Disseminated Histoplasmosis: An Unusual Cause of Bowel Obstruction

Kent J. Peterson, MD; Michael R. Rose, MD, MPH; Caroline Davitt, MD; Kirk A. Ludwig, MD

ABSTRACT

Introduction: Although histoplasmosis is an extremely rare cause of bowel obstruction, this case describes disseminated gastrointestinal histoplasmosis as it progresses from acute colitis to subacute recurrent bowel obstructions.

Case Presentation: A White man in his early 80s with history of multiple myeloma presented to the emergency department with lightheadedness and diarrhea. Following a diagnostic journey for unspecified colitis, urine antigen testing and endoscopic biopsies led to the diagnosis. During the initial 12 weeks of antifungal treatment, the disease process transitioned from an acute inflammatory syndrome into a recurrent bowel obstruction.

Discussion/Conclusions: Only one other case of histoplasmosis causing recurrent bowel obstruction has been reported; however, that patient succumbed to the disease without surgical intervention. No clear guidelines exist of how to manage bowel obstructions from rare infectious sources, such as histoplasmosis, but close surveillance, multidisciplinary care, and an understanding of gastrointestinal pathology can guide clinicians when encountering atypical etiologies of bowel obstruction.

INTRODUCTION

Histoplasma capsulatum (*H capsulatum)*, found primarily in soils contaminated by bird or bat feces, is the most common endemic fungus to cause disease in both immune-compromised and immune-competent hosts.[1] Within the United States, the dimorphic fungus is endemic to the Mississippi and Ohio River valleys.[1] Infection occurs through inhalation of unearthed *H capsulatum*-infested soil—most cited in old buildings, bridges, and caves. Dissemination occurs as macrophages, which can engulf but not destroy the yeast form, spread hematogenously to extrapulmonary sites rich in mononuclear cells.[2,3] Although 50% to 90% of all disseminated histoplasmosis cases involve the dense lymphatics of the gastrointestinal (GI) tract, most patients do not manifest symptoms.[4]

Histoplasmosis, when symptomatic, is most often marked by a transient respiratory infection, and immunocompromised hosts are more likely to present with active or disseminated disease. The presentation of disseminated disease is often nonspecific, with the most common symptoms of GI histoplasmosis being weight loss (87.5%), diarrhea (83.3%), and fever (76.7%).[2,3] *H capsulatum*, more rarely, can also mimic colitis or malignancy by forming ulcerations, strictures, and obstructive masses when manifested in the GI tract.[3-6] Diagnosis of GI histoplasmosis is most often made endoscopically, with pathology showing evidence of intra- and extracellular *H capsulatum* yeast forms with eccentrically placed nuclei and peripheral halo. The clinical course of GI histoplasmosis varies; however, the diagnosis carries a mortality of 22% to 40%.[2,3] The mainstay of treatment is intravenous followed by oral antifungals, and surgical intervention has been indicated to address complications or for diagnostic purposes, with surgery being reported necessary in up to 27% to 44% of GI histoplasmosis cases.[3] Although histoplasmosis is an extremely unusual cause of bowel obstruction, this case details a subacute fibrostenotic progression of gastrointestinal histoplasmosis and provides a guide to clinicians encountering atypical sources of intestinal obstruction.

• • •

Author Affiliations: Division of Colon and Rectal Surgery, Department of Surgery, Medical College of Wisconsin, Milwaukee, Wisconsin (Peterson, Davitt, Ludwig); Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland (Rose).

Corresponding Author: Kent J. Peterson, MD, Department of Surgery, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53226; email kjpeterson@mcw.edu; ORCID ID 0000-0001-8093-2040

CASE PRESENTATION

A man in his early 80s presented to the emergency department with acute chronic diarrhea and hypotension requiring fluid resuscitation and vasopressor support. On review of history, he had visited the emergency department numerous times over the prior 4 months for persistent diarrhea, lightheadedness, and 8 kg weight loss and had an unrevealing outpatient GI workup including stool studies, flexible sigmoidoscopy, and esophagogastroduodenoscopy. Over this time, he reported up to 10 to 15 nonbloody bowel movements a day with associated intermittent abdominal pain.

