Gastrointestinal Histoplasmosis Complicating Pediatric Crohn’s Disease: A Case Report

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Abstract

BACKGROUND

Infection with *Histoplasma capsulatum* can lead to disseminated disease involving the gastrointestinal tract presenting as diffuse abdominal pain and diarrhea which may mimic inflammatory bowel disease (IBD).

CASE SUMMARY

We report a case of 12-year-old boy with presumptive diagnosis of Crohn’s disease (CD) that presented with several months of abdominal pain, weight loss and bloody diarrhea. Colonoscopy showed patchy moderate inflammation characterized by erythema and numerous pseudopolyps involving the terminal ileum, cecum, and ascending colon. Histologic sections from the colon biopsy revealed diffuse cellular infiltrate within the lamina propria with scattered histiocytic aggregates, and occasional non-necrotizing granulomas. Grocott-Gomori’s Methenamine Silver staining confirmed the presence of numerous yeast forms suggestive of *H. capsulatum*, further confirmed with positive urine histoplasma antigen (6.58 ng/mL, range 0.2 - 20 ng/mL) and IgG antibodies to *Histoplasma* (35.9 EU). Intravenous amphotericin was administered then transitioned to oral itraconazole. Follow-up CT imaging showed a left lower lung nodule and mesenteric lymphadenopathy consistent with disseminated histoplasmosis infection.

CONCLUSION

Gastrointestinal involvement with *H. capsulatum* with no accompanying respiratory symptoms is exceedingly rare and recognition is often delayed due to the overlap of symptoms with manifestations of IBD. This case illustrates the importance of excluding infectious etiologies in patients with “biopsy-proven” CD prior to initiating immunosuppressive therapies. Communication between clinicians and pathologists is crucial as blood cultures and antigen testing are key studies that should be performed
in all suspected histoplasmosis cases to avoid misdiagnosis and inappropriate treatment.

**Key Words:** Crohn's disease; disseminated histoplasmosis; endoscopy; colon; inflammatory bowel disease; immunosuppression


**Core Tip:** Impaired cell-mediated immunity is known to increase the risk for disseminated histoplasmosis and has been described in the setting of Crohn’s disease treated with immunosuppressant agents. Endoscopically, the appearance of histoplasmosis varies and includes features of inflammatory mucosal changes. Increasing awareness of this condition is critical to avoid misdiagnosis and inappropriate treatment, particularly in the setting of underlying Crohn’s disease. While no specific recommendations are available, immunosuppressive therapy may be safely initiated in some cases when there appears to be effective response to antifungal therapy and the patient can be monitored closely.

**INTRODUCTION**

Histoplasmosis is an infection caused by inhalation of spores from a fungal organism, *Histoplasma capsulatum*, found in soil enriched with bird and bat droppings and is endemic to the central and eastern states, prevalent in the Ohio and Mississippi River Valleys. (1-2) Clinical manifestations are typically self-limiting in immunocompetent children, whereas immunocompromised children are likely to present with more severe or disseminated disease and may be indistinguishable from malignancy or tuberculosis. (3-4) Single-organ histoplasmosis is rare, primarily affecting the lungs, occasionally lymph nodes, liver, bone marrow, skin and mucosal membranes. (5-8) While the literature contains many reports of disseminated histoplasmosis reminiscent of Crohn’s
disease radiographically and endoscopically in immunocompromised patients, there are relatively few reports of symptomatic gastrointestinal histoplasmosis occurring in immunocompetent patients, the most commonly involved sites are the terminal ileum and the colon. (9) We report case of an immunocompetent pediatric patient presenting with possible disseminated histoplasmosis after presumed initial diagnosis of Crohn’s disease. Early detection is critical to avoid treatment with immunosuppressive therapy and potential complications.

CASE PRESENTATION

Chief complaints
The patient is a 12-year-old boy who presented with several months of abdominal pain, weight loss, and bloody diarrhea.

History of present illness
The patient experienced abdominal pain, weight loss, and bloody diarrhea and was referred for upper and lower GI endoscopy assessment with biopsy.

