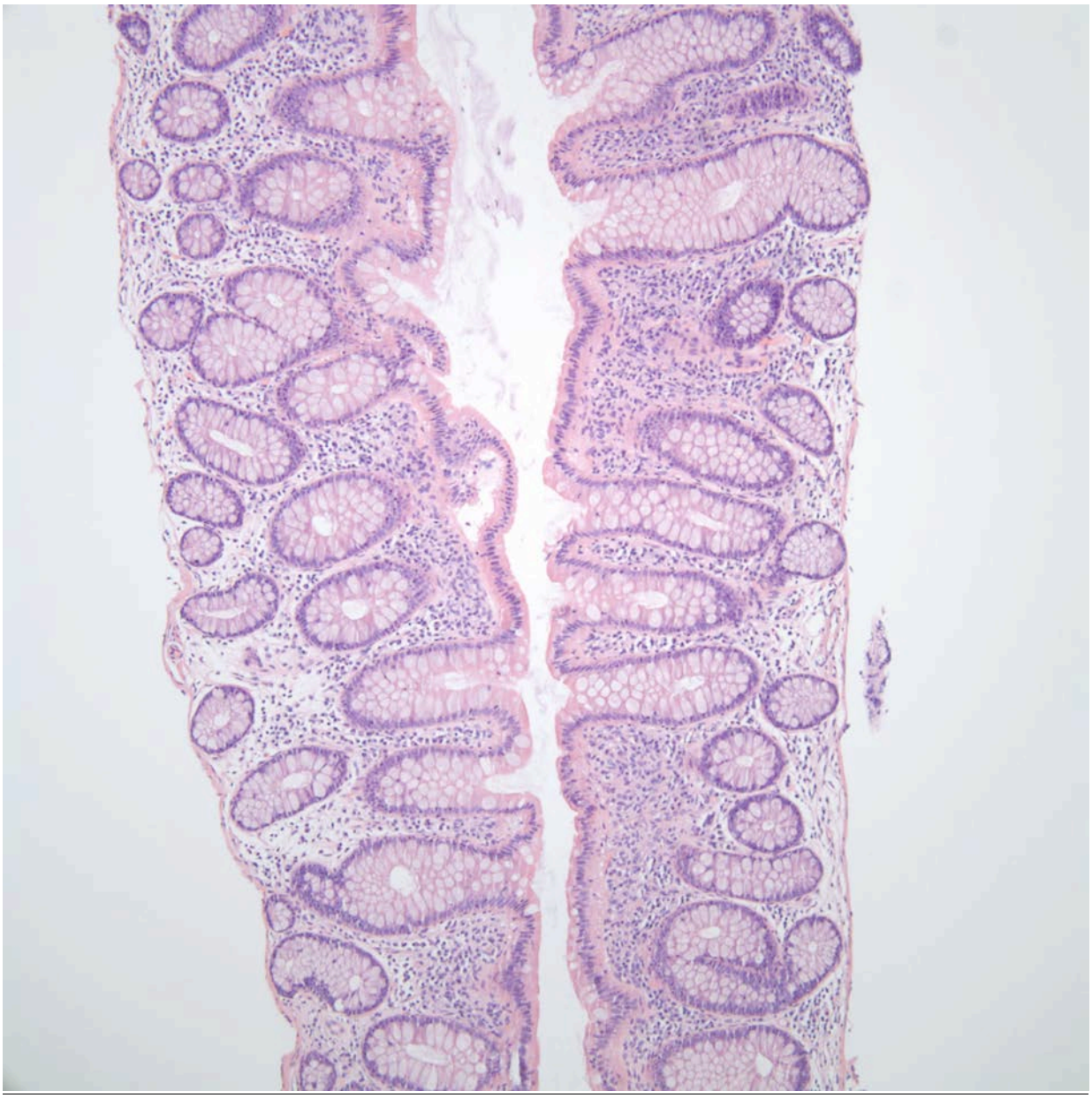
Case Presentation:

This is a 69-year-old man with watery diarrhea that started 6 months ago. It is worsening over the past month with nausea and vomiting. Colonoscopy showed two polyps, but was otherwise normal; random samples were also taken. Two weeks after initial presentation, the patient underwent a bone marrow biopsy for anemia, thrombocytopenia, weight loss. Imaging showed a mottled sacral bone.



