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CASE REPORT

Disseminated histoplasmosis in an HIV/AIDS transgender male-to-female with atypical and persistent GI manifestations

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Abstract

Disseminated histoplasmosis is a rare complication of infection due to *Histoplasma capsulatum*. Typically, histoplasmosis is self-limiting and asymptomatic in infected individuals with immunocompetence. Disseminated disease, however, can arise in high-risk populations with primary or acquired cellular immunodeficiency including HIV/AIDS, transplant recipients, and those undergoing immunosuppressive therapy. Here we describe a unique case of extrapulmonary gastrointestinal histoplasmosis by infiltrative Peyer's patch disease with bone marrow involvement in a transgender HIV-infected woman.

Introduction

Histoplasma capsulatum (*H. capsulatum*) is a dimorphic fungus found predominantly in soil contaminated with bird or bat droppings throughout the world including South America, Asia, Africa, and Australia. In the United States, *H. capsulatum* is most commonly present in areas around the Ohio and Mississippi River Valleys.[1,2] When contaminated soil is disturbed, fungal spores become airborne and are inhaled. Infection often remains confined in the lungs, but can also spread hematogenously and result in disseminated histoplasmosis. This is generally seen in individuals with CD4 counts <100–200 cells/μL and primarily affects the reticuloendothelial system.[2,3]

Case presentation

A 39-year-old transgender woman previously on hormone replacement therapy with a past medical history of hypertension, hyperlipidemia, and HIV with highly active antiretroviral therapy (HAART) noncompliance presented to the emergency department for diarrhea and daily intermittent fevers and chills for 1 week. On admission, she was febrile with pancytopenia. Her CD4 count was 123 cells/μL. Her HIV-1 viral load was 1300 copies/mL. Fungitell-measured (1,3)-β-D-glucan was >500 pg/mL. Polymerase chain reaction (PCR) tests for *Streptococcus pneumoniae*, *Bordetella pertussis*, *Mycoplasma* and *Chlamydia pneumoniae*, *Cryptococcus*, *Aspergillus galactomannan*, and *Clostridium difficile* toxin were negative. *Pneumocystis jirovecii* was negative by direct immunofluorescence. Testing for Epstein–Barr virus using quantitative PCR showed 485 copies/mL. Computed tomography of chest, abdomen, and pelvis revealed retroperitoneal lymphadenopathy. She underwent lymph node and bone marrow biopsy, both of which revealed small budding yeasts consistent with *H. capsulatum*. She was initiated on amphotericin and discharged on itraconazole with advice for follow-up at the infectious disease outpatient clinic. After completing antifungal therapy, she remained noncompliant with HAART and readmitted a year later after developing a small bowel obstruction and large splenic infarct for which she underwent partial small bowel resection with splenectomy. Subsequent pathology revealed excessive fungal infiltration of Peyer's patches, with GMS and PAS stains positive for numerous budding yeasts within histiocytes. The patient was again treated with amphotericin followed by itraconazole and scheduled for outpatient follow-up visit.

Two years thereafter, a surveillance colonoscopy showed a non-obstructing large cecal and ileocecal valve mass with multiple colonic polypoid lesions. Immunohistopathology of the mass revealed histiocytic aggregates with GMS stains positive for fungal elements (Fig. 1a,b, respectively). Her CD4 count and HIV viral load were 203 copies/mL and 47 cells/μL, respectively. She was again treated with antifungals and scheduled for outpatient follow-up.

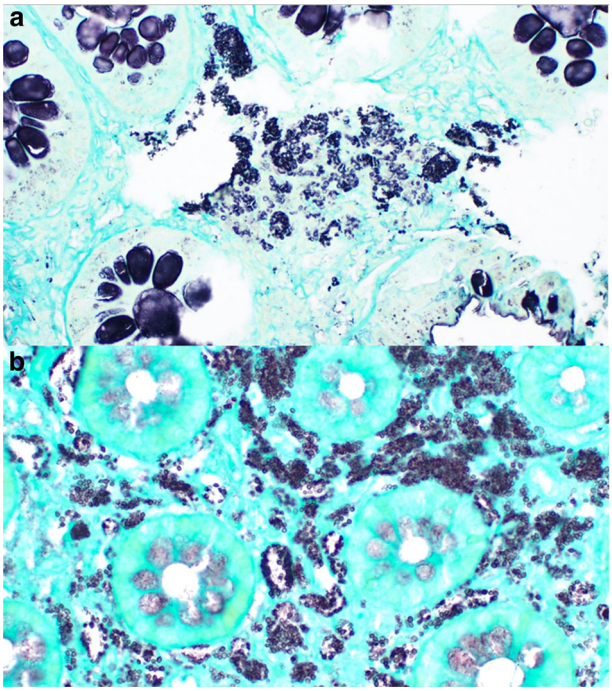

Figure 1 Biopsy from the cecal mass showing clustered yeast within mesenchymal cells among colonic crypts (a: GMS stain) and from the ileocecal valve mass showing small, widely disseminated, uniform, narrow-based budding yeast with acorn-like nuclei clustered within histiocytes in Peyer's patches (b: GMS stain).

