**Case history:**

A 52 year old man with a history of ankylosing spondylitis treated with infliximab was admitted for worsening fatigue, weight loss, diarrhea, and fevers. Serial physical exams revealed oral ulcers and intermittent diffuse abdominal tenderness. A CT of the abdomen and pelvis revealed diffuse colitis, while a chest CT showed a few small nodules in the lungs, including a 6mm nodule in the lingua of the left lung. Colonoscopy revealed diffuse colonic edema with inflammatory pseudopolyps ranging from a few millimeters to a few centimeters, which were biopsied (Figures 1-3).

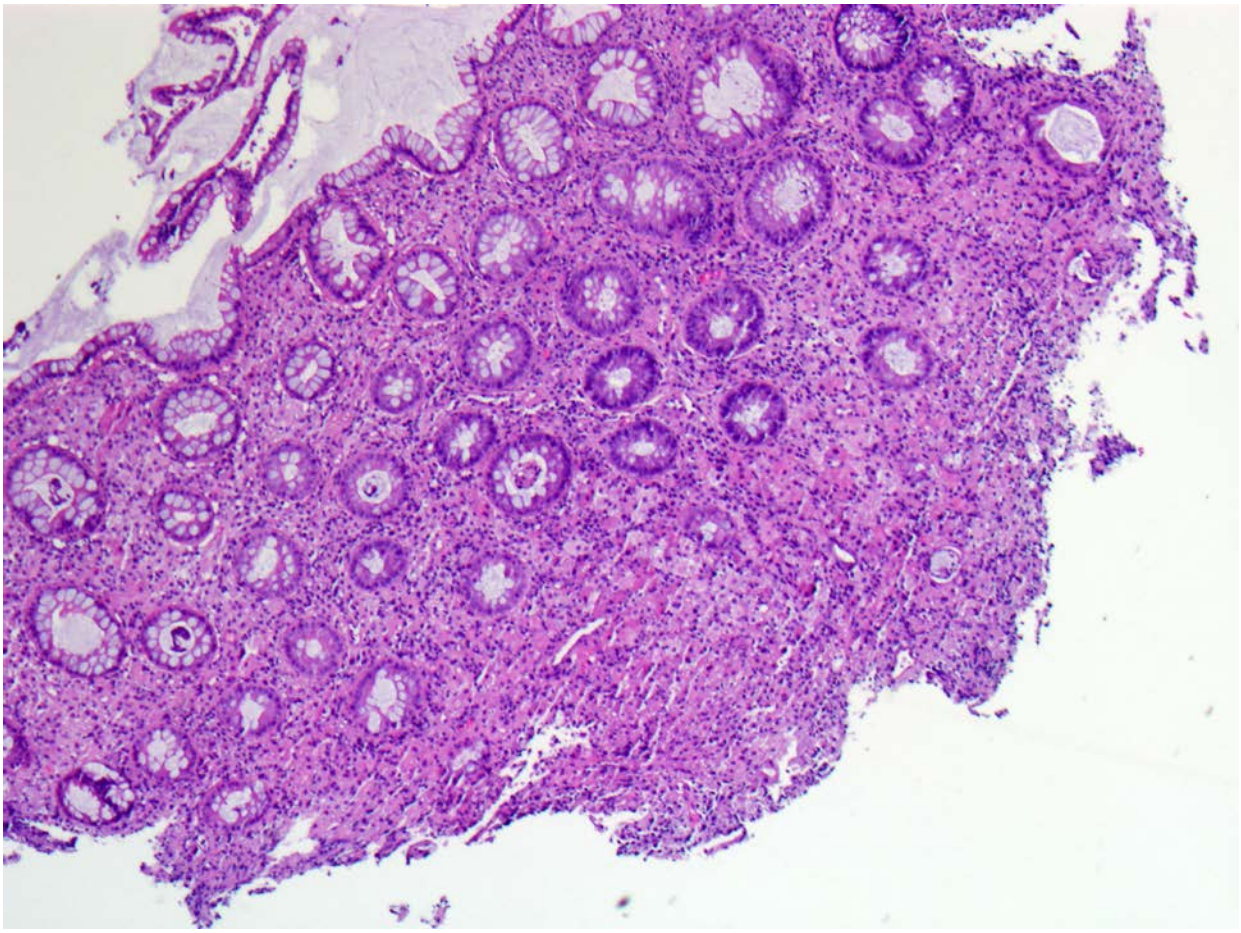

Figure 1. Biopsies from polypoid areas of the colon.