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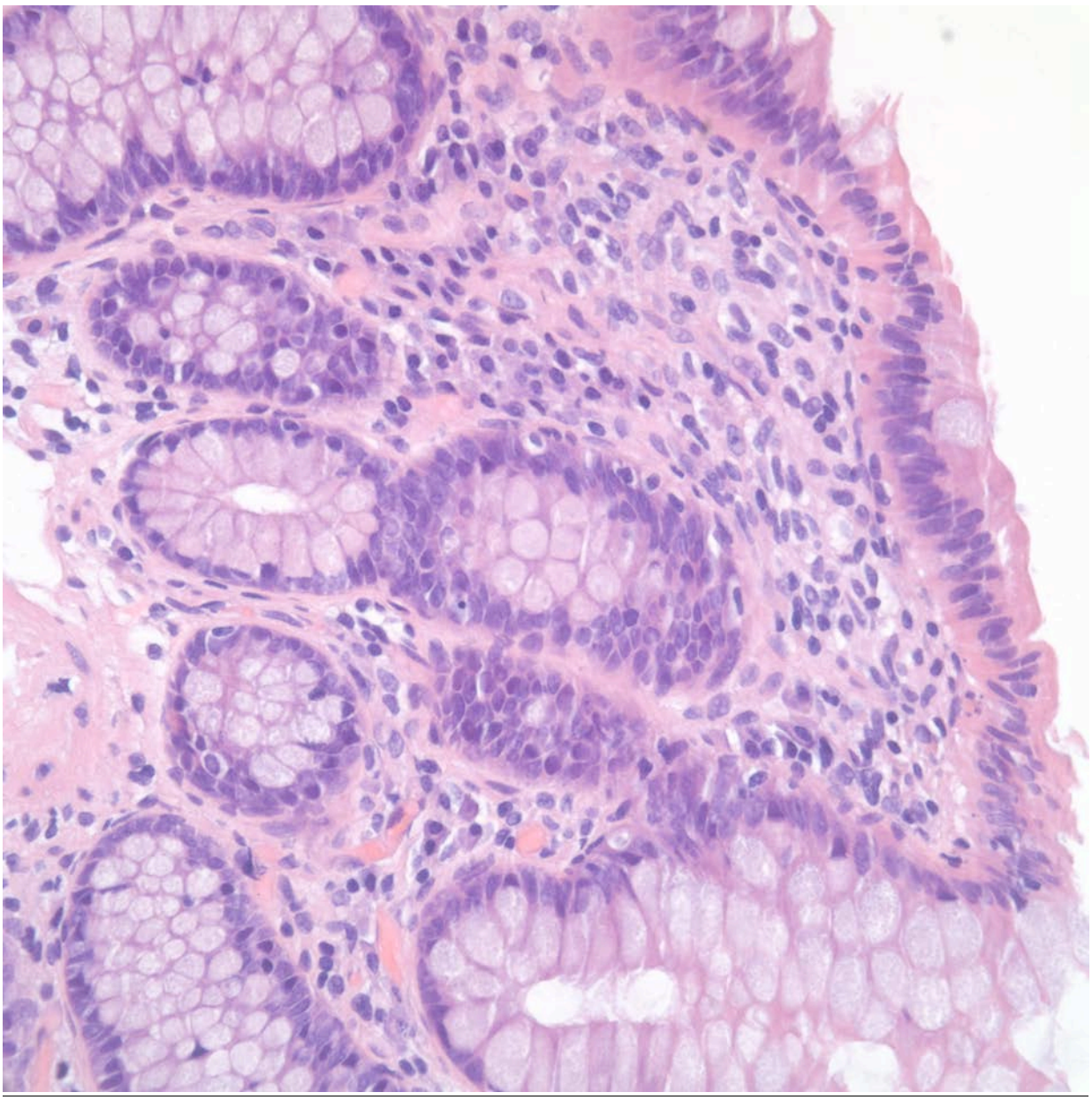

