ACG CASE REPORTS JOURNAL

CASE REPORT | COLON

Isolated Ileal Stricture Secondary to Antigen-Negative GI Histoplasmosis in a Patient on Immunosuppressive Therapy

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ABSTRACT

We present a case of antigen-negative disseminated histoplasmosis manifesting as an isolated ileal stricture in a patient on chronic infliximab and methotrexate. Diagnosis can be challenging due to imperfect tests, and this condition should remain in the differential, even with negative testing. Mortality of untreated disseminated histoplasmosis can be as high as 80%.

INTRODUCTION

Gastrointestinal (GI) histoplasmosis is a form of disseminated histoplasmosis. It is a rare and potentially life-threatening infection, most often presenting in immunocompromised hosts in endemic areas. Symptomatology is highly variable and non-specific.[1] It rarely has been reported to cause small bowel obstruction, and the majority of these obstructive cases have been reported in patients with acquired immune deficiency syndrome (AIDS).[1-5] Diagnosis can be challenging as serum and urine *Histoplasma capsulatum* antigen testing is not 100% sensitive, and this condition should remain in the differential even with negative testing. GI histoplasmosis has the potential to mimic chronic inflammatory bowel disease, and further immunosuppression without pathologic confirmation is potentially harmful.[6] Mortality of untreated disseminated histoplasmosis can be as high as 80%.[7]

CASE REPORT

A 73-year-old white woman was referred to our tertiary care gastroenterology service for 7 months of progressive nausea, post-prandial abdominal pain, non-bloody diarrhea, and a 13.5-kg weight loss over the same time period. Her past medical history was significant only for rheumatoid arthritis (RA), for which she was being treated with both subcutaneous methotrexate and infliximab infusions. An initial workup by her primary care physician, including complete metabolic panel, liver function tests, complete blood count, upper endoscopy/colonoscopy, and abdominal computed tomography (CT) scan, was non-revealing. An upper abdominal series with small bowel follow-through showed findings suggestive of ileal stricture without obstruction, and she was referred to our service for small bowel enteroscopy.

The patient underwent repeat esophagogastroduodenoscopy, which again was non-revealing. On upper balloon enteroscopy, a benign-appearing intrinsic severe stenosis measuring 10 mm in length by 3 mm inner diameter with associated ulcerations was found in the distal ileum (Figure 1). The endoscope was unable traverse the stenosis. Cold forceps biopsies were obtained, and a through-the-scope balloon dilation (8–10 mm) was performed. The scope then was able to pass, and examination of the remaining portions of the ileum had normal appearance.

Microscopic examination of the stricture biopsies showed acute ulcerative and granulomatous ileitis with inflammatory granulation tissue positive for plentiful fungal organisms morphologically typical of *Histoplasma* species

ACG Case Rep J 2017;4: e10. doi:10.14309/crj.2017.10. Published online: January 18, 2017.

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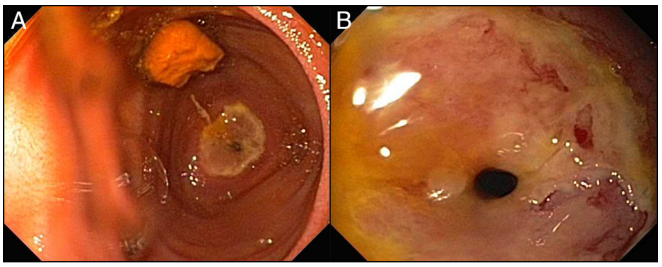

Figure 1. (A and B) Balloon endoscopy showing intrinsic ileal stricture with ulcerative changes.

(Figure 2). Stains for acid-fast bacilli and cryptococcus were negative. Serum and urine *Histoplasma* antigens were negative. The patient subsequently failed outpatient oral itraconazole treatment due to progressive nausea, vomiting, and abdominal pain. She was hospitalized for liposomal amphotericin B treatment without therapeutic response. She was taken for partial small bowel resection, where pathology again confirmed diagnosis of histoplasmosis. She recovered well and continued on oral itraconazole for maintenance therapy for several months. Her immunosuppression was held for the duration of treatment, and she has since resumed treatment with certolizumab, an alternative anti-tumor necrosis factor (TNF) agent. As both serum and urine antigens were negative, periodic monitoring will be based on symptoms and fungal blood cultures drawn at 3-month intervals.