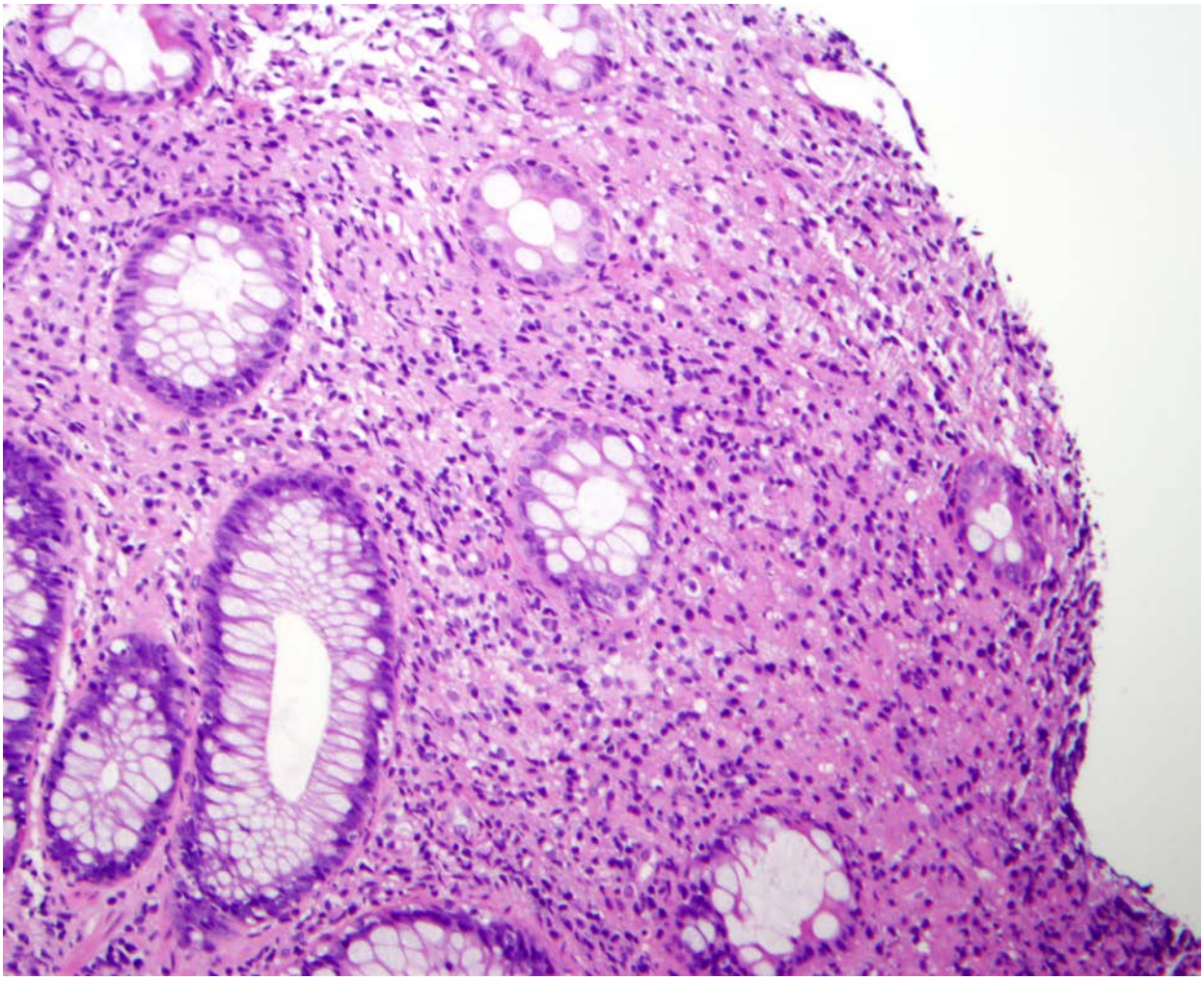

Figure 2.