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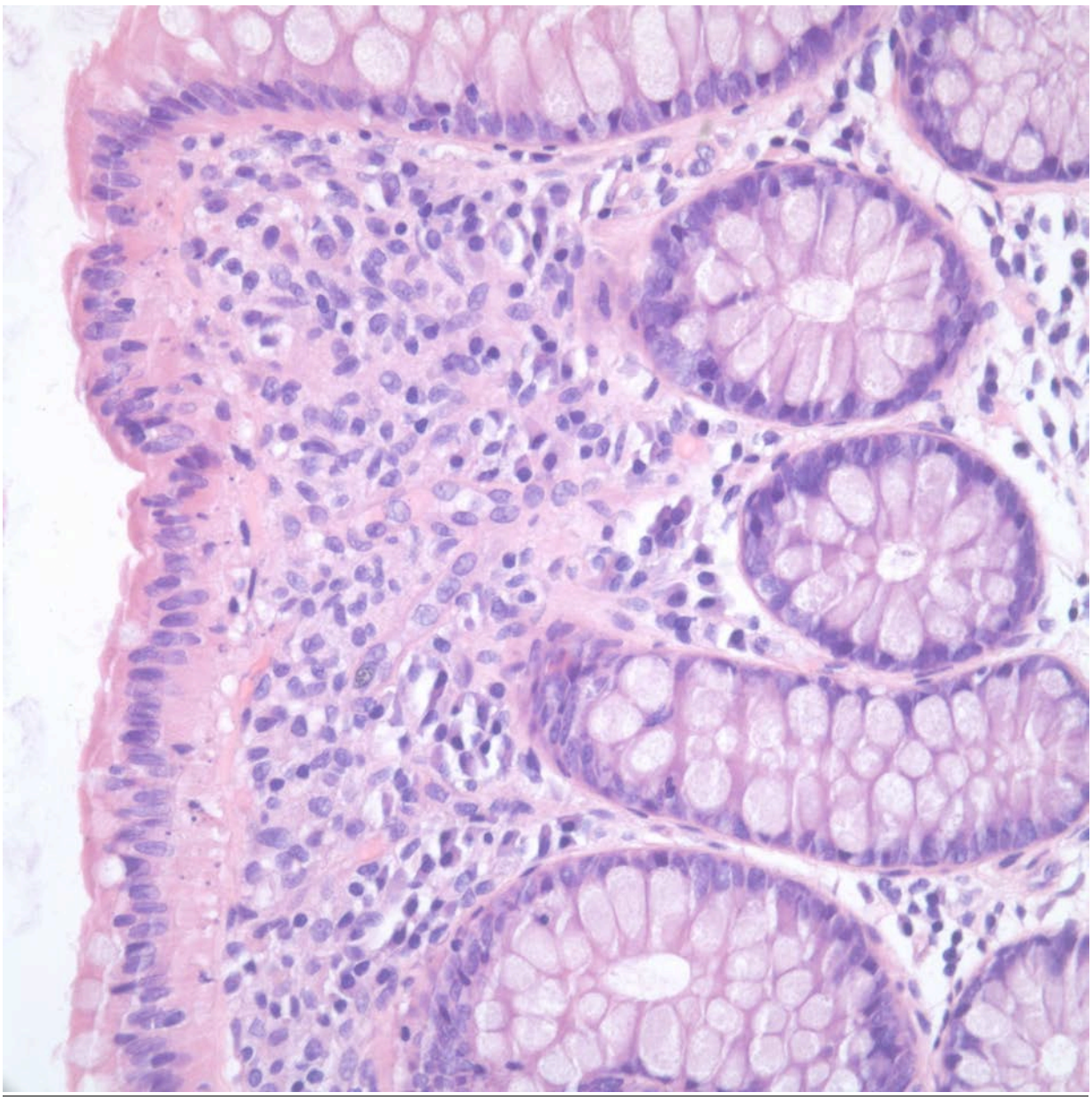

