six patients, Lagorce-Pages *et al* identified two clinical subgroups of patients with collagenous gastritis. One occurred in children and young adults and was characterized by iron deficiency anemia, endoscopically nodular gastric mucosa, and no extra-gastric involvement. The second group consisted of adults with chronic watery diarrhea and associated collagenous colitis. In the largest published case series of forty patients with collagenous gastritis, Arnason *et al* identified three distinct histologic patterns: a lymphocytic gastritis-like pattern, an eosinophil-rich pattern, and an atrophic pattern. In this series, atrophic and eosinophilic-rich patterns were mostly found in children and young adults, and the intraepithelial lymphocytosis pattern was more commonly seen in association with celiac disease, collagenous colitis, collagenous sprue, and increased duodenal lymphocytosis. When eosinophils are prominent in gastric biopsies, a careful search for areas of increased subepithelial collagen should be undertaken because collagenous gastritis is part of the differential diagnosis in gastric biopsies that show eosinophilia.

Because of the rarity of the condition and limited understanding of the pathophysiology of collagenous gastritis, there is no standard therapy. Complicating the pursuit of an effective therapy is that there appears to be adult and pediatric versions of this condition which may have differing etiologies. Therapies which have shown limited success include proton-pump inhibitors, histamine H_2-receptor antagonists, steroids, iron supplementation, and hypoallergenic diets. Sucralfate, mesalazine, bismuth subsalicylate, furazolidone, sulfasalazine, azathioprine, and parenteral nutrition have shown improvement in patient symptoms in a few cases.

2) Lymphocytic Gastritis

Lymphocytic gastritis is a type of chronic gastritis characterized by infiltration of the surface foveolar epithelium by lymphocytes (> 25 lymphocytes per 100 epithelial cells) with associated mononuclear cell inflammation in the lamina propria. Lymphocytes are predominantly CD3-positive T-cells co-expressing CD8. Inflammation is often pangastric. Common clinical association includes celiac disease. It is less commonly associated with HIV infection, Crohn's disease, Ménétrier disease, non-steroidal anti-inflammatory drugs, and lymphocytic or collagenous colitis.

Collagenous gastritis can be associated with a mild inflammatory infiltrate, and in some cases, has increased intraepithelial lymphocytes like lymphocytic gastritis. However, unlike lymphocytic gastritis, CG has areas of increased subepithelial collagen deposition which differentiates the two histologic entities.

3) Eosinophilic Gastritis

Eosinophilic gastritis refers to a spectrum of diseases that present with variable degrees of infiltration of the stomach by eosinophils in the absence of other known causes of tissue eosinophilia. Clinical symptoms and laboratory findings are usually non-specific and may or may not be accompanied by peripheral blood eosinophilia. The extent of eosinophilic infiltration of the gastrointestinal wall (diffuse or patchy, > 20 eosinophils per high-power field) varies from involving only the mucosa to transmural or serosal involvement. The endoscopic findings in eosinophilic gastritis may appear normal or may demonstrate changes like non-specific gastritis (prominent gastric folds, mucosal erythema, friability, and fine granularity or mucosal nodules).

Some cases of collagenous gastritis show prominent eosinophilic inflammation, especially in young patients. When eosinophils are prominent in gastric biopsies, a careful search for areas of increased subepithelial collagen should be undertaken because collagenous gastritis is part of the differential diagnosis gastric eosinophilia.

4) Autoimmune Gastritis or Multifocal H. Pylori Atrophic Gastritis

Autoimmune gastritis, is a corpus-restricted autoimmune condition targeting the H/K-ATPase located on the canalicular membrane of gastric parietal cells. Microscopic features

correspond to three pathologic phases of the disease: early – with lymphocytic and plasmacytic infiltrate in the lamina propria with loss of parietal cells; florid – with persistent inflammation, more widespread loss of parietal cells associated with diffuse replacement by intestinal and pseudopyloric metaplasia; end stage – characterized by reduced inflammation, complete loss of parietal cells and diffuse metaplasia. Endoscopically, there are atrophic body and fundic mucosa with loss of mucosal folds and varying number of polyps. Circulating antibodies against H^+/K^+ATPase and intrinsic factor can be identified, as well as hypergastrinemia, sideropenia and megaloblastic anemia.

