SKIN

BRIEF ARTICLE

Cutaneous Manifestations of Disseminated Histoplasmosis in a Patient with AIDS

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ABSTRACT

Introduction: Disseminated histoplasmosis is often seen in immunocompromised individuals, such those with acquired immunodeficiency syndrome (AIDS). The initial infection mainly involves the lungs but it may develop into a disseminated form especially in immunocompromised patients. Since it can be a systemic disease with cutaneous manifestations, dermatologists must be able to recognize its clinical presentation to ensure prompt management.

Case: We present a man in his 50s with past medical history of AIDS who developed disseminated histoplasmosis with skin and gastrointestinal involvement over a one-month period of time. Despite receiving induction therapy with intravenous amphotericin B followed by oral itraconazole, the patient expired. His death was attributed to his persistently low CD4 T-cell count and secondary bacteremia.

Discussion: This condition should be recognized early and treated aggressively. However, patients with multiple comorbidities are at increased risk of mortality even despite adequate treatment. This case highlights the significant mortality risk of disseminated histoplasmosis in patients with AIDS.

INTRODUCTION

Disseminated histoplasmosis is typically an opportunistic infection in states of immunosuppression, such as in human immunodeficiency virus (HIV)-infected patients. The initial infection primarily affects the lungs, but in patients with acquired immunodeficiency syndrome (AIDS) with low CD4 T-cell counts the disease can evolve into disseminated histoplasmosis leading to poor prognosis.[1] The clinical manifestations of disseminated histoplasmosis depend on the severity of immunodeficiency of the host and the degree of exposure to the pathogen.[1,2] Patients often present with hepatosplenomegaly, pancytopenia, gastrointestinal and oropharyngeal lesions.[2] Furthermore, cutaneous lesions have been described in 10-15% of cases

of disseminated histoplasmosis.[3] We describe a patient with disseminated histoplasmosis in which we highlight that the clinical diagnosis can be challenging and prompt treatment is critical.

CASE REPORT

A man in his 50s with AIDS and a CD4 count of 3 cells/mm^3 was admitted for a 1-month history of malaise, fever, diarrhea and a new skin rash. He reported that the pruritic rash began on his face before spreading to his bilateral upper extremities. He denied a history of a similar rash in the past and had no prior treatment. He was undomiciled and denied recent travel. The patient was not compliant with antiretroviral medications. Physical examination revealed a cachectic and ill-appearing adult man with numerous skin-colored firm papules, some with overlying excoriations, involving his face, bilateral upper extremities and dorsal hands (Figure 1A and B). Initial laboratory examination was notable for an elevated lactate dehydrogenase (LDH), leukopenia and acute kidney injury. Punch biopsy specimens from the distal left upper extremity were performed for histopathological analysis and tissue culture. Skin biopsy demonstrated pseudoepitheliomatous hyperplasia and extensive perivascular macrophage infiltrates containing numerous tiny intracellular organisms, highlighted by the Gomori methanamine silver (GMS) stain (Figure 2A and B). Tissue culture from a lesion identified *Histoplasma capsulatum* and *H. capsulatum* serum antigen was positive. The diagnosis of disseminated histoplasmosis was made. Given the patient's severity of symptoms, a bone marrow biopsy was performed and was negative for involvement. The patient received induction therapy with intravenous amphotericin B for one week and was then continued on oral itraconazole therapy 200 mg twice daily. The patient's antiretroviral therapies were reinitiated. Unfortunately, due to coexisting morbidities, persistently low CD4 count and complicating bacteremia, the patient ultimately expired.

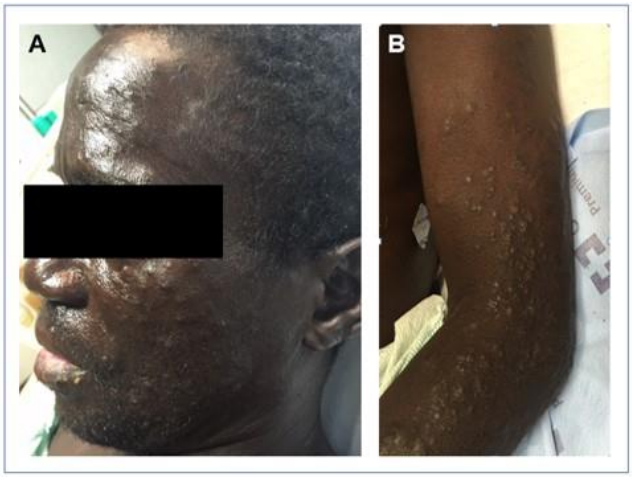

Figure 1. (A) Photograph from clinical examination shows numerous 1-5mm indurated skin-colored papules on the forehead and bilateral malar cheeks; **(B)** coalescing similar lesions observed on the distal upper extremities.