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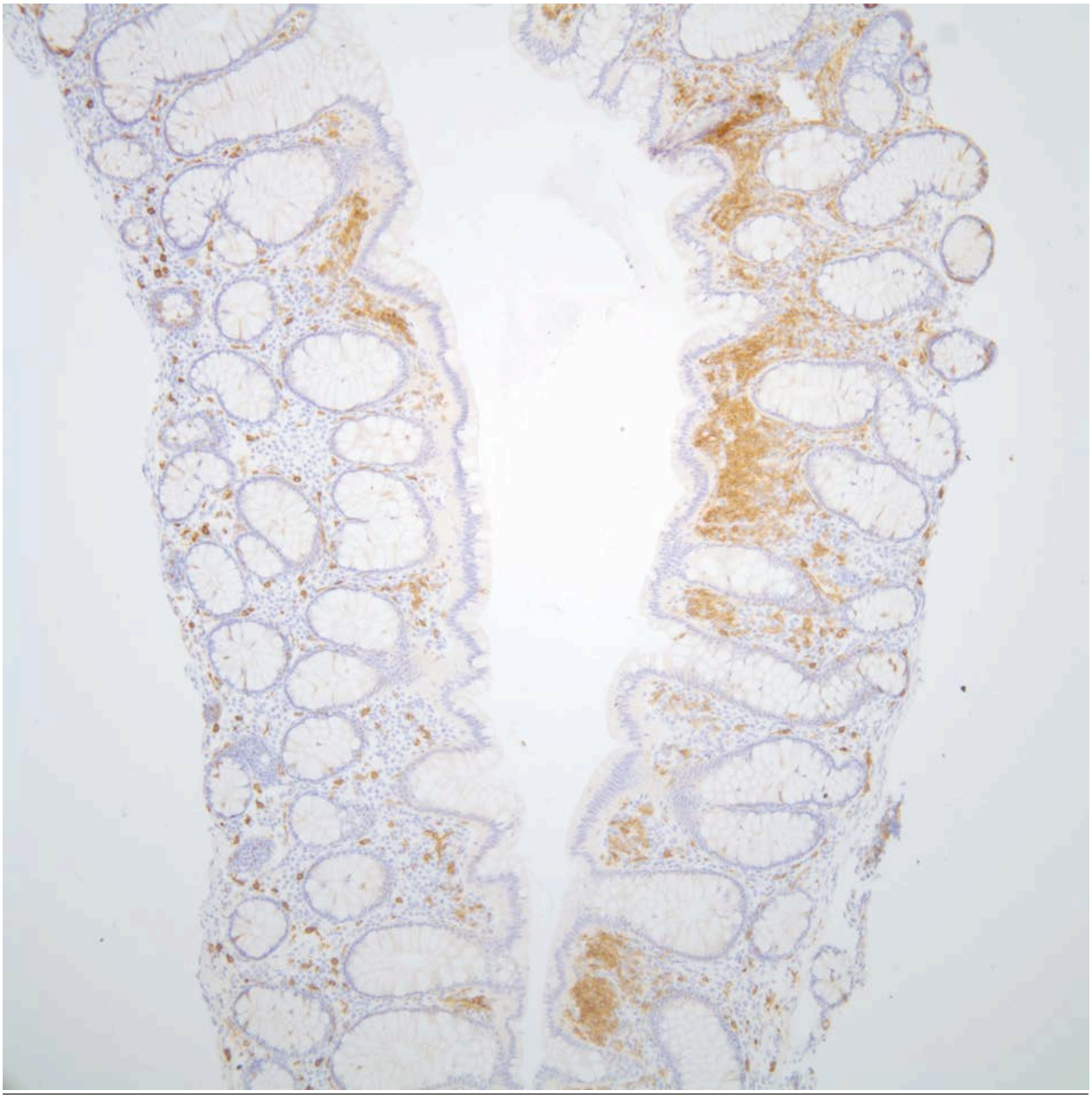