History of past illness
His medical history was remarkable for several mild and self-limiting respiratory illnesses with non-productive cough. The most recent episode occurred fourteen months prior to his current presentation.

Personal and family history
No notable personal or family medical history.

Physical examination
Unremarkable physical examination.

Laboratory examinations
Esophagogastrroduodenoscopy was performed and revealed focally ulcerated gastric mucosa and several inflammatory polyps arising within the second and third portions of the duodenum. Colonoscopy revealed patchy moderate inflammation characterized by erythema and numerous pseudopolyps involving the terminal ileum, cecum, and ascending colon (Fig. 1A-1F). An erythematous region containing shallow ulcers was identified at the hepatic flexure. Multiple biopsies were taken from throughout the colon. A presumptive diagnosis of Crohn’s disease (CD) was made, methylprednisolone (40 mg/kg/d, IV) was administered and the patient was then discharged on oral prednisone (40 mg, QD) and oral mesalamine (1,000 mg, TID).

Histologic examination from a colon biopsy revealed a diffuse cellular infiltrate within the lamina propria with scattered histiocytic aggregates and occasional non-necrotizing granulomas (Fig. 2A-2C). Grocott-Gomori’s methenamine silver (GMS) and Periodic acid-Schiff stain confirmed the presence of numerous yeast forms morphologically suggestive of Histoplasma capsulatum (Fig. 2D-2E), further confirmed with positive urine Histoplasma antigen (6.58 ng/mL, positive range 0.2 - 20 ng/mL) and serum IgG antibodies to Histoplasma (35.9 EU, positive ≥10.0 EU).

Given the unusual nature of the histoplasmosis infection, an immunological workup was initiated and revealed profound hypogammaglobulinemia: serum IgG 94 mg/dL (range 638-1453), IgM 9 mg/dL (range 56-242), and IgA 40 mg/dL (range 45-285) as well as CD8 Lymphopenia (253/mm³, range 331-1,445). Genetic testing was ordered for inborn error of immunity using Invitae Primary Immunodeficiency Panel and one pathogenic variant was identified in CD40LG c.43del (pThr15Leufs*7), associated with X-linked hyper-IgM syndrome (XHIGM) and two likely pathogenic variants in TNFRSF13B c.310T>C (p.Cys104RG) (homozygous), associated with recessive common variable immunodeficiency (CVID).

**Imaging examinations**
Computed tomography (CT) of the chest, abdomen, and pelvis demonstrated a calcified left lower lobe lung nodule with associated hilar lymphadenopathy, diffuse colitis with wall thickening of the distal small bowel through the cecum, abdominal lymphadenopathy, and abnormal-appearing adrenal glands, likely related to disseminated histoplasmosis infection.

**FINAL DIAGNOSIS**

Combined with the patient’s medical history, the final diagnosis was isolated gastrointestinal histoplasmosis complicating newly diagnosed, presumed Crohn’s disease.

**TREATMENT**

An induction regimen of liposomal amphotericin was administered (3 mg/kg/d, IV) followed by 1 year of oral itraconazole (200 mg, BID) and treatment with oral mesalamine (1,000 mg, TID) to maintain endoscopic remission with plans for endoscopy and colonoscopy in the future after trailing off medication at 6 mo.

**OUTCOME AND FOLLOW-UP**

Ongoing follow-up is planned for diagnostic evaluation of Crohn’s disease and the treatment plan includes maintaining clinical improvement and *Histoplasma* antigen clearance. Decisions on whether to initiate treatment for Crohn’s disease are pending as duration of antifungal therapy and safety of immunosuppressive therapy are to be determined. To date, our patient has completed 5 mo of a 12-month course of antifungal therapy and is maintained on mesalamine until follow-up endoscopy and colonoscopy. The patient’s symptoms have largely resolved and remain stable after 5 mo of follow-up.