Relevant past medical history included multiple myeloma with prior autologous hematopoietic cell transplantation and active treatment with lenolidamide maintenance therapy. He was also on warfarin for paroxysmal atrial fibrillation with a CHA2DS2-VASC (congestive heart failure, hypertension, age ≥75 [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74, and sex category [female] score of 2. Surgical history included an appendectomy, as well as a radical prostatectomy decades earlier for definitive treatment of prostate cancer. Prostate-specific antigen was undetectable following resection with no evidence of recurrence or metastatic disease on surveillance. He had no other personal or family history of malignancy and had a documented normal colonoscopy within the last 5 years. Social history revealed that he worked in an office with no unusual exposures or recent travel. The only interaction with soil had been spreading mulch while landscaping months earlier. He reported no pulmonary symptoms on review of systems, which was otherwise negative.

On initial examination, he was frail-appearing with tachycardia and hypotension. There was moderate abdominal distension and right-sided tenderness without evidence of peritonitis. His stool was positive for fecal occult blood but there was no gross evidence of GI bleeding. The cardiopulmonary examination was unremarkable, with oxygen saturations of 98% to 100% on room air.

Figure 1. Computed tomographic images showing right colonic thickening (arrow) with surrounding fat stranding (left) and multiple pulmonary nodules (arrow) with upper lobe predominance (right).

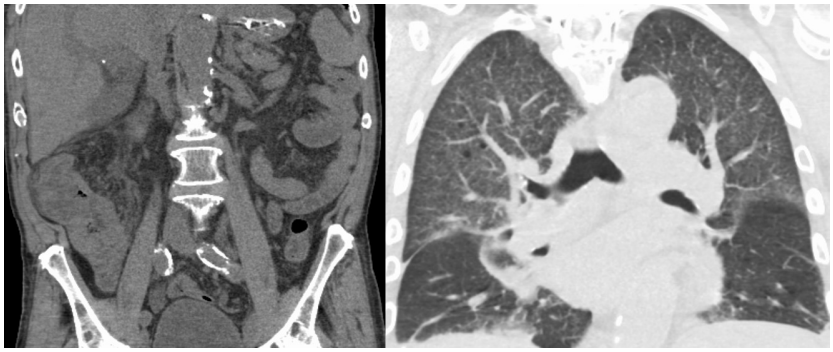
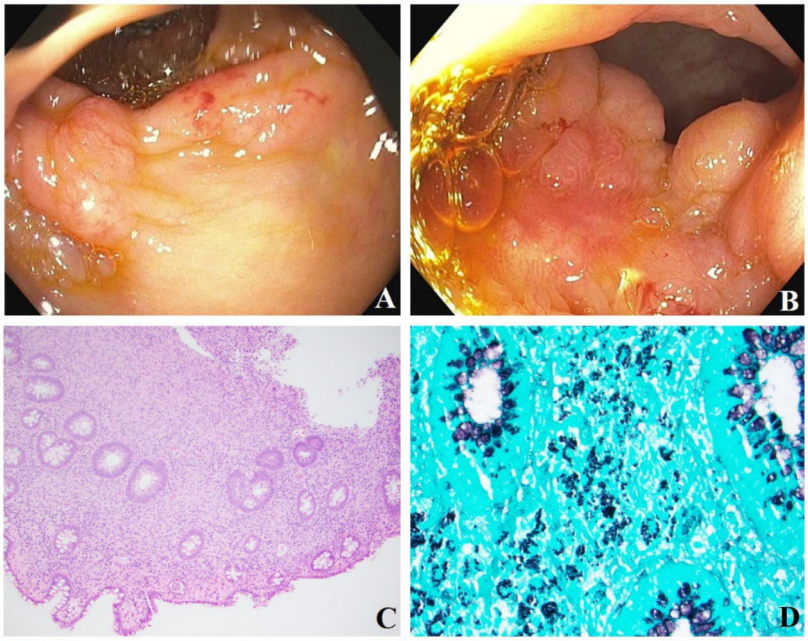