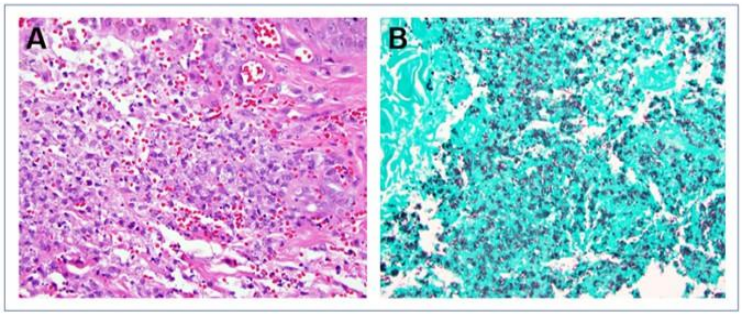

Figure 2. Histopathological findings from the upper extremity show characteristic intracellular 2-4 µm yeast forms within the cytoplasm of macrophages (A), which are further highlighted by GMS staining (B) (H&E, x40).

DISCUSSION

Histoplasmosis is a dimorphic fungal infection caused by *Histoplasma capsulatum* and is the most prevalent endemic mycosis in the United States. Birds and bats serve as the primary reservoirs with endemic areas in the Midwest and Mississippi regions.[4] High-risk areas include caves, construction sites, and chicken coops, locations in which spores are inhaled from the soil by a susceptible host. Immunocompetent hosts may present with subclinical disease, however, with immunosuppression, dissemination of disease can occur.[5] The most common sites of involvement include the lung, spleen, lymph nodes, bone marrow and liver; dissemination to the skin occurs infrequently.[2,5]. Risk factors for dissemination include immunodeficiency, extremes of age, and immunosuppression. A CD4 count of less than 50 cells/mm^3 has been reported in association with disseminated cases in patients with AIDS.[6] TNFα inhibitor therapy has been implicated in 74 cases of disseminated disease in a recent study.[7]

The clinical presentation of disseminated histoplasmosis manifests in a variety of cutaneous presentations. Oral ulcerations are the most common associated findings; however, non-specific papules, nodules and plaques may also arise on the face, extremities and trunk [2]. Additional presentations include psoriasiform lesions, diffuse erythroderma, purpura and even hyperpigmentation secondary to adrenal involvement with resulting Addison's disease.[8]

The differential diagnosis in our patient included pruritic papular eruption of HIV, eosinophilic folliculitis and opportunistic infections including cryptococcosis, blastomycosis, coccidiomycosis, penicillinosis, histoplasmosis, and leishmaniasis.

The characteristic histopathologic features of histoplasmosis, namely intracellular 2-4 µm yeast forms within the cytoplasm of macrophages surrounded by an artefactual halo of clearing were demonstrated in our case. Other diseases manifesting with similar appearing intracellular organisms engulfed by macrophages include leishmaniasis, granuloma inguinale, rhinoscleroma and penicillinosis. Additionally, the organisms are strikingly similar to those seen in leishmaniasis, however, they lack a kinetoplast and are more evenly distributed throughout the cytoplasm. GMS and PAS stains assist in the correct diagnosis.

The work-up involves histologic examination, and the gold standard of diagnosis is fungal culture.[9,10] Determination of the urinary or serum *Histoplasma* antigen can be helpful in monitoring and guiding treatment response.[10] Laboratory evaluation for anemia, transaminitis, bilirubinemia, uremia and hypoalbumenia can be predictive factors for more severe disease within the AIDS population.[11] These patients should be recognized early and treated aggressively.[12]

Treatment involves initial intravenous amphotericin B therapy followed by oral itraconazole therapy twice daily. According to the 2007 Infectious Diseases Society of America (IDSA) guidelines, itraconazole therapy can be discontinued in disseminated cases in patients with AIDS once the following criteria are met: 12 months of

itraconazole therapy, CD4 count of at least 150 cells/mm^3, negative fungal blood cultures, and serum and urine antigen levels less than 4 U/mL.[10] Our patient was treated accordingly, however, due to coexisting morbidities and low CD4 count, the patient ultimately expired. This case serves to highlight that disseminated histoplasmosis may result in substantial morbidity in critically ill patients, especially in patients with AIDS. These patients presenting with disseminated disease are significantly ill and require prompt recognition and management to maximize the efficacy of treatment.

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