Disseminated Histoplasmosis in a Patient With AIDS: Case Report and Review of the Literature

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Disseminated histoplasmosis was uncommon prior to the AIDS epidemic, and cutaneous eruption rarely was seen. Since the onset of the worldwide AIDS epidemic, histoplasmosis has become a more common opportunistic fungal infection and should be considered in the differential diagnosis of mucocutaneous lesions in patients with AIDS in endemic areas. We report a case of classic disseminated histoplasmosis in a patient with AIDS and discuss the epidemiology, clinical presentation, pathogenesis, laboratory and histopathologic findings, and treatment options for disseminated histoplasmosis.


Most histoplasmosis infections are asymptomatic or self-limited influenzalike illnesses, but in the susceptible host, infection may be severe. AIDS is a major risk factor for disseminated histoplasmosis and should be considered in patients with this condition. A high index of suspicion is required to make a timely diagnosis and to implement early treatment with systemic antifungal therapy to reduce mortality, which can approach 80%.

Case Report
A 24-year-old Mexican man presented with a 3-week history of a diffuse, nonpruritic, cutaneous eruption; fatigue; fever; and weight loss. The patient was a construction worker and had become too fatigued to work. He recently had emigrated from Mexico, had no notable past medical history, and took no medications. His risk factors for human immunodeficiency virus (HIV) included intravenous drug use and sex with men. Results of a physical examination revealed a thin ill-appearing man who had a fever of 104°F. He was tachycardic but normotensive. Results of a skin examination revealed a diffuse, erythematous, maculopapular eruption that was most prominent on his face but also was present on his back, chest, and abdomen (Figure 1). Results of laboratory evaluations were notable for an elevated lactate dehydrogenase (LDH) level of 2449 U/L (reference range, 92–240 U/L) and pancytopenia. Results of a chest radiograph and a computed tomographic scan of his head were normal, and his cerebral spinal fluid parameters were within reference range. A punch biopsy of one of the lesions on his back was performed and the specimen was sent for histologic evaluation and culture while awaiting the results of other laboratory tests.

Results of the punch biopsy showed a sparse mixed inflammatory cell infiltrate in the upper dermis that consisted of lymphocytes, histiocytes, and plasma cells surrounding adnexal and vascular structures, as well as parasitized histiocytes and extracellular budding yeast of unequal sizes and narrow bases (Figure 2). There also was focal dermal necrosis and leukocytoclasis. The epidermis showed mild acanthosis and focal horn cysts. Organisms were visible on a Gomori methenamine-silver stain (Figure 3). All of these findings were consistent with disseminated histoplasmosis in the setting of AIDS and were confirmed by a positive urine antigen test and positive blood cultures for Histoplasma capsulatum.

The patient was treated with liposomal amphotericin B 3 mg/kg daily and experienced defervescence within 48 hours. His urine antigen level for histoplasmosis was positive, and blood and tissue
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cultures subsequently grew *H capsulatum*. He also was newly diagnosed with AIDS, with a high HIV viral load of 3.5 million copies/mL (≥5000 copies is considered high) and absolute CD4 cell count of 6 cells/mm³ (reference range, 500–1500 cells/mm³). During the next 2 weeks, his LDH level decreased to 220 U/L, his urine histoplasma antigen level decreased, and his pancytopenia resolved. After induction therapy with liposomal amphotericin B, the patient was discharged with a prescription of oral itraconazole for an indefinite duration. Antiretroviral therapy against HIV was started as an outpatient.

Comment

Prior to the AIDS epidemic, disseminated histoplasmosis was uncommon, occurring only in immunocompromised individuals and in people at the extremes of age (either children or elderly patients). Disseminated histoplasmosis was first recognized in patients with AIDS in 1983 and subsequently was designated as an AIDS-defining illness by the Centers for Disease Control and Prevention in 1987. The incidence of AIDS-related disseminated histoplasmosis is 0.5% to 2.7% in nonendemic areas and up to 10% in endemic areas.

Disseminated histoplasmosis is caused by the dimorphic fungus *H capsulatum*. It is endemic in the Ohio and Mississippi river valleys of the United States, as well as in parts of Central America, South America, Africa, and Asia. *H capsulatum* has specific soil requirements for growth and sustenance that are supported by the excrement of birds, bats, hens, and other domestic fowl. The presence of these factors may account for the reported microfoci of disseminated histoplasmosis in nonendemic areas, which supports the increased incidence of histoplasmosis in people who participate in activities such as demolition, remodeling, excavation, or construction, which aerosolize this medium.

Histoplasmosis is acquired by inhaling conidia from contaminated soil. In immunocompetent individuals, the disease usually is asymptomatic, but medical attention usually is sought for influenzalike illness. However, in immunocompromised patients, the disease may disseminate to organs such as the spleen, liver, bone marrow, leptomeninges, adrenal glands, and skin. This dissemination can lead to clinical manifestations of concern, including mediastinal granulomas, which may partially obstruct the airways and other mediastinal structures; fibrosing mediastinitis; broncholithiasis; pericarditis; rheumatologic syndromes; central nervous system histoplasmosis; adrenal involvement; and endocarditis. It remains controversial if disseminated disease in

Figure 1. Diffuse, erythematous, maculopapular lesions on the face.