Figure 2. Endoscopic images showing active colitis near the ileocecal valve (A and B). Staining with H&E at 100X (C) and GMS at 400X (D) from ileocecal biopsy show lymphohistiocytic expansion and active neutrophilic cryptitis around dark staining histoplasma yeast forms (arrow) diffusely within the lamina propria of the ileocecal crypts.



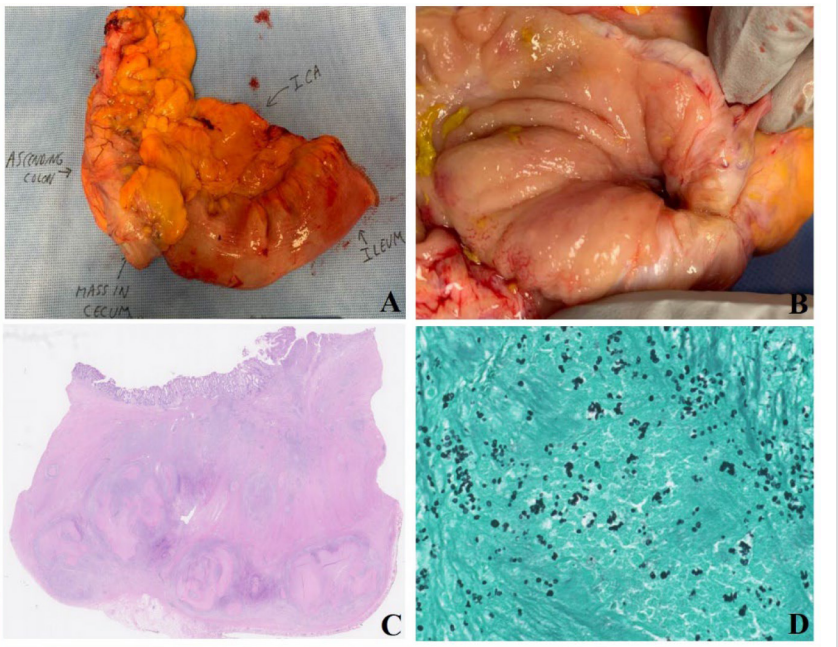
Abbreviations: H&E, haematoxylin and eosin; GMS, Grocott-Gomori's methenamine silver.

His laboratory studies on admission demonstrated a white blood cell count of 3.1 (normal range 4.2-11 K/mcL), absolute neutrophil count of 1.5 (1.8-7.7 K/mcL), hemoglobin level of 9.5 g/dL (13-17 g/dL), mean corpuscular volume of 91.1 fl (78-100 fl), and an international normalized ratio (INR) of 15.7 (2-3). Hemoglobin was decreased from 11.3 g/dL in the emergency department 2 weeks prior. Blood cultures showed no growth, serum cytomegalovirus antibody and polymerase chain reaction tests were negative, and stool studies were unrevealing

for bacterial, viral, or parasitic pathogen. Noncontrast computed tomography (CT) scan of the abdomen and pelvis on admission showed an acute inflammatory process of the ileum and right colon with no abscess or evidence of bowel perforation (Figure 1). Given the patient's immunosuppression, the chief concern was for neutropenic enterocolitis or malignancy.