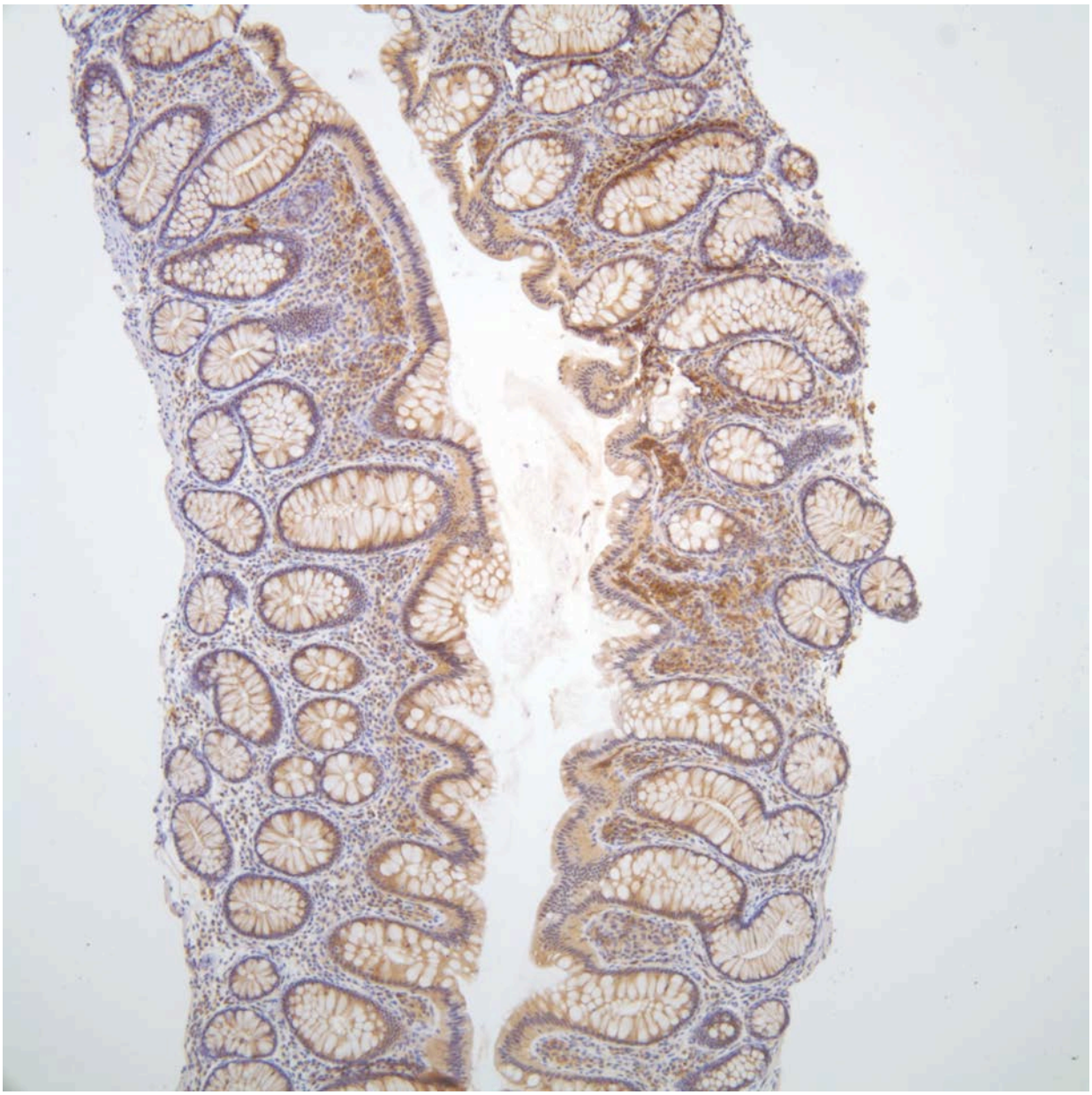
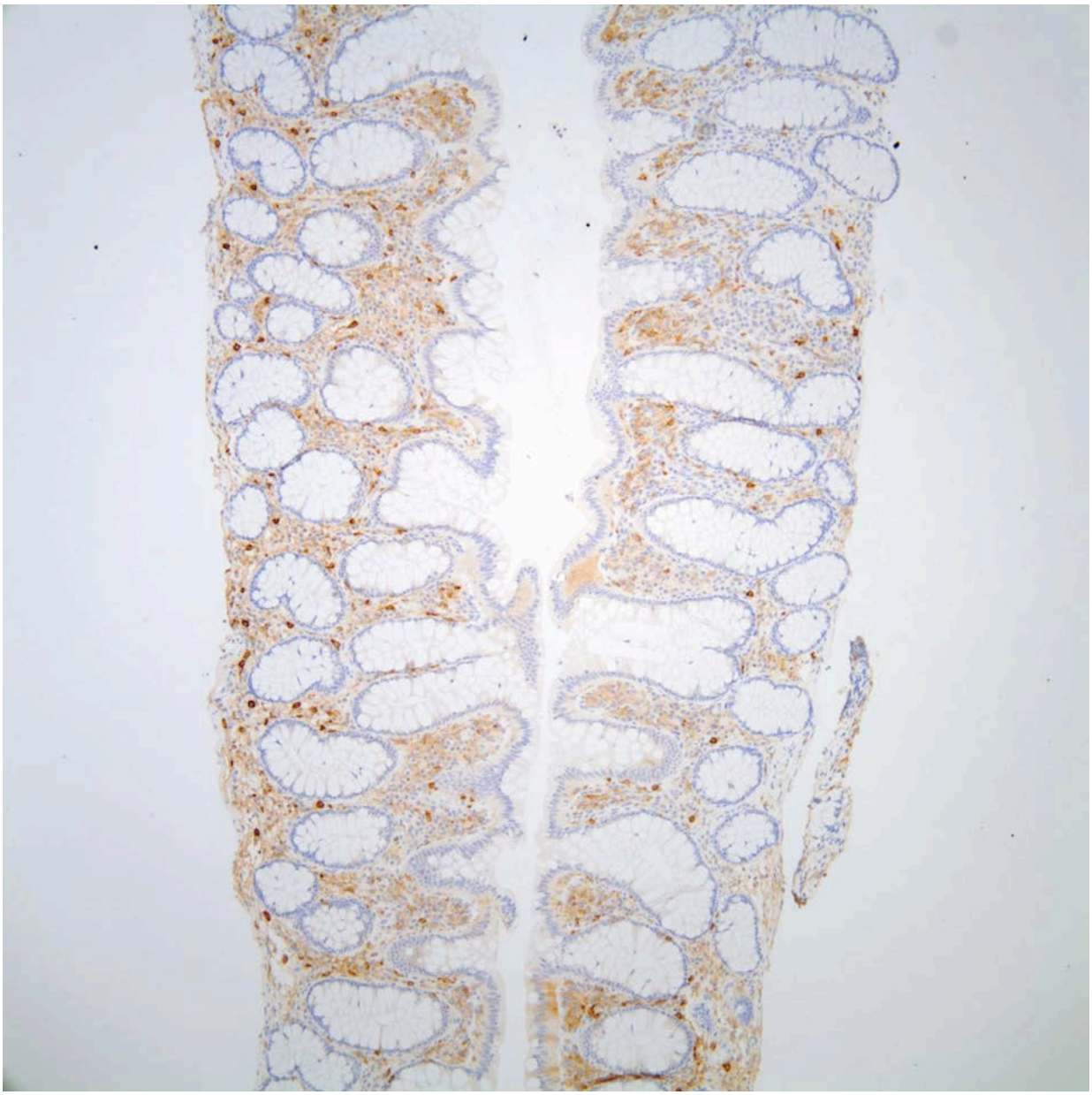