Figure 2. Mixed inflammatory cell infiltrate in the upper dermis and extracellular budding yeast consistent with *Histoplasma capsulatum* (H&E, original magnification ×400). Arrow points to a group of yeasts.

Figure 3. Budding yeast forms in the upper dermis (Gomori methenamine silver, original magnification ×400).
patients with AIDS is a result of a primary infection or reactivation.\textsuperscript{4,5} The presenting symptoms of disseminated histoplasmosis in patients with AIDS vary. Fatigue, fever, weight loss, and malaise occurring for several weeks are the most common symptoms.\textsuperscript{1,4,7,8} Cutaneous lesions generally are a less common complaint, occurring in approximately 10\% to 25\% of patients with AIDS; however, frequencies as high as 80\% have been reported in patients with AIDS in South America, Uruguay, and Argentina.\textsuperscript{4} Cutaneous lesions are variable in patients with AIDS and may manifest as nodules, papules, mucosal ulcers, macules, patches, plaques, erythema multiforme, verruciform plaques, eczematous dermatitis, panniculitis, cellulitis, abscesses, or pyoderma.\textsuperscript{7} These lesions usually result from disseminated histoplasmosis, though primary cutaneous histoplasmosis has been reported.\textsuperscript{2} The most common locations of skin lesions include the face, arms, and legs, followed by less common involvement of the hands, feet, chest, and back, as well as the penis and perianal area.\textsuperscript{7} Gastrointestinal tract ulcers also may be found.

Certain laboratory values have been identified as markers of severe disease, necessitating more aggressive therapy (ie, thrombocytopenia [platelet count $<100,000/\mu L$], elevated LDH levels [$>2\times$ upper limit of reference range], elevated serum creatinine levels [reference range, 0.6 – 1.2 mg/dL], hypoalbuminemia).\textsuperscript{6,9} Other laboratory value abnormalities that commonly may be found are anemia, leukopenia, and hypercalcemia. Radiographic imaging has been less helpful in diagnosing disseminated histoplasmosis because up to half of the patients with disease may have a normal chest radiograph. Abnormal chest radiographs may show diffuse, interstitial, reticulonodular infiltrates, or, less commonly, mediastinal lymphadenopathy.\textsuperscript{6} The Table lists the laboratory evaluation findings associated with disseminated histoplasmosis.

The definitive diagnosis of disseminated histoplasmosis is established by fungal culture on Sabouraud agar at 25°C to 30°C.\textsuperscript{7} Cultures from lung biopsy, bronchoscopy, bone marrow, and blood lysis centrifugation specimens are positive in approximately 85\% of cases of disseminated histoplasmosis.\textsuperscript{6} Because cultures may take 2 to 3 weeks for growth to occur and there is a high mortality rate associated with untreated histoplasmosis, other methods are preferred for rapid diagnosis. Biopsy with the use of special fungal stains, such as periodic acid-Schiff or Gomori methenamine silver, is one method commonly used. Antigen detection in the urine is another useful method for rapid diagnosis and is positive in up to 90\% of patients with disseminated histoplasmosis. The urine antigen test also is necessary for monitoring disease resolution.

Cutaneous lesions usually respond rapidly to appropriate systemic antifungal therapy. The therapies for disseminated histoplasmosis are amphotericin B or liposomal amphotericin B.\textsuperscript{6} Current management guidelines recommend treating patients with AIDS and disseminated histoplasmosis with 12 weeks of induction therapy with

<table>
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<tr>
<th>Abnormality</th>
<th>Finding</th>
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<tr>
<td>Thrombocytopenia</td>
<td>Platelet count $&lt;100,000/\mu L$</td>
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<tr>
<td>Lactate dehydrogenase levels</td>
<td>$&gt;2\times$ upper limit of reference range (reference range, 92 – 240 U/L)</td>
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<td>Serum creatinine</td>
<td>Elevated (reference range, 0.6 – 1.2 mg/dL)</td>
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<tr>
<td>Hypoalbuminemia</td>
<td>Present</td>
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<tr>
<td>Anemia, leukopenia, hypercalcemia</td>
<td>Present</td>
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<td>Diffuse, interstitial, reticulonodular infiltrates</td>
<td>Possible</td>
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<td>Mediastinal lymphadenopathy</td>
<td>Possible, but less common</td>
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amphotericin B followed by a lifelong maintenance course of oral itraconazole to prevent relapse.\(^\text{10}\)

This case represents a classic presentation of disseminated histoplasmosis and the concomitant diagnosis of AIDS. This patient’s presenting symptoms were fatigue, fever, weight loss, and maculopapular skin lesions most prominent on the face, back, chest, and abdomen. Disseminated histoplasmosis initially was diagnosed by identification of the fungus via same-day fungal stains of skin biopsy specimens. These skin biopsy and positive urine antigen results then were confirmed by the results of blood and tissue cultures. The patient responded well to therapy with liposomal amphotericin B for his severe disease. Effective management of disseminated histoplasmosis begins with timely diagnosis based on clinical suspicion and rapid institution of therapy.

REFERENCES