On hospital day 7, following an unrevealing infectious workup and minimal response to broad-spectrum antibiotic treatment, a chest CT was performed due to a new oxygen requirement. The CT revealed innumerable miliary pulmonary nodules with upper lung field predominance and moderate-sized bilateral pleural effusions (Figure 1). Given these findings, infectious disease specialists recommended evaluation for potential mycobacterial and fungal etiologies. Bronchoalveolar lavage and thoracentesis samples were smear and culture negative for bacteria, mycobacterial, or fungal pathogens. Cytology of both bronchoalveolar and pleural samples were negative for malignancy. Interferon gamma release assay and galactomannan antigen testing were negative. Histoplasmosis urine antigen returned positive at greater than 19 ng/mL, the upper limit of quantification. The diagnosis of disseminated GI histoplasmosis was subsequently confirmed by colonoscopic biopsies, with histopathology showing narrow-based budding yeast forms within the ileocecal (IC) crypts (Figure 2).

Figure 3. Resected ileocolic specimen (A) with evident bowel wall thickening and severe stricturing at the ileocecal valve (B). H&E digital whole slide (C) and GMS 600X magnification (D) show transmural necrotizing granulomatous changes with dark staining yeast forms (arrow) at the edge of central necrosis.



Abbreviations: H&E, haematoxylin and eosin; GMS, Grocott-Gomori's methenamine silver.

In regard to treatment during the index hospitalization, the initial resuscitation included intravenous crystalloid fluids, normalization of the patient's INR with prothrombin complex concentrate and vitamin K, and 2 units of packed red blood cells for worsened anemia without evidence of gross GI bleeding or hemolysis. He was weaned from vasopressor agents within 48 hours of presentation and transferred out of the intensive care unit. He was continued on broad-spectrum antibiotics with anaerobic coverage for a suspected GI source. Empiric fungal coverage for a lower GI process is not typically performed in our practice unless there is a reason to suspect the diagnosis, but following the diagnosis of histoplasmosis, the patient was started on liposomal amphotericin B under the guidance of infectious disease specialists. He was transitioned to and discharged on 200 mg of oral itraconazole capsules 3 time daily for 3 days, followed by twice daily maintenance therapy.

In the months following diagnosis, urine antigen levels decreased but remained detectable on outpatient monitoring (2.1-2.88 ng/mL) despite antifungal treatment. The pulmonary nodules resolved on repeat CT; however, he continued to lose 7 kg of weight due to persistent GI symptoms—now with a predominance of nausea and vomiting. A repeat colonoscopy showed resolution of colitis but with a new stricturing at the IC valve. To define the extent of the disease causing the bowel obstruction, CT enterography was performed, showing submucosal wall thickening and enhancement throughout 20 cm of the terminal ileum, IC valve, and cecum. It was felt that the disease process had now transitioned from the aforementioned acute inflammatory syndrome into a fibrostenotic stricturing process. The patient required 5 admissions for bowel obstruction within the following 4 months from the index admission but improved on each subsequent admission with nonoperative therapy, including bowel rest, nasogastric decompression, and symptomatic management. His diet was supported with high caloric, high protein oral nutritional supplementation over this time. With continued weight loss and diminished quality of life, intra- and interdisciplinary discussions occurred between the patient, primary medical team, infectious disease specialists, gastroenterologists, and colorectal surgeons regarding operative intervention. The treatment decision to transition to a surgical approach was difficult given that the GI involvement may have resolved with further antifungal treatment. However, with the conversion from an inflammatory reaction to a fibrotic process

without adequate infectious source control, evidenced by repeat colonoscopy, CT enterography, and persistently detectable urine antigen, it was felt the colonic involvement was unlikely to resolve with medical therapy alone.

Six months following initial diagnosis, the patient underwent a hand-assisted laparoscopic ileocolonic resection with primary anastomosis. Intraoperatively, the distal ileum was noted to be chronically thickened and dilated; however, the colon appeared unaffected by disease apart from a mass-like stricture at the cecum and adenopathy palpable within the mesentery. The more proximal ileum appeared healthy without stenosis, active inflammation, or wall thickening, so a functional end-to-end anastomosis was created using the chronically dilated but otherwise unaffected ileum. The specimen was opened on the back table showing a stricture at the IC valve narrowing the lumen to less than 1 cm (Figure 3A and B). Pathologic examination of the specimen revealed chronic necrotizing granulomatous inflammation of the bowel wall (Figure 3C). Grocott-Gomori's methenamine silver stain highlighted numerous yeast forms morphologically compatible with persistent *H capsulatum* (Figure 3D).

