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Antigen negative gastrointestinal histoplasmosis in an AIDS patient

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 51
Final Diagnosis: Gastrointestinal histoplasmosis
Symptoms: Abdominal pain • nausea • vomiting
Medication: —
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology

Objective: Adverse events of drug therapy

Background: Gastrointestinal involvement in patients with disseminated histoplasmosis is considered common since the organism is identified in the GI tract of approximately 70–90% of autopsy cases. This infection is rarely recognized by clinicians due to its non-specific symptoms. Lesions may occur anywhere in the GI tract but most commonly affects the terminal ileum. Patients present with GI bleeding, intestinal obstruction, ulcerations, masses, and peritonitis. Serum and urine serological antigens are useful for diagnosis because they are positive in over 90% of patients with disseminated disease but may be falsely negative in patients with localized GI involvement. Although histopathology and tissue cultures are specific, limitations include insensitivity and need for invasive procedures. Antifungal agents include intravenous amphotericin B for severe or unstable disease and oral itraconazole for stable disease.

Case Report: A 51-year-old HIV positive female presented with abdominal pain, nausea and vomiting. A CT scan of the abdomen revealed circumferential narrowing around a segment of the sigmoid colon with the cecum demonstrating irregular thickened walls. A biopsy of an obstructing duodenal mass found on endoscopy revealed granulomatous inflammation and budding yeasts consistent with *Histoplasma spp*. She was started on intravenous liposomal amphotericin B and after 2 weeks switched to itraconazole oral solution. Urine and serum histoplasma antigens sent out 2 weeks after antifungal treatment were negative.

Conclusions: This case report illustrates the importance of recognizing gastrointestinal histoplasmosis in AIDS patients presenting with non-specific GI symptoms.

MeSH Keywords: AIDS • HIV Enteropathy • Histoplasmosis

Full-text PDF: http://www.amjcaserep.com/download/index/idArt/889940

Background

Histoplasmosis is one of the most common opportunistic fungal infections in AIDS patients living in endemic areas. The gastrointestinal (GI) system is affected in up to 70-90% of cases [1]. This involvement is usually asymptomatic and clinically unrecognized. A MEDLINE search from 2002 to 2013 and a review of references of retrieved articles revealed a multitude of case reports of histoplasmosis with GI involvement. However, there are no reports where histoplasmosis presents as a mass lesion in the duodenum. We report a case of histoplasmosis presenting as duodenal obstruction in which urine and serum quantitative histoplasma antigens were non-diagnostic.

Case Report

A 51-year-old HIV positive female was admitted to the hospital for a one week history of abdominal pain, nausea and vomiting. Patient reported vomiting about 5-6 hours after eating. Vomitus consisted of bilious material and undigested food particles. She was diagnosed with HIV infection three months prior and was immediately started on efavirenz, lamivudine and tenofovir. Three months later, her CD4 count was 79 and HIV viral load was undetectable (baseline results before treatment are unknown). On physical examination, she appeared cachectic and had an erythematous oropharynx with white exudates. Her abdomen was tender to deep palpation. CT scan of the abdomen revealed circumferential narrowing around a segment of the sigmoid colon with the cecum demonstrating irregular thickened walls, splenic and liver hypodensities, and pulmonary nodules. A Histoplasma urine antigen was ordered upon admission but was lost in transit to the laboratory. Endoscopy showed an obstructing duodenal mass (Figure 1). Biopsy revealed granulomatous inflammation and budding yeasts consistent with *Histoplasma spp*. (Figure 2) and multiple non-necrotizing granulomas. The patient was started on intravenous liposomal amphotericin B (5 mg/kg/day). After 2 weeks, she was switched to itraconazole oral solution. Repeat urine and serum histoplasma antigens sent out 2 weeks after antifungal treatment was started were negative. The mass remained unchanged on repeat endoscopy but biopsies showed less granulomas. She was also found to have a mass in her transverse colon that showed non-necrotizing granulomatous inflammation with no evidence of viral cytopathic effect (Figure 3). Patient was still not tolerating diet and a gastrojejunostomy, transverse colectomy with stapled anastomosis, and a percutaneous gastrostomy tube placement were performed. Her hospital course was complicated by duodenal perforation into the retroperitoneum. She was temporarily treated with TPN and then gastrostomy tube feedings, and subsequently on a clear liquid diet as tolerated. She was discharged on oral voriconazole to complete a year of treatment. Efavirenz was changed to raltegravir due to concern of drug interactions with antifungal treatment. On a three month-outpatient follow up visit, she was doing well and tolerating all medications. Her repeat CD4 count was 85 and her HIV viral load remained undetectable.