**DISCUSSION**
Gastrointestinal involvement commonly occurs as part of disseminated histoplasmosis; however isolated colonic involvement with lack of respiratory symptoms is rare. (10) Histoplasmosis can occur at any age. Nonspecific clinical manifestations of gastrointestinal involvement such as abdominal pain, fever, weight loss, and diarrhea are variably present and may only be mild. (6, 10-11) Immunocompromised patients are at increased risk of developing disseminated disease and may experience complications such as bleeding or intestinal obstruction more readily than immunocompetent individuals. A high index of suspicion is required for diagnosing histoplasmosis and the gold standard for diagnosis includes isolation of the fungus in blood culture and antigen testing in suspected cases, utilizing both serum and urine consistently provides the highest sensitivity for detection. Testing for anti-Histoplasma antibodies further increase sensitivity for diagnosis. (12)

The terminal ileum is most commonly involved, presumably because of the lymphoid-rich tissue in this area, but can found throughout the gastrointestinal tract. (9) The pathologic findings of gastrointestinal histoplasmosis include mucosal ulceration, polypoid lesions, and obstructing masses. (6,11,13) Histologically, tissue shows diffuse expansion of lamina propria and submucosa by macrophages containing intracellular yeast forms. (6,10) As in our case, due to similarities in presentation, pattern of involvement and associated granulomatous inflammation, gastrointestinal histoplasmosis may be mimic as Crohn’s disease. (6,14-17)

To our knowledge, only 7 cases of isolated gastrointestinal histoplasmosis occurring in the pediatric age group (younger than 18 years of age) have been previously reported, mostly from individual case reports (Table 1) (18-22) and one small case series. (23) Ages ranged from 4 to 16 years with a median age of 13 years. Of the previously described cases, the male/female ratio was 5:2. Our patient presented at a slightly younger age than the median (12 years vs 13 years). The most common presenting symptoms included abdominal pain and weight loss, with diarrhea, anorexia, and fever
appearing occasionally. Pulmonary symptoms at presentation or during the disease course were not reported in any case. Five patients were presumed immunocompetent (20-22), while two patients were known to have immunocompromising conditions (hyper-IgE syndrome) prior to their presentation. (18-19) One patient with hyper-IgE syndrome was effectively treated seven months prior for cough and fever of unknown origin. (19) As in our case, 5 patients were given a presumptive diagnosis of Crohn’s disease based on clinical presentation and endoscopic findings. (20-23) A broad range of diagnostic laboratory tests were performed including immunological tests for antigen and/or antibody detection. Microscopic examination of revealed yeast forms (by routine hematoxylin and eosin staining and/or special staining methods) in all cases.

In our present case, the patient presented with gastrointestinal symptoms alone and endoscopic findings suggestive for Crohn’s disease and was started on corticosteroids and subsequently mesalamine. An interesting feature of our case is that while the gastrointestinal tract was the only site of symptomatic disease, it is unlikely to be the primary focus of infection. It is more likely that after inhalation of the fungus, dissemination by the bloodstream occurred before an immune response was mounted with some unidentifiable factor favoring persistence in the gastrointestinal tract exclusively. After additional workup, the patient was identified as more susceptible to histoplasmosis because of the dysregulation of cell-mediated immunity associated with his XHIGM and CVID, as suggested by his immunological testing results. Distinction of these entities is vital as the optimal treatment for one disease could lead to exacerbation of the other. A list of infectious diseases that should be excluded in patients diagnose as inflammatory bowel disease is provided in Table 2. (24-47)

**CONCLUSION**

Gastrointestinal involvement with *H. capsulatum* in the absence of pulmonary manifestations is exceedingly rare and may lead to delay in recognition due to overlapping symptoms with inflammatory bowel disease. This case highlights the
importance of excluding infectious etiologies in patients with “biopsy-proven” CD prior to initiating immunosuppressive therapies, especially in the setting of recent travel or exposure in an endemic area. Communication between clinicians and pathologists is crucial as tests for *Histoplasma* antigen in urine or serum should be performed once histoplasmosis is suspected.