CD 117



CD 25



Tryptase

What is your diagnosis?

A. Colonic mucosa with no significant histopathologic changes

B. Parasitic infection

C. Ulcerative colitis

D. Lymphocytic colitis

E. Consistent with involvement by systemic mastocytosis

Answer: E. Consistent with involvement by systemic mastocytosis

Discussion:

Mastocytosis describes a group of disorders in which pathologic mast cells accumulate in tissues. These diseases can be limited to the skin (cutaneous mastocytosis [CM]) or involve extracutaneous tissues, most commonly bone marrow (systemic mastocytosis [SM]). The cutaneous form is more common in children. Adults more often have systemic forms of the disease, and these disorders tend to persist. In SM, 70% to 80% of patients have GI symptoms and include diarrhea, peptic ulcer pain, GI bleeding, nondyspeptic abdominal pain, urgency, and fecal incontinence. Gastrointestinal manifestations may arise from mast cell mediator release or organ infiltration (stomach and duodenum most commonly involved).

Gastrointestinal biopsies –In the colon, histologic presentation is variable and can range from subtle to marked expansion of the lamina propria, associated eosinophilic infiltrate, and architectural distortion including irregular crypt spacing and crypt foreshortening. It is important to note that increased mast cell numbers is not specific to Mastocytosis and can be found in gastrointestinal tract biopsies from patients with inflammatory bowel diseases and bacterial and parasitic infections. There are conflicting reports about the gastrointestinal mast cell density in patients with SM. Some groups have found aggregates of mast cells up to 100/hpf, while other studies have reported scattered, but increased, normal, and decreased numbers of mast cells compared with normal controls (Escribano, L et. al. 1998; Jensen, R.T. 2000). One study found greater than 20 mast cells per high power field in a subset of patients with chronic intractable diarrhea without evidence of mastocytosis or other inflammatory bowel disease. These patients were termed as having mastocytic enterocolitis (Jakate, S. et. al 2006).

