

Disseminated Histoplasmosis in AIDS : A Report of Three Patients

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Summary

Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum*. Although uncommon, it should be considered among the list of important opportunistic infections in severely immunocompromised patients. Patients living with AIDS are at particular risk of disseminated histoplasmosis. Diagnosis requires a high level of clinical suspicion. The infection is best confirmed by demonstration of the organism in tissue specimens or by culture. Amphotericin B is the most effective drug for severe disseminated histoplasmosis. Response is good but life-long maintenance is required to prevent relapse.

Key Words: Disseminated histoplasmosis, AIDS, Malaysia

Introduction

Histoplasmosis is a serious opportunistic infection in patients with AIDS, representing the index diagnosis in 50% to 70% of patients in endemic regions^{1,2}. In 1985, in recognition of the association of progressive disseminated histoplasmosis with human immunodeficiency virus (HIV) infection, the Center for Disease Control in America (CDC) broadened its case definition of progression to AIDS to include histoplasmosis.

The AIDS epidemic has completely changed the epidemiology of histoplasma infection in Malaysia: from what was once an uncommon infection to what is now an important diagnostic consideration in any advanced HIV-infected patient with a suspected opportunistic infection.

We wish to report three HIV-infected patients with disseminated histoplasmosis seen at the Department of Medicine, Universiti Kebangsaan Malaysia.

Case Report

Case 1

A 33 year-old heterosexual Chinese man infected with HIV, presented with a 6 months history of fever, anorexia and marked weight loss. He also gave a history of an unproductive cough and generalised maculopapular rashes (Fig. 1) for 2 months prior to admission. Examination revealed a thin, pale and ill-looking man. There were generalised maculopapular rashes on the trunk and extremities. His liver and spleen were both enlarged. Blood investigations revealed a pancytopenia. His haemoglobin was 3.4gm%, TWBC $1.1 \times 1000/\text{mm}^3$, platelets $60,000/\text{mm}^3$. His CD 4 count was $40 \text{ cell}/\text{mm}^3$, and his HIV RNA viral load was 750,000 copies/ml. A bone marrow biopsy (Fig. 2) clinched the diagnosis of disseminated histoplasmosis. He responded very well to intravenous amphotericin B and has not had a relapse of his histoplasmosis on maintenance dose of oral itraconazole. His HIV infection is treated with saquinavir and didanosine.

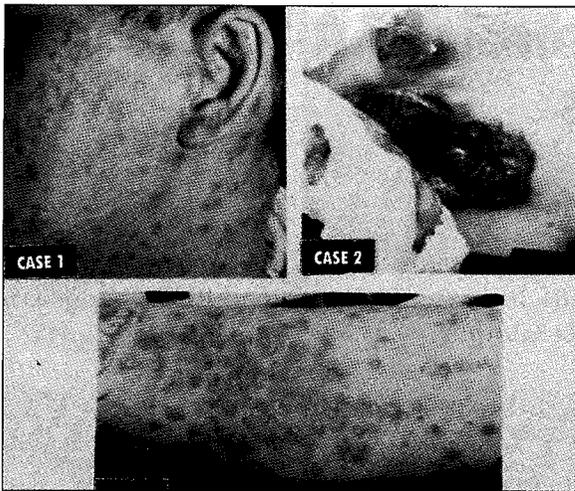


Fig. 1: Cutaneous lesions in disseminated histoplasmosis.

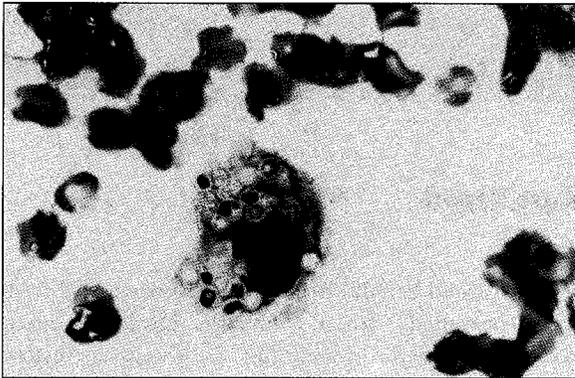


Fig. 2: Bone marrow aspiration showing typical encapsulated yeast form of *Histoplasma capsulatum* (H & E, x 600 magnification).