Discussion

Infection with *H. capsulatum* begins when microconidia of the fungus are inhaled into the lungs where they then transform into yeast. Macrophages phagocytize the yeast and spread hematogenously throughout the reticuloendothelial system.[2,3] Immunocompromised individuals such as those with HIV/AIDS, bone marrow or organ transplant recipients, or are currently receiving immunosuppressive therapy are particularly susceptible to dissemination. Disseminated histoplasmosis is rare and is established as an AIDS-defining opportunistic infection in patients with HIV.[6,7] It can affect multiple organ systems such as the lungs, skin, central nervous system (CNS), liver, spleen, and the gastrointestinal (GI) tract; however, clinical manifestations vary depending on the immune status.[1,8] GI involvement is common, occurring in roughly 70–90% of cases with disseminated fungal infection, but only 3–12% of these patients are symptomatic.[1,4,6,9,10] Symptoms are nonspecific and include diarrhea, abdominal pain, fever, fatigue, weight loss, pancytopenia, and hepatosplenomegaly.[4,6,8,11] Atypical yet more worrisome findings include submucosal nodules, diffuse histiocytic infiltration, hematochezia, melena, splenic infarction, obstructing masses, and bowel perforation.[4,9] Areas along the terminal ileum and ileocecal valve as well as in the colon are most commonly involved because of the abundance of lymphoid tissue.[1,4,10] GI bleeding and bowel obstruction generally occur as a result of enlarging lymphoid tissue and inflammatory masses that may mimic malignancy, occurring more in immunocompromised individuals.[9]

Detection of histoplasmosis can be made by serological testing, immunofixation, PCR, and microscopy.[5,11,12] Histopathological evidence by biopsy or blood culture, however, remains the gold standard.[1,12] Histopathology may reveal diffuse lymphoplasmacytic infiltration, ulcerated epithelium, and granulomatous formation. Immunostaining with GMS and PAS is often used to identify and characterize fungal budding, hyphae, or branching.[1,13,14] Oftentimes, testing for serum and urine histoplasma antigen enzyme, which also increases in disseminated disease, is used because of quicker turnaround times and >92% sensitivity and specificity.[1,5,10,15] In one study, the highest positivity of histoplasmosis was noted in bone marrow biopsy at >75% of cases, followed by blood cultures in 50–70% of cases.[3] Additionally, reinfection can occur in 10–20% of patients with previous disseminated disease and up to 80% of individuals with AIDS diagnosis.[3] Along with reinfection, reactivation of latent disease by remaining organisms can occur; however, this is mainly seen in the immunocompromised.[3] As our patient was

immunocompromised and especially with poor adherence to HAART, she was at high risk for reinfection. Her continued GI complaints were suggestive of a recurring fungal infection and her subsequent colonoscopy with biopsy confirmed disseminated disease.

For patients without CNS involvement and for severe disease, treatment for disseminated histoplasmosis is with amphotericin for 1–2 weeks followed by oral itraconazole for 12 months. Oral therapy should be started simultaneously during the last few days of infusion to ensure serum concentration of itraconazole is measurable once amphotericin is discontinued.[7,13,16] If unable to tolerate itraconazole, other options exist including posaconazole, voriconazole, isavuconazole, or fluconazole; however, some data suggest that they are less efficient than itraconazole; also, there are no clinical trials directly comparing azoles for the treatment of histoplasmosis. Patients should be monitored using histoplasma antigen serum/urine testing at 1–3-month intervals for response to therapy. Monitoring should also continue for 1–2 years after stopping treatment for signs of relapse.[7] For CNS involvement, a longer duration of amphotericin induction is warranted, followed by 12 months of itraconazole, or in some cases for lifetime, depending on risk of relapse.[7,16]

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Ethics approval and consent to participate

The study was approved by the Bioethics Committee at NewYork-Presbyterian Brooklyn Methodist Hospital. The study was conducted according to the principles of the World Medical Association Declaration of Helsinki, Good Clinical Practice Guidelines, and local laws and regulations.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report.

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