Case History:

61 year old female presents to GI clinic with history of non-bloody, watery diarrhea that waxed and waned for years, but was more consistent in the past 4 months. The diarrhea typically occurs at night and can be up to 10 times per day. She has a few pounds of unintentional weight loss from her baseline that she attributes to chronic diarrhea. She was on antibiotics a few months prior for a presumptive UTI. She has no past medical history other than iron deficiency anemia. She has no family history of GI disease, exotic travel, prior abdominal surgery, or other exposures. She has no nausea, vomiting, fevers, or chills. Colonoscopy was performed and demonstrated mild left-sided diverticulosis and normal-appearing mucosa with no inflammation. Random biopsies of the colon were obtained to rule out microscopic colitis.

Histologic sections of the colon biopsies along with ancillary special stains are depicted below (Figures 1-5).

Figure 1. Hematoxylin and eosin, (40x)

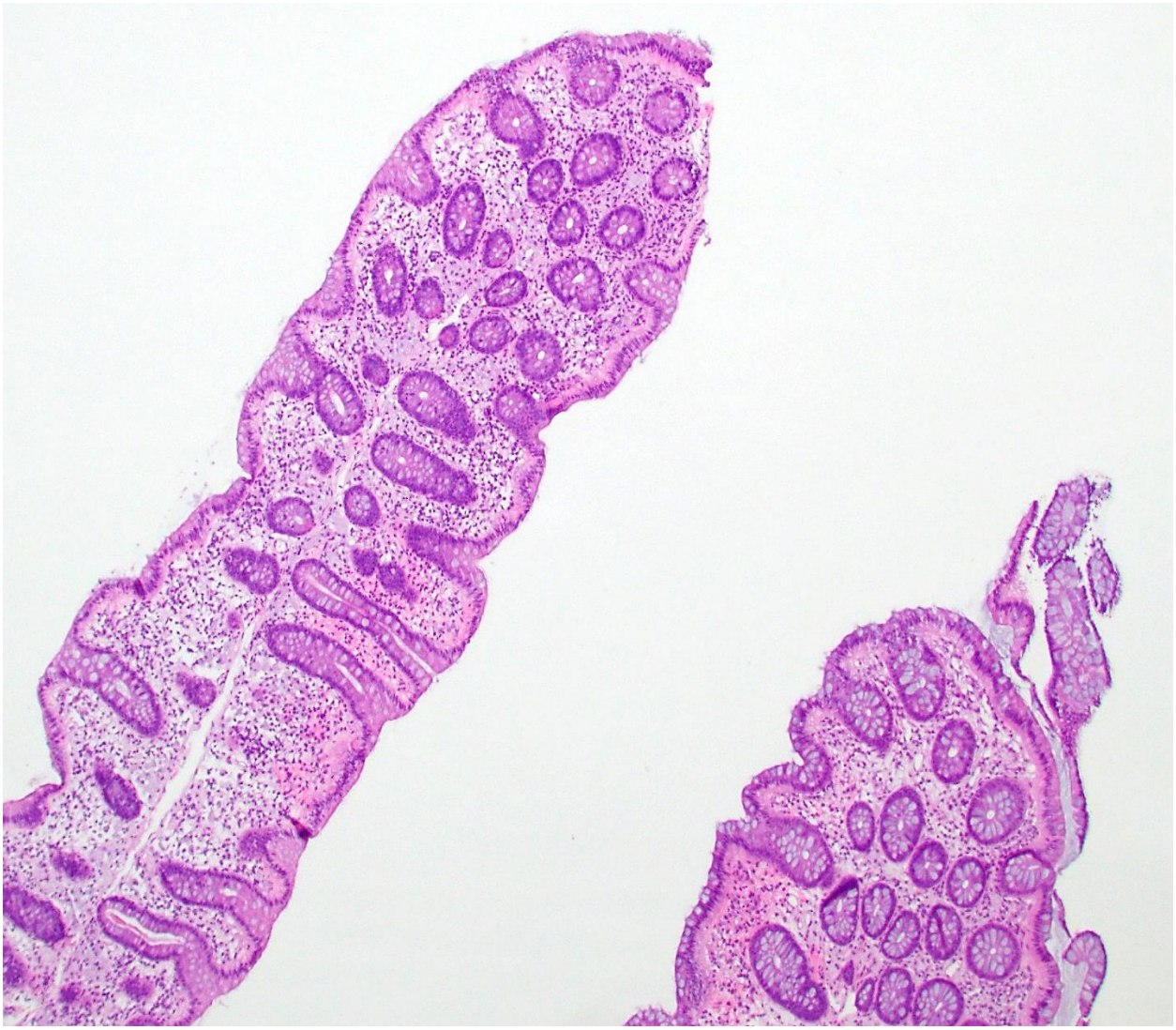


Figure 2. Hematoxylin and eosin, (100x)

