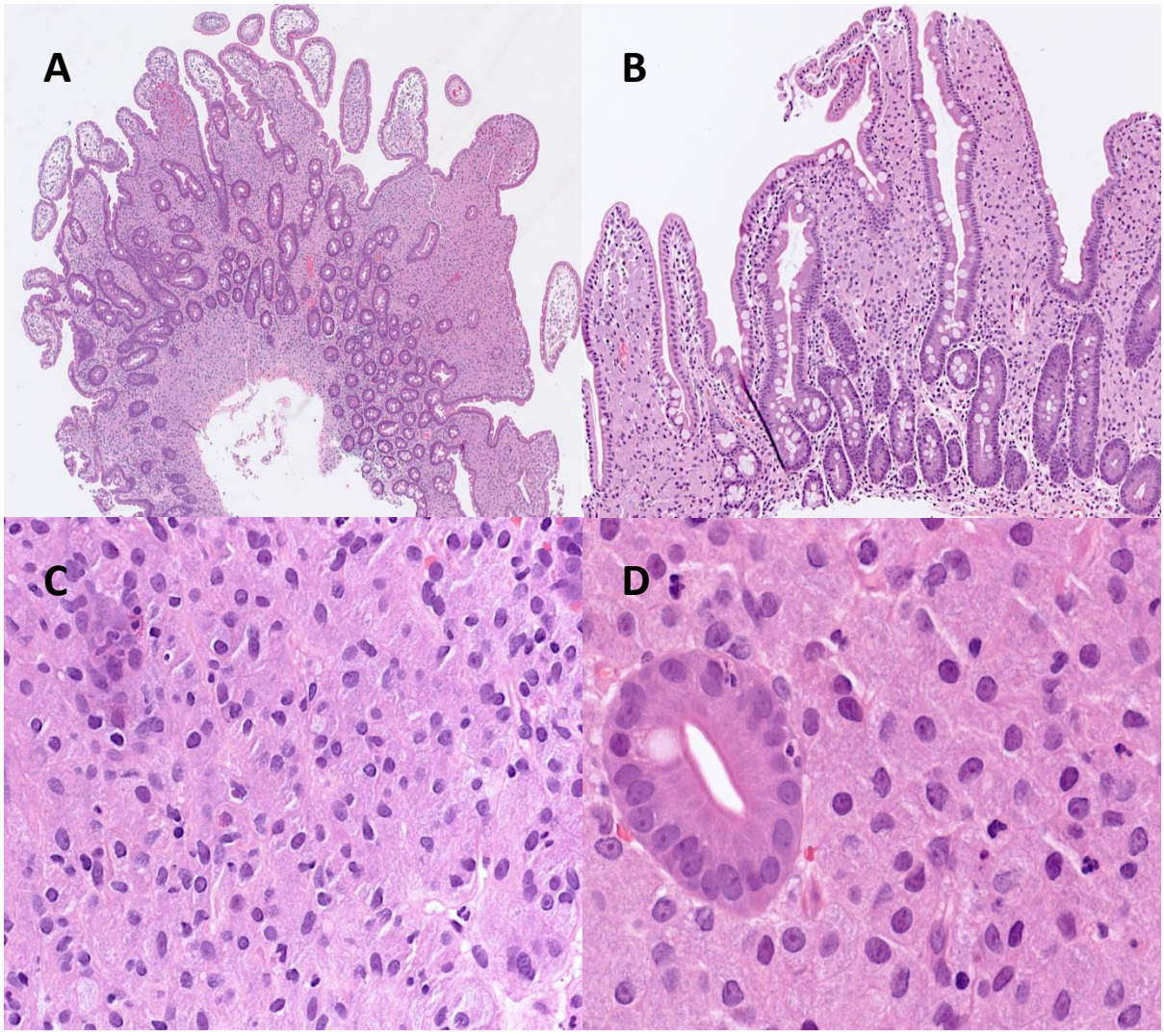
A 33 y.o. male with a past medical history significant for HIV/AIDS (absolute CD4 of 3/uL) and medication non-compliance presented with a 4-day history of abdominal pain and no fever. He underwent CT chest and abdomen/pelvis with contrast, which showed multiple cysts and nodules throughout both lungs with massive splenomegaly and mild mediastinal/hilar and mesenteric adenopathy. He then underwent EGD which showed patchy, non-bleeding ulceration at the GE junction, erosive gastritis, and duodenal mucosa with erythema and erosions. Multiple cold forceps biopsies were performed and sent for histologic examination. Representative H&E images of the duodenal biopsy are depicted below:

