A 31-Year-Old Man With AIDS, Fever, and a Rash

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CASE PRESENTATION

A 31-year-old man came to the emergency department complaining of two-week history of intermittent subjective fevers, night sweats, chills, and nonpruritic rash, which started over his right upper extremity and spread to the rest of the body. Watery diarrhea developed four days prior to admission. He complained of headache and photophobia, but denied neck pain. He also complained of poor appetite, fatigue, and unintentional weight loss of approximately 15 to 20 pounds over a period of three months. He denied shortness of breath, cough, or chest pain.

He had a past medical history of acquired immunodeficiency syndrome (AIDS) with a CD4 cell count of 37 cells/mm³ one year prior, cryptococcal meningitis, and pulmonary tuberculosis. He had not been seen in the human immunodeficiency virus (HIV) outpatient clinic for one year and had stopped taking antiretroviral treatment and opportunistic infection prophylaxis. He moved to New Orleans from Honduras seven years ago, and he works currently as a painter.

In the emergency department, the patient was ill-appearing with diaphoresis, tachycardia, and a rapid respiratory rate that was not labored. His temperature was 106°F, heart rate was 130 beats/minute, blood pressure 100/67 mm Hg, respiratory rate 24/min, and oxygen saturation at 100% on room air. He weighed 80 kilograms and was 165 centimeters tall; the body mass index was 21.3. Physical exam was remarkable for a purple, non-blanching, maculopapular rash on his face, trunk, and arms lesions. There was no central clearing, blistering, vesicles, or desquamation (Figure 1).

An arterial blood gas revealed a pH 7.46, PCO2 28 mm Hg, PaO2 69 mm Hg, bicarbonate 21 mmol/L, and O2 saturation 97%. The alveolar-arterial gradient (A-a gradient) was 99.5 torr. His complete blood count and comprehensive metabolic profile were normal except for an elevated LDH of 561 U/L (Reference Range <201 U/L). His CD4 cell count was 104 cells/mm³ (Reference Range is 228-2290), and the CD4% was 10.8% (Reference Range is 37-63%). His lumbar puncture was negative for evidence of blood or infection.

His chest X-ray showed a patchy nonhomogeneous opacity consistent with pneumonia in the lingular division of the left upper lobe (Figure 2).

He was placed in respiratory isolation and empirically administered trimethoprim-sulfamethoxazole and prednisone for Pneumocystis jiroveci pneumonia (PJP); fluconazole for possible fungal infection; and vancomycin, cefepime, and azithromycin for bacterial pneumonia. Three acid-fast bacillus (AFB) smears were negative. Cryptococcal
antigen studies of the blood and cerebrospinal fluid were negative. The skin biopsy and urine antigen tests were positive for histoplasmosis (Figures 3, 4). The patient was initially treated with liposomal amphotericin and was later switched to itraconazole. Antiretroviral therapy was to be initiated in outpatient clinic setting.

DISCUSSION

Epidemiology and Etiology

Histoplasma capsulatum is a thermally dimorphic fungus, growing as a mold in the environment and as a yeast at 37°C. Infection develops when Histoplasma microconidia are inhaled into the lungs, where they change from a filamentous to a yeast form. Neutrophils, macrophages, lymphocytes, and natural killer (NK) cells are attracted in response to the infection. As in tuberculosis, macrophages assist in dissemination of the organism via lymphatics and the blood to the adjacent lymph nodes and throughout the reticuloendothelial system (liver, spleen, lymph nodes, adrenal glands, and bone marrow). T cell immunity plays the predominant role in recovery from Histoplasma infection. Once cellular immunity to Histoplasma develops, macrophages become activated to kill the organism. Cytokines, including interleukin (IL)-12 and interferon-gamma (IFN-gamma), assist macrophages in eradicating the fungus and halting progression of disease. Histoplasmosis is an important infectious disease among patients with advanced AIDS and continues to cause severe morbidity and mortality in endemic areas such as Mississippi, Ohio, the St. Lawrence River valleys, the Caribbean, southern Mexico, certain parts of Central and South America, Africa, and Asia.

