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Case report

Disseminated histoplasmosis and hemophagocytic lymphohistiocytosis in a patient receiving TNF-alpha inhibitor therapy

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ABSTRACT

Histoplasmosis commonly presents as an asymptomatic or self-limited infection in immunocompetent patients, but immunocompromised hosts may present with severe and disseminated disease. Herein, we present a 26-year-old male with history of ulcerative colitis receiving long-term TNF-alpha inhibitor therapy who presented with six months of diarrhea and recently fever and hematochezia. On admission, he was febrile and hypotensive, with initial workup revealing pancytopenia and imaging reporting pulmonary infiltrates, pancolitis, and enlarged mesenteric lymph nodes. Disseminated histoplasmosis was ultimately diagnosed after examination of the colonic biopsy. Bone marrow biopsy was also consistent with the diagnosis of histoplasmosis but also demonstrated hemophagocytic lymphohistiocytosis. The patient was ultimately treated with amphotericin B, intravenous immunoglobulin, etoposide, and corticosteroids.

Introduction

Histoplasmosis is caused by the endemic, dimorphic fungus *Histoplasma capsulatum*. While found worldwide, *Histoplasma* spp is mainly found in North America and is the most prevalent endemic mycosis in the United States [1]. Histoplasmosis may present with a spectrum of phenotypes – from asymptomatic infection to a localized pulmonary involvement or to a fatal disseminated disease. Presentation depends on intensity of inoculum exposure and status of the host immune system [2]. Patients with impaired cell-mediated immunity are unable to mount the immune response to kill the *Histoplasma* spp organisms. Traditionally, high-risk groups for developing severe histoplasmosis included patients with AIDS, hematologic malignancies, transplant recipients, patients on chronic corticosteroids or biologic therapy, or those at extremes of age [2]. With the introduction of tumor necrosis factor (TNF)-alpha inhibitors to the therapeutic armamentarium to treat a broad range of diseases, including inflammatory bowel disease (IBD), it is paramount for providers to recognize the risk of infection associated with their use. Here, we present a case of a patient receiving tumor necrosis factor (TNF)-alpha inhibitors, who developed disseminated histoplasmosis complicated by hemophagocytic lymphohistiocytosis (HLH).

Case

A 26-year-old male with long-standing ulcerative colitis was transferred from an outside hospital due to persistent fever, hematochezia, and pancytopenia. Two weeks prior to his transfer, he was hospitalized due to persistent diarrhea, intermittent episodes of hematochezia, and fifty-pound weight loss over the preceding 6 months. The patient lived in California but traveled to Tennessee and Florida before presenting with these symptoms. He was treated with adalimumab for 8 years but was recently switched to ustekunimab and corticosteroids for suspected ulcerative colitis flare, without improvement of his diarrhea and weight

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loss. Laboratory testing revealed a positive *Clostridium difficile* stool PCR test. The patient was treated with oral vancomycin and intravenous metronidazole, without improvement of his symptoms. A colonoscopy reported inflammatory changes and large patches of punched-out ulcers in the colon; colonic biopsy was reportedly unremarkable and negative on cytomegalovirus immunostaining. Patient was subsequently transferred to our hospital for escalation of care.

On admission, his temperature was 38.3 °C, heart rate 137 beats per minute, blood pressure 75/49 mmHg, and oxygen saturation of 92 % at room air. Physical exam was remarkable for cachexia, anasarca, and diffuse tenderness to palpation of the abdomen. Laboratory investigations were notable for hemoglobin of 6.9 g/dL, white blood cells 2300/μL; platelets 15,000/μL, aspartate aminotransferase 58 U/L, alanine transaminase 25 U/L, alkaline phosphatase 1163 U/L, lactate dehydrogenase 489 U/L, and ferritin 6154 μg /L. Imaging demonstrated a pulmonary nodule within the right lower lobe, pancolitis, splenomegaly, and multiple enlarged mesenteric lymph nodes. The patient underwent a flexible sigmoidoscopy (Fig. 1) which revealed non-bleeding severely ulcerated mucosa. Colonic mucosa was biopsied and revealed closely packed histiocytes loaded with round, 2–5 μm intracellular organisms consistent with yeast forms of *Histoplasma* spp (Fig. 2). Histological examination of a bone marrow biopsy demonstrated leukophagocytosis and erythrophagocytosis with extensive marrow involvement by fungal organisms consistent with *Histoplasma* spp. (Fig. 3). Bone marrow PCR was positive for *Histoplasma capsulatum.*

Further testing revealed serum Beta D Glucan > 500 pg/mL, galactomannan > = 3.750, urine *Histoplasma* antigen was > 25.0 ng/mL, *Histoplasma* mycelia antibody titer 1:128, *Histoplasma* yeast antibody titer 1:64, and presence of H&M bands. *Histoplasma* species complex grew in blood and respiratory cultures. Patient received liposomal amphotericin B for disseminated histoplasmosis, and intravenous immunoglobulin, etoposide, and corticosteroids for secondary hemophagocytic lymphohistiocytosis. In the following days, as his clinical condition improved, amphotericin B was switched to itraconazole but was unable to achieve therapeutic levels. He was transitioned to posaconazole with a plan to receive at least 12 months of therapy and was discharged from the hospital.