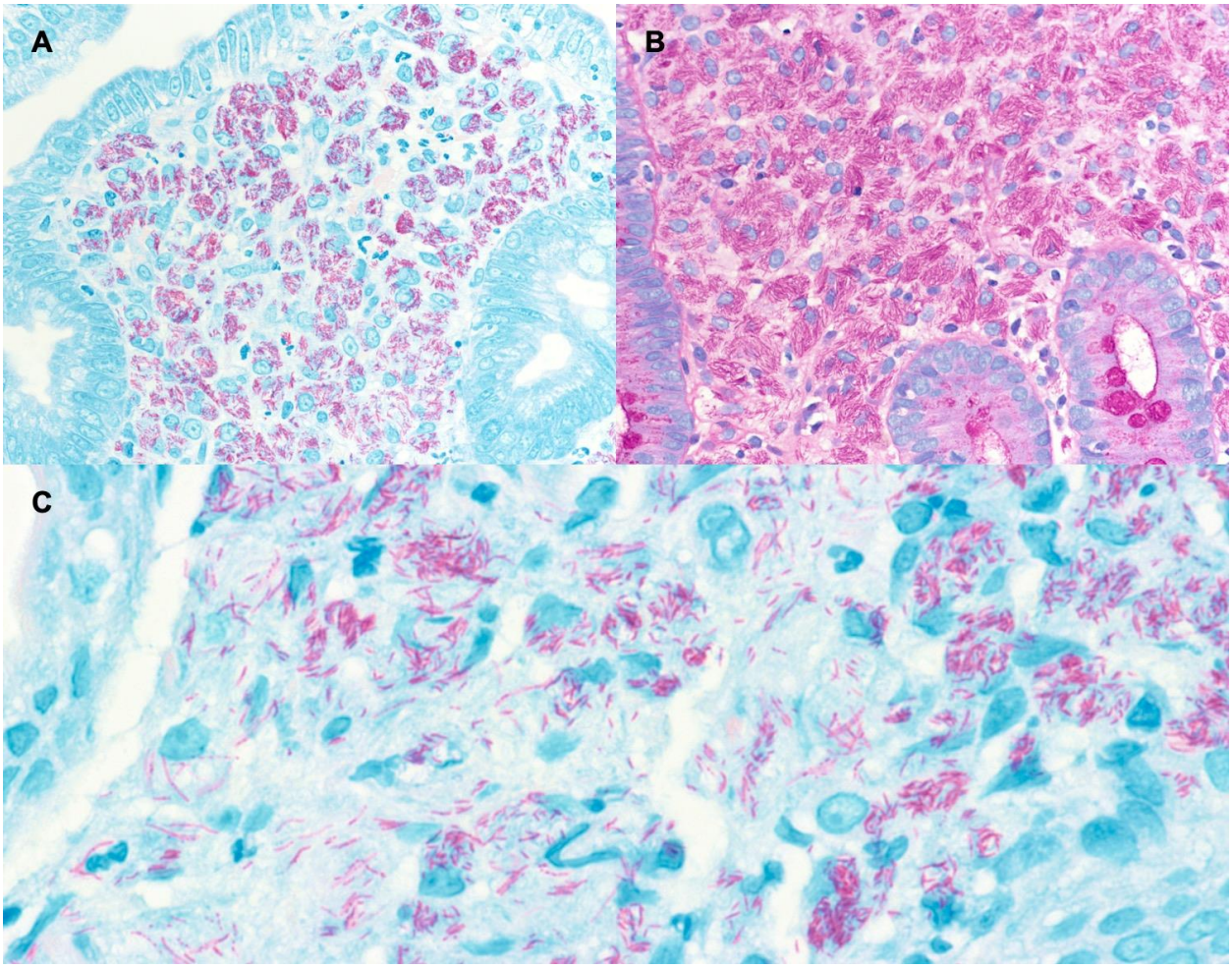
Figure 1: A) H&E 20x, B) H&E 40x, C) H&E 200x, D) H&E 400x



What is the differential diagnosis?

A) Disseminated histoplasmosis
B) *Mycobacterium avium* complex infection
C) Langerhans cell histiocytosis
D) Malakoplakia
E) Whipple's disease

Figure 2: A) AFB 200x, B) PAS with diastase 400x, C) AFB 600x
A GMS stain as well as immunostains for CD1a and Treponema were negative.



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ANSWER AND DISCUSSION ON NEXT PAGE

Answer and discussion:

Correct answer is B: *Mycobacterium avium* complex (MAC) infection.

Histologic sections of the duodenal biopsy demonstrate fragments of duodenal mucosa with marked lamina propria expansion by histiocytic inflammation and partial villous blunting. An immunostain for CD68 highlighted the histiocytes within the lamina propria while the AFB and PAS with diastase showed numerous acid-fast bacilli within them. A GMS was negative for fungal forms while and *Treponema* immunostain was negative. An AFB culture later returned positive for *Mycobacterium avium-intracellulare*.