The postoperative course was uncomplicated, and the patient was discharged to home on postoperative day 3. Following surgery, there were no further readmissions and H capsulatum urine antigen promptly became undetectable. At 1-month follow-up, he reported a much better quality of life, now tolerating a general diet. His weight improved to 66 kg from 58.4 kg by 3 months' time. He was maintained on lifelong oral itraconazole, and his surveillance colonoscopy at 1 year showed no histologic or endoscopic evidence of colitis, recurrent stricturing, or mucosal abnormalities. Itraconazole levels were monitored and noted to be within therapeutic range (ranging between 0.7-1.8, laboratory normal range 0.5-5.0 ug/mL).

DISCUSSION

Histoplasmosis often has an indolent presentation, and disseminated disease can mimic a wide variety of pathologies.[1,4,7-10] A familiarity with the varied presentations of histoplasmosis—particularly in the absence of pulmonary complaints—can enrich a clinician's illness script for this not entirely uncommon, but often protean, disease. This case provides insight into the clinical progression of GI histoplasmosis from the initial acute inflammatory reaction to the fibrostenotic process that required surgical resection. To our knowledge, this is the first reported case to describe the transition from medical to surgical management of a histoplasmosis bowel obstruction outside of the emergent setting. As such, the case offers guidance when encountering atypical infectious etiologies of bowel obstruction in the subacute setting.

A key decision-making point was assessing response to treatment. Vigilant surveillance delineated when the GI histoplasmosis was no longer reversible with medical treatment alone, a factor being that, after 12 weeks of antifungal treatment, there was apparent resolution of pulmonary disease but a persistence of GI disease and urine antigen positivity. This decision was guided by serial colonoscopies with biopsies showing resolution of active inflammation and the development of an ileocolic stricture. Additionally, CT enterography helped rule out secondary proximal strictures and discriminate between inflammatory and fibrotic stricturing. This clinical and radiologic surveillance allowed confidence that the bowel wall thickening was then due to a chronic fibrostenotic process, likely containing residual disease and, therefore, was unlikely to resolve without surgical intervention. Yeast forms found within the surgical pathology specimen, in addition to *H capsulatum* urine antigen becoming undetectable following resection, confirmed the suspicion that the GI tract was harboring a smoldering infection.

While it is not unheard of for GI histoplasmosis to require surgical intervention, currently the only reported cases have been performed in the emergent setting, typically prior to diagnosis.[3,6,11] Because of this, there is limited evidence to guide management of bowel obstructions secondary to histoplasmosis in the subacute or chronic setting. In fact, published clinical practice guidelines do not address surgical management of GI histoplasmosis.[12,13] However, it is reasonable to extrapolate management strategies using treatment approaches for a common inflammatory disease—Crohn's disease—as a guide. While ileum-predominant obstructive symptoms of acute and chronic Crohn's inflammation may resolve with administration of antiinflammatory medications, such as steroids, once the obstructive process has turned fibrotic, management shifts from medical to surgical.[14] A fungal-related bowel obstruction or other infectious source similarly differs from most forms of intestinal obstruction in that medical treatment has a reasonably high likelihood of resolving the obstruction.[3,11] Like other potentially reversible inflammatory etiologies, however, the patient may benefit from surgical resection once considered fibrostenotic and, thus, medically refractory.

Regardless the cause of obstruction, the decision to surgically intervene is clinically nuanced and heavily case dependent. Because of this, close endoscopic, radiologic, and immunopathogenic surveillance, along with multidisciplinary consultation, is vital in determining when the disease is unlikely to be eradicated by medical therapy alone. This case advocates for a medical approach in the acute setting while reserving surgical intervention, when able, for refractory cases.