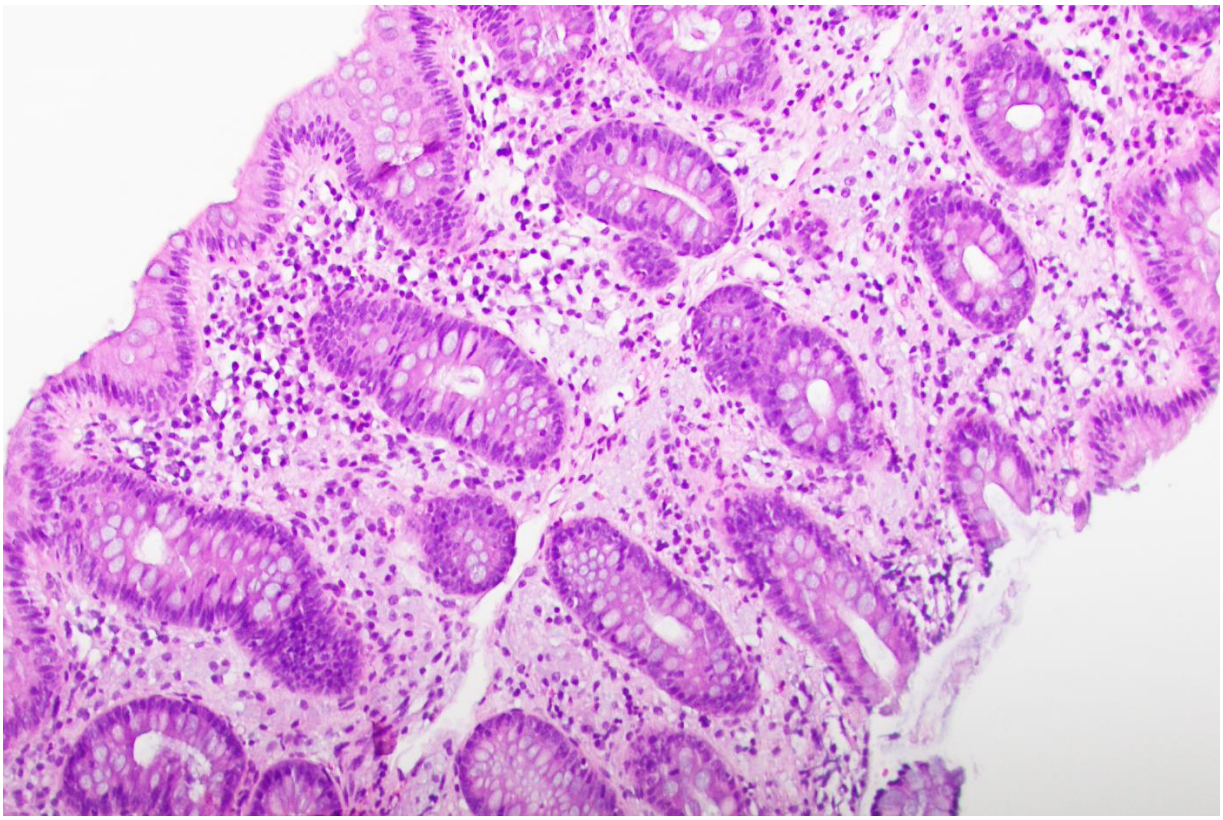


Figure 3. Hematoxylin and eosin, (400x)