Multifocal *H. pylori* atrophic gastritis (MAG) affects all areas of the stomach in a patchy way. *H. pylori* infection and active inflammation seen as neutrophilic pititis or pit abscess formation is sometimes found, however, may not be detected. It is generally accepted that MAG represents burnt out chronic *H. pylori* infection. Histologic features are similar to those found in atrophic autoimmune gastritis, and include less diffuse atrophy of the oxyntic glands, varying amounts of chronic inflammation and intestinal metaplasia.

Some cases of collagenous gastritis (such as our case presented here) show features of atrophy, such as loss of specialized gastric glands and chronic inflammatory cells. However, CG, is typically not associated with intestinal metaplasia and shows characteristic increase in subepithelial collagen which is not seen in autoimmune gastritis or MAG.

5) Gastric Amyloidosis

Amyloidosis is caused by extracellular deposition of insoluble aggregates of misfolded proteins with twisted β-pleated sheet tertiary structure in the stomach. Endoscopically, the findings are nonspecific and include erythema, erosions, granular or plaque-like mucosa of the stomach, and polypoid protrusions. Biopsies of the gastroduodenal mucosa are more sensitive than subcutaneous fat to screen for systemic amyloidosis. Histologic features include thickened vessel walls, crypt hyperplasia, surface denudation, ulceration, hyalinization of lamina propria and mural-vascular deposits with thromboses. Amyloid deposition can be visualized with Congo red staining. Toluidine blue, PAS-D, Crystal violet, and Thioflavin can be used as well. Trichrome stain may be weakly positive.

Increased subepithelial collagen in case of CG may mimic amyloid deposition, especially if it is extensive. Congo red and trichrome stains are useful to distinguish between the two entities.

References:

1. Kamimura K, Kobayashi M, Sato Y, Aoyagi Y, Terai S. Collagenous gastritis: Review. World J Gastrointest Endosc. 2015 Mar 16;7(3):265-73.

2. Arnason T, Brown IS, Goldsmith JD, Anderson W, O'Brien BH, Wilson C, Winter H, Lauwers GY. Collagenous gastritis: a morphologic and immunohistochemical study of 40 patients. Mod Pathol. 2015 Apr;28(4):533-44.
3. Lagorce-Pages C, Fabiani B, Bouvier R, Scoazec JY, Durand L, Flejou JF. Collagenous gastritis: a report of six cases. Am J Surg Pathol. 2001 Sep;25(9):1174-9.
4. Suskind D, Wahbeh G, Murray K, Christie D, Kapur RP. Collagenous gastritis, a new spectrum of disease in pediatric patients: two case reports. Cases J. 2009 Jun 10;2:7511.
5. Ma C, Park JY, Montgomery EA, Arnold CA, McDonald OG, Liu TC, Salaria SN, Limketkai BN, McGrath KM, Musahl T, Singhi AD. A Comparative Clinicopathologic Study of Collagenous Gastritis in Children and Adults: The Same Disorder with Associated Immune-mediated Diseases. Am J Surg Pathol. 2015 Jun;39(6):802-12.
6. Wu TT, Hamilton SR. Lymphocytic gastritis: association with etiology and topology. Am J Surg Pathol. 1999 Feb;23(2):153-8.
7. Drut R, Drut RM. Lymphocytic gastritis in pediatric celiac disease – immunohistochemical study of the intraepithelial lymphocytic component. Med Sci Monit. 2004 Jan;10(1):CR38-42.
8. Uppal V, Kreiger P, Kutsch E. Eosinophilic Gastroenteritis and Colitis: A Comprehensive Review. Clin Rev Allergy Immunol. 2016 Apr;50(2):175-88.
9. Lucendo AJ, Arias A. Eosinophilic gastroenteritis: an update. Expert Rev Gastroenterol Hepatol. 2012 Sep;6(5):591-601.
10. Coati I, Fassan M, Farinati F, Graham DY, Genta RM, Rugge M. Autoimmune gastritis: Pathologist's viewpoint. World J Gastroenterol. 2015 Nov 14;21(42):12179-89.
11. Bettington M, Brown I. Autoimmune gastritis: novel clues to histological diagnosis. Pathology. 2013 Feb;45(2):145-9.
12. Petre S, Shah IA, Gilani N. Review article: gastrointestinal amyloidosis - clinical features, diagnosis, and therapy. Aliment Pharmacol Ther. 2008 Jun 1;27(11):1006-16.
13. Sattianayagam PT, Hawkins PN, Gillmore JD. Systemic amyloidosis and the gastrointestinal tract. Nat Rev Gastroenterol Hepatol. 2009 Oct;6(10):608-17.

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