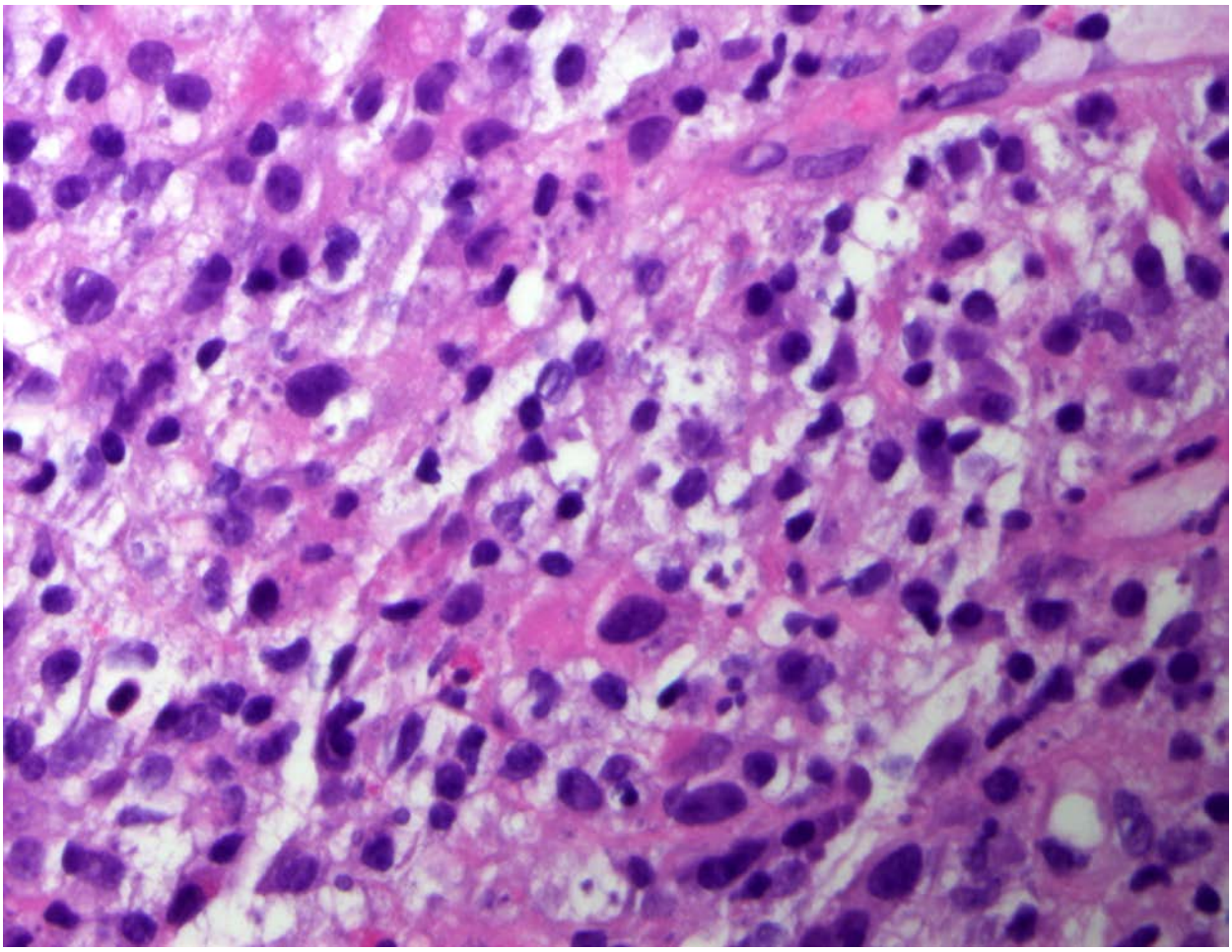

Figure 3.

**Question:**

Based on the microscopic findings, which condition does this patient most likely have?

A. Crohn's disease
B. Mycobacterial infection
C. Histoplasmosis
D. Mantle cell lymphoma
E. Leishmaniosis

**Answer:** C. Histoplasmosis

**Discussion:**

The biopsy shows lamina propria expansion by lymphocytes and histiocytes containing ovoid, 2-5 µm intracellular yeast forms consistent with histoplasmosis. *Histoplasma capsulatum (H. capsulatum*) was initially described in 1905 by an American physician, Samuel Darling, during the construction of the Panama Canal (1); however, *H. capsulatum* is also endemic to the central United States, especially the Ohio, Missouri, and Mississippi River valleys (2). *H. capsulatum* is a thermally dimorphic fungus, existing in the mycelial form at room temperature and the yeast form at mammalian body temperature (3-5). The fungus grows particularly well in soil enriched by avian or bat guano, exposure to which may serve as an important clue for further evaluation for histoplasmosis (2,6-8). The organisms enter humans primarily by inhalation of airborne conidia, however primary gastrointestinal infection has been also suggested by consuming contaminated water (9-11). Upon inhalation, *Histoplasma* is ingested by pulmonary tissue macrophages, where the organism may proliferate intracellularly, spread to regional lymph nodes, and disseminate throughout the body via hematogenous and lymphatic routes (9, 12). In most immunocompetent individuals *Histoplasma* infection is an asymptomatic pulmonary disease (4,9). However, in immunocompromised individuals *H. capsulatum* can cause life-threatening pulmonary infections, including severe chronic cavitary pulmonary process and fibrosing mediastinitis (9). Disseminated histoplasmosis, involving multiple organ systems, is estimated to occur in 55% of *Histoplasma* infected immunocompromised patients and 4% of immunocompetent patients (9, 14-16). Gastrointestinal involvement occurs in 70% to 90% of patients with disseminated histoplasmosis (12,13).

Lamps et al. studied disseminated histoplasmosis in 52 immunocompromised and immunocompetent patients with gastrointestinal or hepatic involvement identified by H&E and silver staining (17). Of these cases, 43% presented with gastrointestinal symptoms. Gross gastrointestinal features included ulcers (49% of patients), hemorrhage (13%), nodules (21%) and obstructive masses (6%). Grossly normal mucosa was observed in 23% of patients with biopsy proven gastrointestinal involvement. Histologically, gastrointestinal findings included diffuse lymphohistiocytic infiltration (83%), lymphohistiocytic nodules (25%), minimal inflammatory reaction (15%), and rare well-formed granulomas (8.5%). Although well-formed granulomas are commonly seen in pulmonary histoplasmosis, they are much less characteristic of disseminated gastrointestinal disease. More commonly, as seen in the above figures and described in this case, gastrointestinal involvement is seen as lymphohistiocytic infiltration of the mucosa and looser granulomas (17).

In conclusion, pathologists should be aware that patients are vulnerable to histoplasmosis in the context of immunosuppression with anti-TNF-alpha therapy (18) and should be aware of the broad range of gastrointestinal inflammatory patterns seen in disseminated histoplasmosis.

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