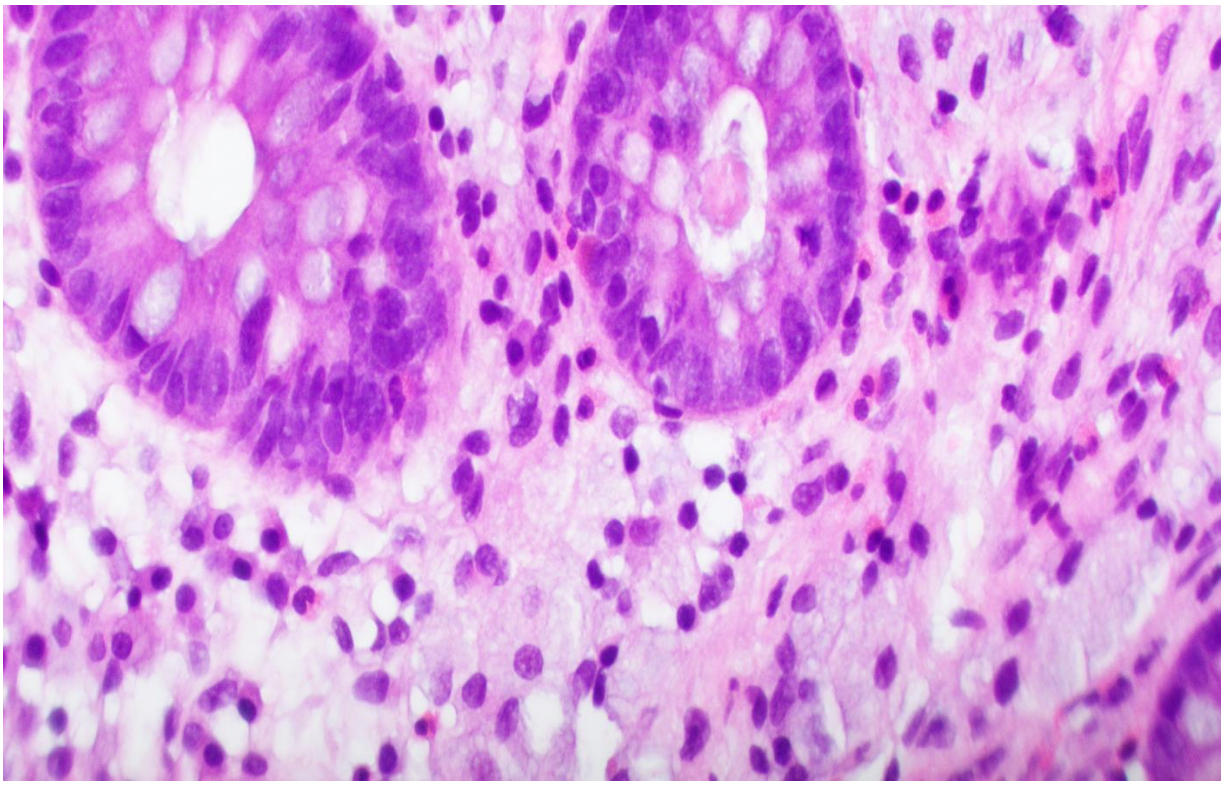


Figure 4. PAS stain (400x).