DISCUSSION

GI histoplasmosis is a rare but reported complication of immunosuppressed states, including patients on TNF inhibitors.[8-10] The most common presenting symptoms are fever, hepatosplenomegaly, weight loss, and hematologic findings, with GI symptoms occurring in approximately one-third of patients.[1] Diagnosis often is delayed due to non-specific symptoms at presentation. In one institutional review of 111 patients with disseminated histoplasmosis of any nature, only 59% were immunocompromised, highlighting the importance of considering the diagnosis even in immunocompetent hosts.[1] Five percent of those patients were reported to be on TNF inhibitors.

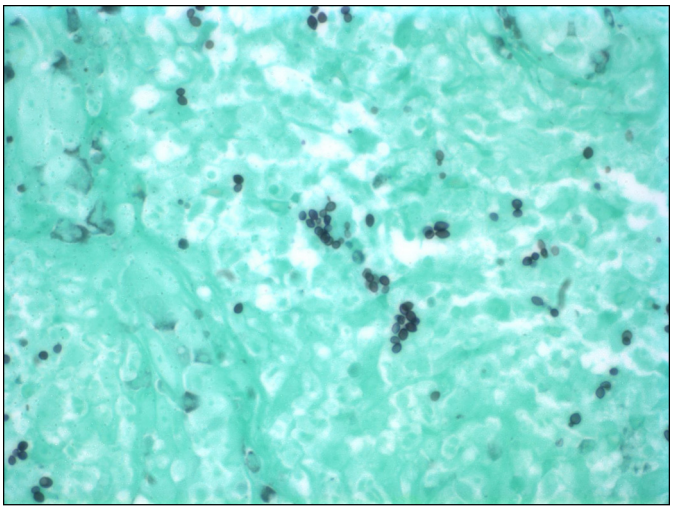

Figure 2. Grocott-Gomori's methenamine silver stain from small bowel biopsy demonstrating *Histoplasma capsulatum*.

Diagnosis hinges largely on serum and urine antigen tests, which are reportedly up to 90% sensitive for the detection of disseminated disease.[11] Even in this case, the majority of patients eventually require tissue biopsy for definitive diagnosis and approximately one-third require surgical intervention.[1] The use of fungal DNA detection using internal transcribed spacer primer sets has been reported in cases of antigen-negative disease.[12] In one pathology series of 52 cases, typical findings on GI specimens included ulcerations, hemorrhagic lesions, and nodules; however, only 6% were reported to have findings of obstructive process.[13] Ileocecal fistulizing disease has been reported, as has pseudotumor mimicking malignancy.[12,14] Endoscopic findings have the potential to mimic inflammatory bowel disease, and in the case of negative antigen testing, pathologic exclusion of infectious etiology is necessary prior to initiating or increasing immunosuppressive therapy.[6]

Treatment is based on extended antifungal therapy with oral itraconazole or, in severe cases, amphotericin.[15] Surgical resection may be required. Long-term maintenance therapy is required in many cases because recurrence rates are high, especially in those with intrinsic or acquired immunodeficiency. In cases of iatrogenic immunodeficiency, alteration or discontinuation of offending agents should be considered if possible.

This case illustrates the utility of small bowel enteroscopy in diagnosing suspected strictures found on imaging for which the differential diagnosis remains broad. Tissue diagnosis is required to guide management. Additionally, it is known that balloon dilation of small bowel strictures associated with Crohn's disease results in statistically significant improvements in surgery-free intervals; however, it is unknown whether there is a similar trend for infectious strictures of this nature.[16] In this case, dilation delayed surgery by several months.

Balloon enteroscopy is a useful modality for the diagnosis and treatment of small bowel manifestations of disseminated histoplasmosis. GI histoplasmosis should be considered in both immunocompromised and immunocompetent hosts who have persistent fever, hepatosplenomegaly, GI complaints, and weight loss.[1,3,15] Serum and urine antigen detection tests are not 100% sensitive, and further workup should be performed if clinical suspicion remains high, considering the mortality of untreated disseminated histoplasmosis can be as high as

80%. Tissue diagnosis may be required, especially in the case of negative *Histoplasma* antigen testing.

DISCLOSURES

Author contributions: KM Rowe is the primary author and article guarantor. M. Green and F. Nehme co-wrote the manuscript. N. Tofteland edited the manuscript.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received August 2, 2016; Accepted October 28, 2016

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