Discussion

Histoplasmosis, caused by the thermally dimorphic fungus *Histoplasma capsulatum*, is the most prevalent endemic mycosis in the United States with highly endemic areas located in the Mississippi and Ohio River valleys [1]. It is especially associated with exposure to birds and bat droppings. Two varieties of *H. capsulatum* are pathogenic to humans – *H. capsulatum* var. capsulatum and *H. capsulatum* var. *duboisii*, with the former predominant in North and Central America and the latter in Africa [2]. When the *Histoplasma* microconidia is inhaled, the pathogen transitions to a yeast form, prompting the recruitment of neutrophils, macrophages, lymphocytes, and natural killer cells to the lungs. TNF-alpha is a key component for granuloma formation, inflammatory cell recruitment, and cytokine production [3]. Histoplasmosis causes a wide range of clinical presentations, from localized pulmonary involvement to life-threatening, disseminated disease. As in our patient, disseminated histoplasmosis has been described in patients with rheumatoid arthritis or inflammatory bowel disease receiving TNF-alpha inhibitors [3–5]. Other risk factors include organ transplantation, especially with antirejection medications [6], IFN-gamma receptor deficiency [7], and human immunodeficiency virus (HIV) infection [8]. Mortality from histoplasmosis infection (including localized and disseminated disease) in patients receiving TNF-alpha inhibitors has been reported to be high as 19 % [3].

Definitive diagnosis of disseminated histoplasmosis requires the isolation of *H. capsulatum* from various specimens via culture or histopathology. Antigen detection, serological testing, and molecular testing may also aid in the diagnosis. For patients receiving anti-TNF-alpha therapy, sensitivity has been reported to be as high as 100 % when combining blood and urine antigen testing [4]. Antibodies are only detected 4–8 weeks after infection and thus are more useful in the diagnosis of subacute or chronic histoplasmosis infection. Furthermore, antibody sensitivity can vary widely based on the immunosuppressive state of the host, ranging from 83 % in patients receiving anti-TNF-alpha therapy [5] to 38 % in solid organ transplant recipients [9]. Molecular testing may also aid in the diagnosis of *H. capsulatum* given its high sensitivity and specificity [10,11], although its precise role is still evolving [12].

Treatment of histoplasmosis depends on disease severity, central nervous system (CNS) involvement, and HIV status. Overall, guidelines recommend Itraconazole as therapy of choice for mild and moderate histoplasmosis, and liposomal amphotericin B in severe presentations and CNS disease [13]. Duration of treatment is less delineated but is recommended for at least one year [13].

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition caused by an overactive immune state [14]. HLH can be primary or secondary to infections (mostly associated to Epstein-Barr virus, cytomegalovirus, parvovirus B19, and HIV), malignancy (lymphoid cancer and solid tumors), and inherited immunodeficiency disorders [14]. HLH secondary to histoplasmosis is rare, comprising of less than 1 % of cases worldwide [15]. The mechanism of histoplasmosis triggered HLH has not been fully elucidated. However, it is likely related to a T-cell mediated immune response, macrophage activation and cytokine storm [3,16]. Mortality with HLH-associated histoplasmosis has a fatality rate of 31 % [17]. There are no treatment guidelines for HLH secondary to histoplasmosis [18], but in practice patients receive a combination of steroids, etoposide, anakinra along with antifungals [17].

This case highlights the importance of considering histoplasmosis as a complication in patients with IBD presenting with diarrhea and cytopenias, and prior epidemiological exposure to areas where this fungi is endemic.

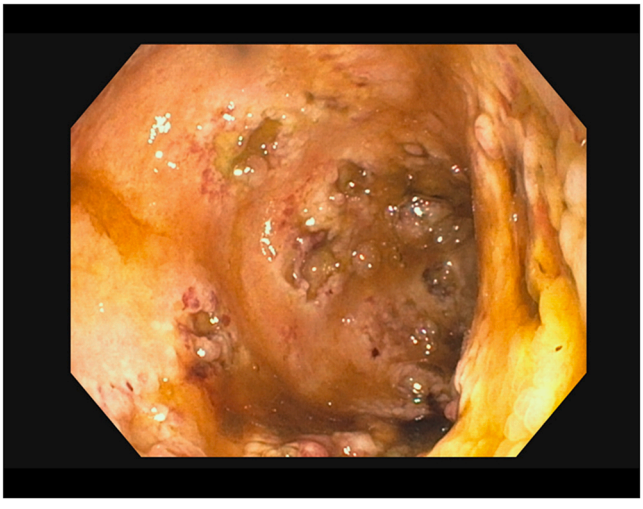

Fig. 1. Endoscopic imaging from the sigmoid colon showing non-bleeding severely ulcerated mucosa that were present throughout the entire left side of the colon.