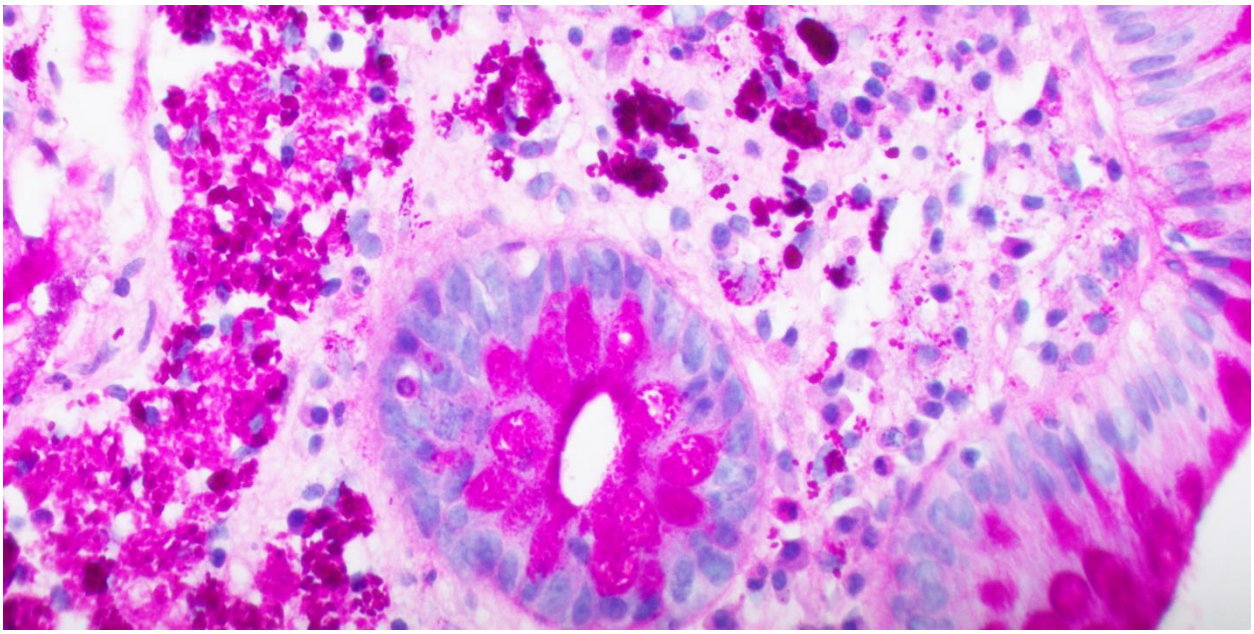
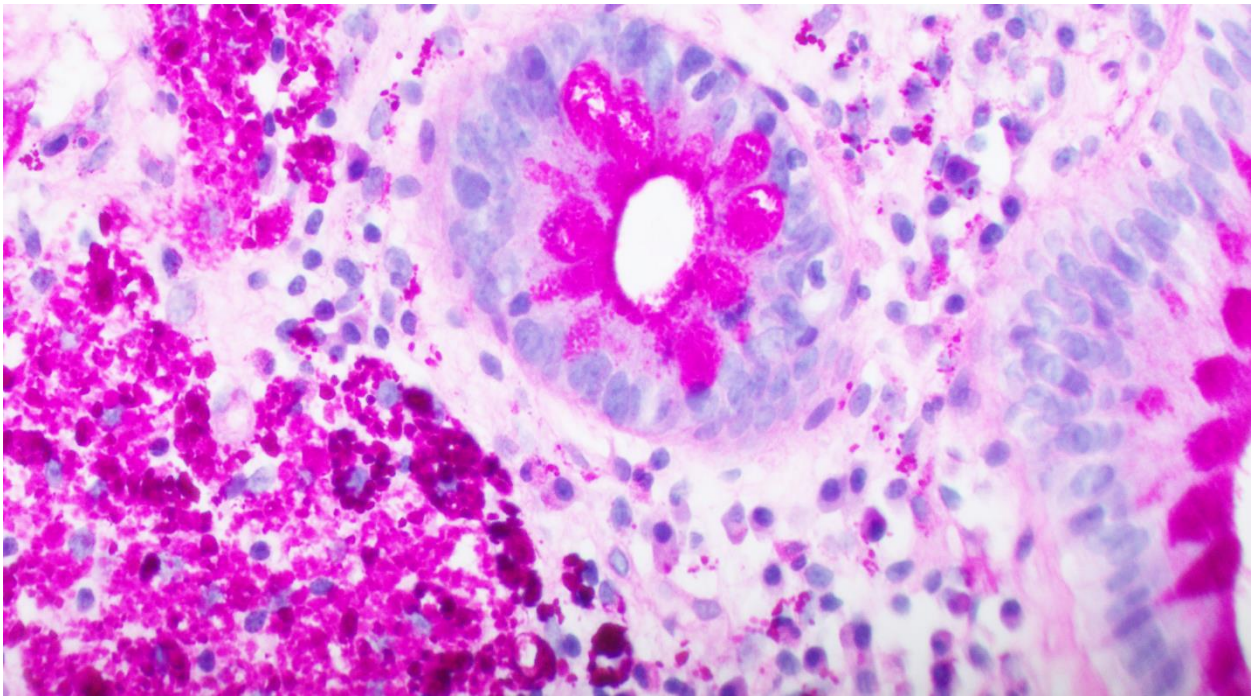


Figure 5. PAS/D stain (400x).



Note: AFB Ziehl-Neelsen and AFB Fite stains (not pictured) were negative.

What is the most likely diagnosis?