Mycobacterium avium complex (MAC) infection of the gastrointestinal tract occurs mostly in immunocompromised patients, particularly in patients with acquired immunodeficiency syndrome (AIDS) with CD4 cell counts less than 100/uL. These patients may present with abdominal pain, fever, weight loss and diarrhea. Endoscopically, the mucosa can appear normal, coarsely granular, or show white plaques/nodules. Histologically, the lamina propria will be expanded by a marked foamy histiocytic infiltrate. However, unlike cases of *Mycobacterium tuberculosis*, well-formed granulomata are not generally seen. Acid-fast (Ziehl-Neelsen) histochemical stains will highlight numerous organisms within the macrophages. MAC is also PAS-positive diastase-resistant, with faint staining of the bacillary forms within macrophages, which is not to be confused with microorganisms of Whipple's disease (see below).

Disseminated histoplasmosis affects multiple organs including the GI tract where involvement of multiple sites in the GI tract is common. Amongst tubular GI tract sites, the terminal ileum is most commonly involved, which is thought to be due to the density of lymphoid tissue in the Peyer's patches. Disseminated gastrointestinal histoplasmosis may present as diarrhea, GI bleeding, abdominal pain, nausea, vomiting, flu-like symptoms or obstruction. Histopathologic findings include lymphohistiocytic infiltrates, the presence of variable numbers of primarily intracellular small yeast forms within histiocytes, lymphoid hyperplasia, infiltrates of eosinophils, neutrophils, and, rarely, necrotizing granulomas. Staining with GMS or PAS reveals intracellular yeast forms that are ovoid in shape, measure 2 to 4 um in size, have thin non-refractile cell walls, and manifest characteristic narrow-base budding. (Answer A: Incorrect)

Langerhans cell histiocytosis (LCH) is an abnormal histiocytic proliferation that may occur in any age group, but is most common in children aged 1-4 years. Adults with LCH involving the GI tract are usually asymptomatic. Endoscopic exam may show polypoid or elevated mucosal lesions. Histologically, the lamina propria and/or submucosa is markedly expanded by Langerhans cells with admixed eosinophils (often very prominent), neutrophils, plasma cells, and lymphocytes. Langerhans cells will have positive immunohistochemical staining for CD1a, Langerin (CD207), S100, CD68, HLA-DR, and vimentin. (Answer C: Incorrect)

While malakoplakia occurs most commonly in the GU tract, the GI tract is the second most common organ system involved, and malakoplakia may occur in any of the organs of the GI tract. The etiology of malakoplakia is uncertain, but is theorized to be due to a defective inflammatory reaction to bacteria or defective lysozyme function. Malakoplakia may present in the bowel as a tumor, polypoid lesion, or yellow plaque-like lesion. Microscopically, the lamina propria and/or bowel wall is expanded by a sheet-like infiltrate of histiocytes with granular eosinophilic cytoplasm. Within the cytoplasm, scattered 3 to 10-micron rounded basophilic, lamellated, PAS-positive diastase-resistant inclusions known as

Michaelis-Gutmann bodies (also known as calculospherites) are found. These distinctive inclusions are thought to represent the remnants of bacteria within phagosomes that have been mineralized by calcium and iron and can be highlighted with a von Kossa or Prussian blue stain. (Answer D: Incorrect)

Whipple's disease, a chronic systemic illness, most commonly presents with GI symptoms including diarrhea, abdominal pain, steatorrhea and weight loss, and is caused by *Tropheryma whipplei*, a gram-positive intracellular actinomycete bacterium. Histologically, the small bowel lamina propria is expanded by macrophages with foamy pink cytoplasm that broaden and flatten the villi. Dilated lacteals containing lipid deposits are a helpful H&E finding. The macrophage cytoplasm contains intensely PAS-positive, diastase-resistant cytoplasmic inclusions, and non-acid-fast gram-positive bacteria. The H&E appearance may be similar to MAC, but MAC involvement of the small intestine tends to be patchy, whereas Whipple's disease is diffuse, and the lipid vacuoles of Whipple's disease are not seen in MAC. PAS-positive, diastase-resistant inclusions within the macrophages are found in both Whipple's disease and MAC; however, the shapes are different. In Whipple disease, the inclusion is bright staining and coarsely granular; in MAC, the PAS with diastase stain reveals a faintly positive bacillary form. Distinction between the two entities is readily made by use of the acid-fast stain that is positive in MAC but negative in Whipple's disease. (Answer E: Incorrect)

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