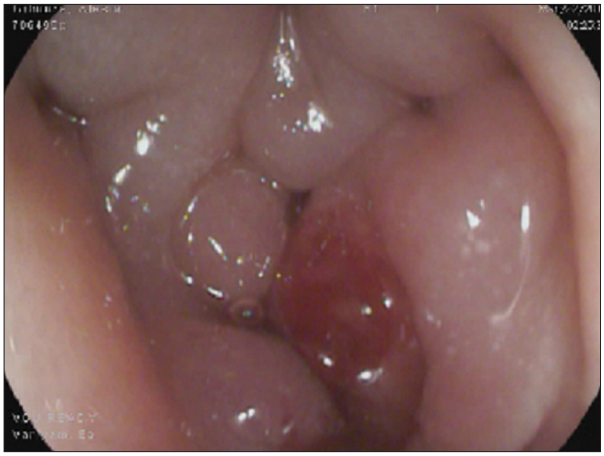

Figure 1. Endoscopy. Ulcerated and obstructing mass in the second portion of the duodenum.

Discussion

Gastrointestinal (GI) involvement is very common in AIDS patients with progressive disseminated histoplasmosis. *Histoplasma capsulatum* can be identified in the GI tract of 70–90% of these patients [1]. Although GI involvement is common, GI symptoms occur in only 3–12% of patients. This disparity could indicate that GI histoplasmosis (GIH) is an underdiagnosed entity [1]. Symptoms are non-specific such as fever, diarrhea, abdominal pain, hepatomegaly, or oropharyngeal ulceration [2]. Intestinal disease in GIH can manifest in different forms. Lesions present mainly in the ileocecal region because of an abundance of lymphoid tissue [3]. Patients can present with more worrisome symptoms including hematochezia, melena, obstruction and perforation of the small and large bowel, leading to peritonitis. GI bleeding and colonic obstruction due to large inflammatory masses mimicking a malignant process appear to be more common in AIDS patients compared to immunocompetent patients. Small bowel obstruction presents as strictures, segmental inflammation, ulceration that affects sites between the duodenum and terminal ileum. GIH may be misdiagnosed as appendicitis, inflammatory bowel disease, malignancy and other intestinal diseases leading to the use of inappropriate and ineffective therapies and unnecessary surgical interventions. Patients with bowel obstruction, perforation, or bleeding and systemic findings suggestive of histoplasmosis should be evaluated for GIH. Immune reconstitution inflammatory syndrome (IRIS) was considered in the differential diagnosis as the patient had recently begun antiretroviral therapy (ART). Histoplasmosis is a known fungal infection that