A. *Mycobacterium avium intracellulare* complex

B. *Histoplasma capsulatum* (Histoplasmosis)

C. *Pneumocystis jiroveci*

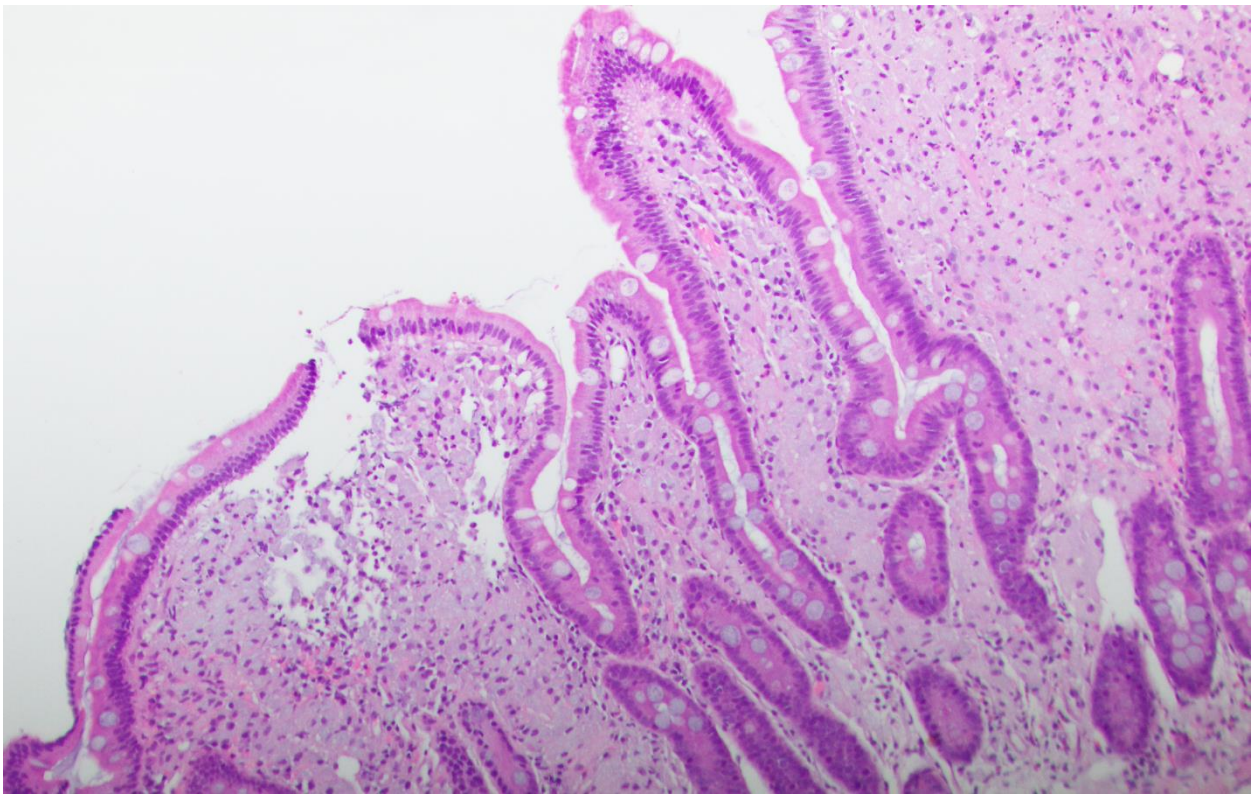
D. *Tropheryma whipplei* (Whipple Disease)

E. *Rhodococcus equi*

Correct diagnosis: D. *Tropheryma whipplei* (Whipple Disease)

A subsequent esophagogastroduodenoscopy was performed and demonstrated normal esophagus and stomach, mild erythema in the bulb and the second portion of duodenum with no atrophy. Random biopsies of the duodenum were obtained. A histologic section of the duodenal biopsy is depicted below (Figure 6).

Figure 6. Hematoxylin and eosin (H&E), (100x objective)



Case Discussion:

The histologic sections of the colon biopsy demonstrate unremarkable colonic mucosa that is relatively "normal" on low power magnification (Figure 1). On higher-power magnification (Figures 2-3), the histologic sections show infiltration of foamy macrophages within the lamina propria. There is no evidence of active or chronic colitis, granulomas, dysplasia, or malignancy. Histologic features of microscopic colitis (i.e. lymphocytic colitis or collagenous colitis) are not appreciated in the biopsy.