Risk Factors

Most patients with disseminated histoplasmosis have underlying conditions that impair their ability to defend against intracellular pathogens. These conditions include HIV infection with CD4 count <100 cells/μL, primary immunodeficiency or other immunosuppressive disorders, use of immunosuppressive medications such as glucocorticoids, anti-rejection therapies in solid organ transplant recipients, TNF-alpha inhibitor therapies, and extremes of age. A separate group of patients, most of whom are middle-aged to older men, have chronic progressive disseminated histoplasmosis and have no known underlying immunosuppression. In these patients, unidentified defects in cellular immunity likely explain their inability to control the infection.

Clinical Presentation

In the immunocompetent host, histoplasmosis can present as a mild self-limiting pulmonary illness. However, patients with advanced AIDS or immunosuppression may develop progressive disseminated histoplasmosis (PDH). They may present with lymphadenopathy, mucocutaneous lesions, hepatosplenomegaly, pancytopenia, transaminitis, altered mental status, neurological abnormalities, nausea, vomiting, diarrhea, weight loss, and fever. Approximately 40%-50% of AIDS patients with PDH have pulmonary involvement, often presenting with cough and dyspnea. Isolated pulmonary involvement without dissemination occurs in less than 5% of cases. Ten to fifteen percent of patients with disseminated histoplasmosis have skin lesions. Adrenal glands are affected in approximately 80%-90% of autopsied cases, but overt adrenal insufficiency is unseen in less than 10% of the cases. Central nervous system involvement may manifest as encephalitis, meningitis, focal brain, or spinal cord lesions.

Characteristics of severe disease include a sepsis-like syndrome with multi-organ failure (including respiratory or renal failure) or concomitant meningitis. Despite appropriate therapy, mortality rates can be as high as 50% in patients with AIDS. Patients with chronic disseminated histoplasmosis are usually non-immunocompromised and often present with pancytopenia, hepatosplenicomegaly, hepatic enzyme elevation, and oropharyngeal or gastrointestinal lesions. Other sites of involvement may also include the skin, brain, and lungs, especially with underlying lung disease like emphysema and adrenal glands.

Diagnostic Evaluation

There are multiple diagnostic tests for disseminated Histoplasma capsulatum infection, including culture, serol-
ogy, antigen testing, and direct microscopy; the diagnostic yield will depend on the stage of disease.\textsuperscript{14} In HIV-associated disseminated disease, the most sensitive and specific test is detection of Histoplasma antigen.\textsuperscript{15,16} In one case report the Histoplasma antigen was detected in the following samples: urine (97%), blood (83%), and cerebrospinal fluid (67%).\textsuperscript{8} Direct microscopy can rapidly make the diagnosis by visualization of the organism within cells on a Wright’s stained smear of either peripheral blood or auffy coat. This method allows rapid identification and is very inexpensive, although the sensitivity is low (less than 10%).\textsuperscript{15,17} Histopathologic examination of tissues has a sensitivity that is similar to direct microscopy; stains for fungi performed on skin biopsy specimens revealed the organism in 86%-100% of cases of HIV-associated disseminated histoplasmosis.\textsuperscript{18,20} Standard serology has limited value.\textsuperscript{8} Culture of blood, respiratory samples, or other tissues (eg. bone marrow) remains the “gold standard” for diagnosis.\textsuperscript{19}

**Treatment and Prophylaxis**

The treatment for mild-to-moderate disseminated histoplasmosis is oral itraconazole for at least 12 months.\textsuperscript{18} For moderately severe and severe disseminated disease, therapy should be initiated as soon as possible due to a high mortality rate. One or two weeks of induction therapy with daily intravenous liposomal amphotericin B (preferred over the other amphotericin formulations due to its greater efficacy, lower nephrotoxicity, and better overall survival) or until symptoms improve is recommended, after which time the patient can be switched to oral itraconazole.\textsuperscript{14,18,21} Suppressive therapy with daily oral itraconazole prevents relapse in up to ninety five percent of cases and should be administered continually after completion of one-year maintenance therapy and can be discontinued safely if patients fulfill the following criteria: completion of a minimum of one-year maintenance therapy, histoplasma antigen levels are negative or remain low (<2 ng/mL), blood cultures are negative, CD4 cell counts have increased to >150 cells/\textmu L.\textsuperscript{18,22-25} The 2009 NIH/CDC/IDSA guidelines recommend consideration of prophylactic itraconazole for patients with a CD4 count below 150/\textmu L who are at high risk because of occupational exposure or who live in hyperendemic area with histoplasmosis.\textsuperscript{14}

**REFERENCES**


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