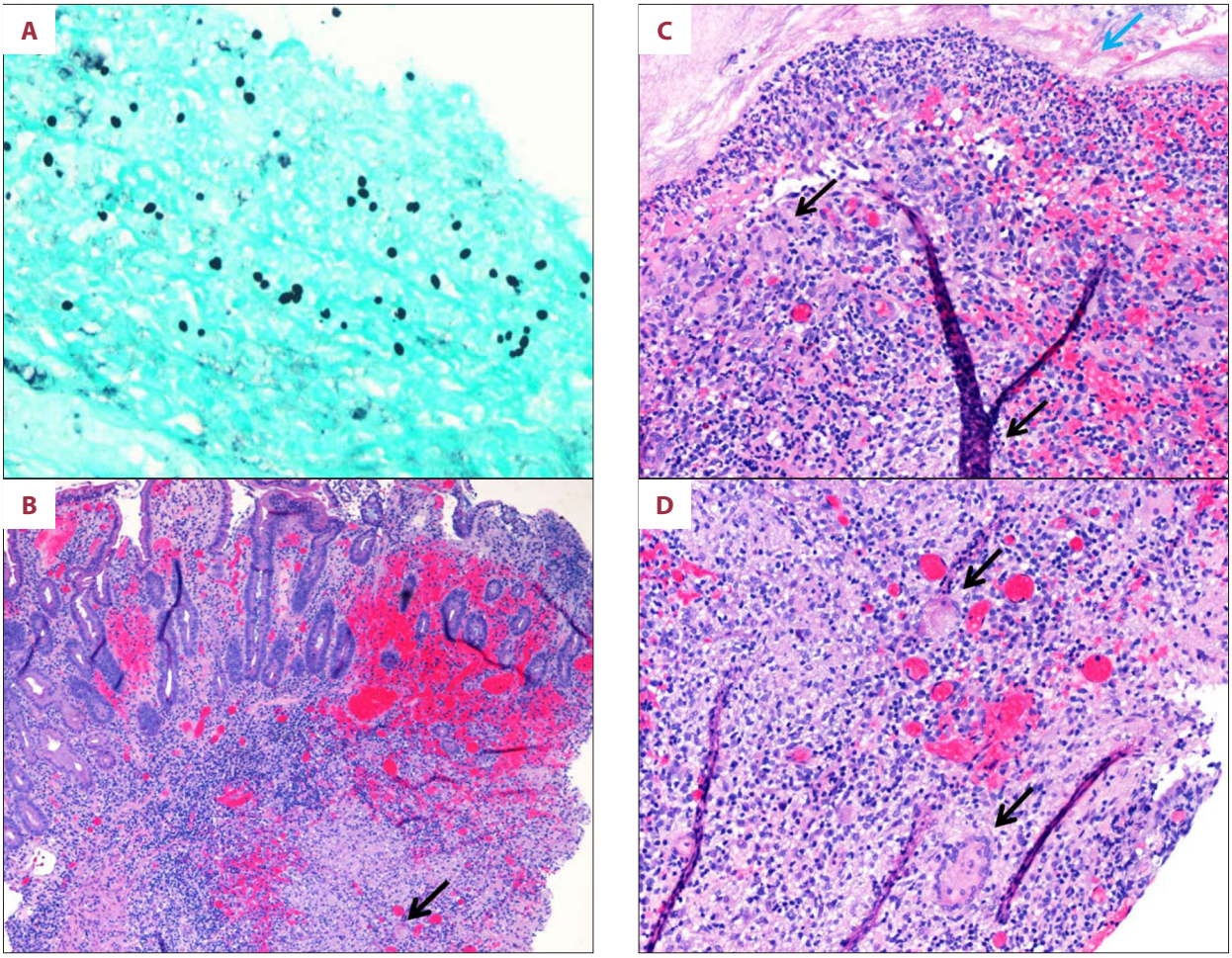

Figure 2. Duodenal biopsy. (**A**) GMS stain with budding yeasts consistent with *Histoplasma spp*. (**B**) Duodenal mucosa with ulcerated surface with ill-formed granuloma (blue arrow). (**C**) Fibrinopurulent exudate (blue arrow) with underlying granulation tissue and chronic inflammation with ill-formed granulomas and multinucleated giant cells (black arrows). (**D**) Higher power multinucleated giant cells.