The special stains for PAS without and with diastase digestion (Figures 4 and 5, respectively) highlight numerous PAS-positive, diastase-resistant granules consistent with bacteria within the foamy macrophages. The organisms are also seen within the lamina propria extracellular space, fibroblasts, and endothelial cells. Special stains for AFB Ziehl-Neelsen and AFB Fite are negative. The subsequent duodenal biopsy (Figure 6) highlights blunted and rounded villi with foamy macrophages with likely the same organisms. Overall, the histologic and special staining findings are diagnostic of Whipple disease.

Whipple disease is systemic infection caused by *Tropheryma whipplei*. The duodenum and jejunum are the most common sites of infection, but other less common sites such as colon, appendix, liver, brain, endocardium, and retroperitoneum have been reported. Clinically, the patients are predominantly Caucasian males presenting in the fourth and fifth decades. The reported symptoms are protracted and nonspecific, and include diarrhea, low-grade fever, weight loss, abdominal pain, nausea, vomiting, gastrointestinal tract bleeding, malabsorption, anemia, lymphadenopathy, central nervous system symptoms, and arthritis. Endoscopically, the findings range from normal to erythema, edema, white patches, bleeding, and dilated villi. The latency period from initial symptoms to diagnosis ranges from 1 to 10 years on average. Treatment with antibiotics typically results in a dramatic positive response, but patients may have chronic relapsing disease in some cases. Microscopically, the histologic features and ancillary studies are as described above and may also include lipid globules in the lamina propria. In addition to histology and special stains, the Whipple antigen can be identified by immunohistochemistry using a polyclonal rabbit antibody produced against a cultured *Tropheryma whipplei* strain. Other diagnostic assays include polymerase chain reaction for 16S ribosomal RNA genes of *Tropheryma whipplei,* which is particularly helpful in ambiguous situations.

Answer A. *Mycobacterium avium intracellulare* complex is typically seen in immunocompromised patients (especially with acquired immunodeficiency syndrome) as an opportunistic infection. Patients have CD4 counts less than 100 per µl. Symptoms are similar to those seen in Whipple disease. Histologic findings are also similar and show infiltration of foamy macrophages within the lamina propria without mononuclear inflammatory infiltrate. Granulomas can be seen in immunocompetent patients, but are not typically present in immunocompromised patients. Lipid globules encountered in the villi in Whipple disease are not a feature of *Mycobacterium avium intracellulare* complex infection. PAS with diastase

stain reveals fibrillary staining pattern in contrast to granular staining characteristic of Whipple disease. AFB stain is positive confirming the presence of acid-fast bacilli.

Answer B. Patients with *Histoplasma capsulatum* (Histoplasmosis) infection usually present with nonspecific gastrointestinal symptoms. The ileum is the most commonly involved, but histoplasmosis has been documented throughout the gastrointestinal tract. The histologic sections demonstrate diffuse lymphohistiocytic infiltrate and nodules involving the mucosa and submucosa. The lesions are usually associated with the Peyer's patches within the ileum and can be seen admixed with granulomas, giant cells, and ulcers. The organisms are identified with fungal stains (i.e. GMS or PAS) as small, ovoid intracellular yeast forms with small budding.

Answer C. *Pneumocystis jiroveci* typically occurs in patients with acquired immunodeficiency syndrome and pulmonary manifestations, but extrapulmonary presentations (including gastrointestinal tract) have also been reported. This infection can also be seen in immunocompromized patients with a history of organ transplantation, hematopoietic malignancies, and chronic steroid use. Histologically, the sections show granular and foamy eosinophilic casts within the lamina propria and mucosal vessels. They can be seen in association with varying inflammatory infiltrates, such as macrophages and granulomas. Special stain for GMS highlights 5 to 7 µm spherules that are crescent or cup-shaped.

Answer E. *Rhodococcus equi* is a gram-positive coccobacillus that typically infects immunocompromised patients. Infection of the gastrointestinal tract results in chronic bloody diarrhea with systemic involvement. The histologic sections usually show inflammatory-type polyps with foamy macrophages packed with intracellular organisms that stain positively with PAS and Gram stains, and partially with AFB stain.

References:

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