A more recent and systematic study by Hahn H. et. al. looked to quantify and compare mast cells in mucosal biopsies from patients with Mastocytosis (both SM and CM), with a diverse control group (including normal, ulcerative colitis, Crohn colitis, lymphocytic and collagenous colitis, irritable bowel syndrome, parasitic infection and eosinophilic colitis). In the colon, they found mast cells numbered >100/hpf in nearly all SM cases (mean 196; range 74-339). This was significantly higher than in GI biopsies from CM patients (mean 17; range 8-32) and all inflammatory disease (range 3-70). Interestingly, biopsies from patients with parasitic infections showed significantly increased mast cells (mean 47; range 31-70) compared with normal controls and may be a potential diagnostic pitfall in the diagnosis of SM. Of note, other than SM, these were the only subset of cases with significantly increased mucosal mast cells. Importantly, this study found aggregates of sheets of mast cells were only identified in SM biopsies. In addition, they confirmed that immunostaining with CD 25 distinguishes neoplastic from reactive mast cells in GI biopsies.

Diagnosis: According to the World Health Organization's (WHO) diagnostic criteria, the definitive diagnosis of systemic mastocytosis requires either the presence of one major *and* one minor criteria OR three minor criteria: Major criterion — The major criterion is the presence in bone marrow or other extracutaneous organs of multifocal dense aggregates of greater than 15 mast cells as detected with tryptase or other special stains. Minor criteria — Four minor criteria have been defined: (1) Atypical

morphology or spindle shapes in >25 percent of the mast cells in bone marrow sections, bone marrow aspirate, or other extracutaneous tissues, (2) Mutational analysis of KIT showing a codon 816 mutation (eg, Asp816Val) in bone marrow, blood, or extracutaneous organs, (3) Bone marrow or other extracutaneous mast cells expressing the surface markers CD2, CD25, or both, (4) Serum tryptase levels (when the patient is in a baseline state) >20 ng/Ml. In general, it is recommended bone marrow biopsy is the optimal means of pursuing the diagnosis of systemic mastocytosis.

Our case showed subtle expansion of the lamina propria and focal areas of vague spindled lamina propria morphology (20x) involving 5 of 15 biopsies taken from upper and lower sites. While other inflammatory diseases can have increased mast cells, no neutrophilic cryptitis, crypt abscess formation, intraepithelial lymphocytosis, granulomas, or subepithelial collagen were seen. An eosinophilic infiltrate can be present in association with SM, and when present, can raise the possibility of parasitic infection. A significant eosinophilic population was not present in our case. Indeed, the toughest differential in this particular case was no histopathologic abnormality. Knowledge of the clinical picture is of paramount importance. The CD 117 showed mast cells in aggregate and with aberrant expression of CD 25.

Because studies determining mast cell density in the gastrointestinal tract are limited and conflicting, increased mast cell numbers in gastrointestinal biopsies should not be interpreted as diagnostic of a systemic mast cell disease in the absence of the appropriate clinical picture. Expression of CD 25 and CD 2 can bolster the suspicion of the presence of a neoplastic mast cell infiltrate. While co-expression of either is considered aberrant, CD 2 can be more difficult to interpret due to the presence of T cells.

Non-neoplastic mast cells are consistently positive for LCA, CD11c, CD33, CD43, and CD117. They are consistently negative for CD25, CD34, and CD138, the monocyte markers CD14, CD15, and the lymphoid markers CD2, CD3, CD5, and CD20. Neoplastic mast cells co-express CD117 and CD25. Expression of CD25 correlates with the presence of CKIT mutations and is indicative of malignancy. Neoplastic mast cells also aberrantly express CD2.

References

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Horny HP, Metcalfe DD, Bennett JM, et AL. Mastocytosis. In: World Health Organization Classification of tumours of haematopoietic and lymphoid tissues, Swerdlow SH, Campo E, Harris NL, et al (Eds), IARC Press, Lyon 2008.

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