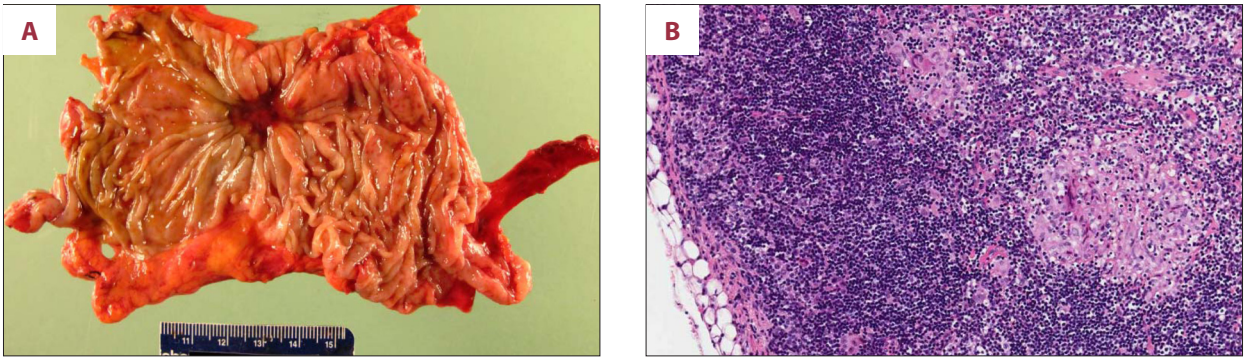

Figure 3. Transverse colon. (**A**) Gross surgical specimen from transverse colectomy showing an ulcerated lesion (**B**) Colonic mucosa and submucosa showing non-necrotizing granulomatous inflammation with no evidence of viral cytopathic effect.

worsens with initiation of HIV treatment. It is the T-cell dependent macrophage activation that is responsible for the conversion of the histiocytic infiltrates to well-formed epithelioid and giant cell granulomas once treatment is initiated [4]. When this occurs, the ART causes an inflammatory flare-up due to immune reconstitution that worsens symptoms such as obstruction or abdominal pain as it was seen in our case [5]. For this reason, it is important to screen patients for fungal infections

in endemic areas prior to initiation of therapy. Although it is difficult to assess, we speculate that in our patient, IRIS may have worsened her histoplasmosis infection despite lack of a robust CD4 count response after ART initiation.

Antigen detection in serum or urine is a widely used and a rapid method for the diagnosis of disseminated histoplasmosis in AIDS. Although antigen testing has not been studied specifically in patients with localized GI involvement, there have been reports of false negative histoplasma antigen results in pulmonary histoplasmosis [6]. Our patient had negative histoplasma antigen in both urine and serum four times during a 3-month period. The method of detection of histoplasmosis urine antigen in our patient was semiquantitative with a cutoff 2 EIA units below indicating a negative result and 2 EIA units above yielding a positive result. Serum and urine antigen tests are dependent on the fungal burden. They yield more positive results in disseminated infection rather than in localized infections. The antigen can be detected in the urine of over 90% of patients with disseminated disease. False negative results are most common in patients with localized sites of dissemination in the GI mucosa with few other findings of disseminated disease. Even though we cannot exclude dissemination in our case, the clinical picture was dominated by localized GI involvement. In addition, ongoing antifungal and ART may have reduced the systemic burden of infection. Antigen testing is also helpful for monitoring therapeutic response because the levels fall with successful therapy to eventually reach the undetectable range when the infection is under control with chronic maintenance therapy [1].

Another important aspect of this case was that the patient was on an ART regimen that conflicted with the antifungal treatment for histoplasmosis. Itraconazole is metabolized primarily by the cytochrome P450 3A4 enzyme to hydroxyitraconazole [7]. This pathway also mediates the metabolism of non-nucleoside reverse-transcriptase inhibitors such as efavirenz [8]. When these two drugs are co-administered, there is reduced concentration of itraconazole through the CYP3A4 enzyme. Based on reviews of case reports, patients who were on both a non-nucleoside reverse-transcriptase inhibitor based antiretroviral regimen and itraconazole had persistent elevation in urine histoplasma antigen level and subtherapeutic levels of itraconazole even a year after induction of therapy [9]. For patients with histoplasmosis, it is important to ensure that they are not on ART regimens that interact with antifungal treatment.

Conclusions

This case report illustrates the importance of recognizing histoplasmosis in AIDS patients with non-specific GI symptoms. In these patients, a negative histoplasma antigen does not rule out a fungal infection since localized infections do not produce enough antigens to be detected in serum or urine. Once histoplasmosis is suspected in AIDS patients, their ART regimen needs to be taken into account due to drug-drug interactions between antiretroviral and antifungal agents.

Conflicts of interest and source of funding

All participating authors in this study declare no financial, professional, or personal conflicts. No grant was received for this case report.

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