CONCLUSIONS

Histoplasmosis should be considered in immunocompromised hosts presenting with inflammatory GI disease of unclear etiology, particularly in endemic areas. While medical management is first line for partial bowel obstruction, surgical intervention may be needed for those with refractory fibrostenotic disease. Source control through means of surgical resection is a consideration

in patients with residual GI disease, despite adequate antifungal treatment, and in complex and atypical cases such as this, a multidisciplinary and patient-centered approach is critical.

Funding/Support: None declared.

Financial Disclosures: None declared.

Acknowledgments: The authors thank Patricia Lye, MD; Jacqueline Kuzminski, MD; Jacqueline Gauger; Judy Borchardt; and the Children's Wisconsin Transport Team for their assistance with this project.

REFERENCES

1. Psarros G, Kauffman CA. Colonic histoplasmosis: a difficult diagnostic problem. *Gastroenterol Hepatol (N Y).* 2007;3(6):461-463.

2. Sharma R, Lipi L, Gajendra S, et al. Gastrointestinal histoplasmosis: a case series. Int J Surg Pathol. 2017;25(7):592-598. doi:10.1177/1066896917709945

3. Assi M, McKinsey DS, Driks MR, et al. Gastrointestinal histoplasmosis in the acquired immunodeficiency syndrome: report of 18 cases and literature review. *Diagn Microbiol Infect Dis.* 2006;55(3):195-201. doi:10.1016/j.diagmicrobio.2006.01.015

4. Yang B, Lu L, Li D, et al. Colonic involvement in disseminated histoplasmosis of an immunocompetent adult: case report and literature review. *BMC Infect Dis*. 2013;13:143. Published 2013 Mar 20. doi:10.1186/1471-2334-13-143

5. Spivak H, Schlasinger MH, Tabanda-Lichauco R, Ferstenberg H. Small bowel obstruction from gastrointestinal histoplasmosis in acquired immune deficiency syndrome. *Am Surg.* 1996;62(5):369-372.

6. Anderson BR, Marriott J, Bulathsinghala C, Anjum H, Surani S. Gastrointestinal histoplasmosis presenting as an acute abdomen with jejunal perforation. *Case Rep Med.* 2018;2018:8923972. doi:10.1155/2018/8923972

7. Gupta S, Hinkamp CA, Lo M. Urine antigen-negative disseminated histoplasmosis mimicking post-transplant lymphoproliferative disorder. *BMJ Case Rep.* 2020;13(6):e233976. doi:10.1136/bcr-2019-233976

8. Lee AI, Koo S, Vaidya A, Katz JT, Loscalzo J. Clinical problem-solving. A bird's-eye view of fever. *N Engl J Med.* 2011;365(18):1727-1732. doi:10.1056/NEJMcps1012518

9. Hertan H, Nair S, Arguello P. Progressive gastrointestinal histoplasmosis leading to colonic obstruction two years after initial presentation. *Am J Gastroenterol.* 2001;96(1):221-222. doi:10.1111/j.1572-0241.2001.03479.x

10. Kooblall M, Keane B, Murray G, Moloney E. Histoplasmosis mimicking primary lung neoplasm. *BMJ Case Rep.* 2014;2014:bcr2013203335. doi:10.1136/bcr-2013-203335

11. Suh KN, Anekthananon T, Mariuz PR. Gastrointestinal histoplasmosis in patients with AIDS: case report and review. *Clin Infect Dis*. 2001;32(3):483-491. doi:10.1086/318485

12. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007;45(7):807-825. doi:10.1086/521259

13. Araúz AB, Papineni P. Histoplasmosis. *Infect Dis Clin North Am*. 2021;35(2):471-491. doi:10.1016/j.idc.2021.03.011

14. Strong S, Steele SR, Boutrous M, et al. Clinical practice guideline for the surgical management of Crohn's disease. *Dis Colon Rectum.* 2015;58(11):1021-1036. doi:10.1097/DCR.0000000000000450

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

Visit www.wmjonline.org to learn more.