CRediT authorship contribution statement

Qiaonan Zhong: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Eloy E. Ordaya:** Conceptualization, Investigation, Writing – review & editing. **Santiago Delgado Fernandez:** Providing histopathology pictures, Writing – review & editing. **Kristin Lescalleet:** Providing sigmoidoscopy pictures, Writing – review & editing. **Daniel Larson:** Providing histopathology pictures,

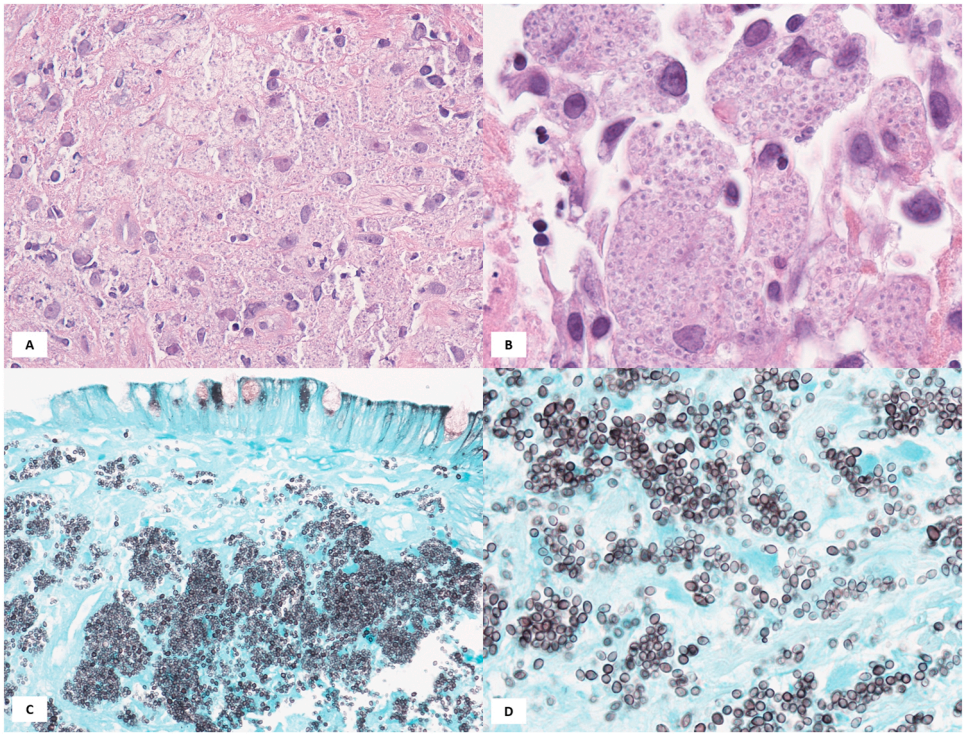

Fig. 2. (A), (B): Hematoxylin-eosin stain of the patient's colon biopsy, showing foamy histiocytes filling the lamina propria. Round, 2–5 μm intracellular organisms are identified, compatible with yeast forms of *Histoplasma* spp. (A) 400x, (B) 1000x. (C), (D): Grocott's Methenamine Silver stain highlights abundant 2–5 μm yeast with narrow-base budding, consistent with *Histoplasma* spp. (C) 400x, (D) 1000x.

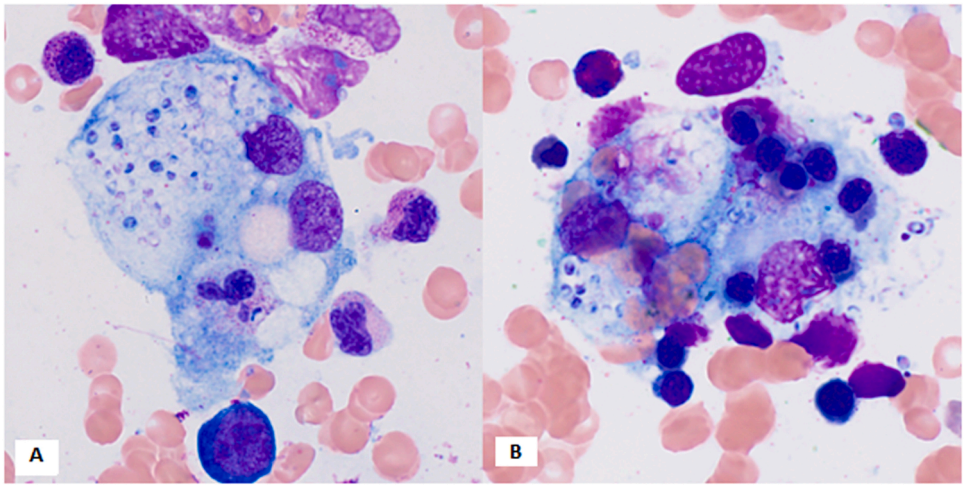

Fig. 3. Representative high magnification images of the bone marrow aspirate (Wright-Giemsa stain, 1000x) show histiocytes which have numerous engulfed yeast forms and additionally demonstrate hemophagocytosis, both leukophagocytosis (A) and erythrophagocytosis (B).

Writing – review & editing. **Bobbi Pritt:** Providing histopathology pictures, Writing – review & editing. **Elie Berbari:** Supervision, Writing – review & editing.

Conflict of Interest Statement

All authors have no financial discourse or conflicts of interest.

Consent statement

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request

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