Case 2

A 45 year-old Chinese construction worker presented with a one year history of itchy maculopapular skin lesions on the trunk which later ulcerated. Like his brother above (Case 1), he acquired HIV infection through sexual intercourse with multiple partners including commercial sex-workers. Examination revealed many vesiculopapular eruptions on the limbs

and a few fungating ulcers on the trunk (Fig.1). His CD4 cell count was 24 cell/mm³. A diagnosis of disseminated histoplasmosis was confirmed from a biopsy of one of the fungating lesions. He responded well to a combination of amphotericin B and itraconazole with complete healing of the skin and fungating lesions. He remains well on maintenance dose of oral itraconazole.

Case 3

A 33 year-old Chinese man, who services air-conditioners, presented with fever, cough and vomiting for two weeks. He acquired HIV infection through sexual intercourse with commercial sex workers. On examination he was unwell and his temperature was 38°C. There was oral thrush and his nodes were enlarged in the neck and axillae. In the background of many body tattoos, there was a generalised erythematous non-pruritic maculopapular skin rash (Fig. 1). Investigations revealed pancytopenia with haemoglobin 6.8gm%, TWBC count 2.7 x 1000/mm³, and platelets 76,000/mm³. Septic work up was negative. His CD 4 cell count was 96 cell/mm³. A skin biopsy confirmed *Histoplasma capsulatum* infection. He received intravenous amphotericin B and oral itraconazole with good response. He was discharged on maintenance dose of itraconazole and continues to be seen regularly in the clinic. His antiretroviral treatment was stopped recently due to financial difficulties.

Discussion

Histoplasma capsulatum is a thermal dimorphic fungus. It is found along the major river valleys in the temperate part of North America. Cases of histoplasmosis have also been reported in Europe, Africa, Southeast Asia, the Caribbean, and areas in Central and South Americas. Many patients reported in non-endemic areas have previously visited or resided in areas of the world where histoplasmosis is endemic. It grows as a mould in soil contaminated by bird or bat droppings, producing macroconidia and smaller, infective microconidia. After inhalation, the microconidia are converted into yeast form in the lungs. The yeasts are phagocytosed by and multiply within alveolar macrophages, destroying the macrophages in the process. Specific cell-mediated immunity develops and activates macrophages to

inhibit yeast proliferation, with gradual containment of the disease process in most immunocompetent hosts. In HIV-infected patients, the phagocytic and fungistatic function of macrophages against *H. capsulatum* is defective. The greatest risk for disseminated histoplasmosis occurs when the CD4 cell count falls below 100 cell/mm³. Person-to-person or animal-to-person transmission do not occur.

Histoplasmosis is disseminated in 95% of cases among patients with AIDS². Most patients present subacutely with fever and weight loss. Cough and dyspnea occur in half of the patients. Hepatosplenomegaly and lymphadenitis occur in 25% of patients. Skin lesions (as reported in all three patients here) in AIDS patients with disseminated histoplasmosis are common and have been reported to occur in up to 20% of patients¹. These include papules, maculopapules, pustular folliculitis, ulcerative plaques, erythematous lesions with necrotic centers, eczematous lesions, *erthema multiforme*, and rosacea-like lesions. Central nervous system manifestations of meningitis, encephalitis, or cerebral granulomas occur in 5% to 20% of cases. Unusual manifestations include pericarditis, rhabdomyolysis, chorioretinitis, pancreatitis, colonic ulcers and masses, mesenteric and omental nodules, cholecystitis, and prostatitis. Some patients, particularly in advanced disease, may even present with hypotension indistinguishable with other forms of septic shock.

Definitive diagnosis of disseminated histoplasmosis depends on identification of the yeast in culture. Culture of bone marrow aspirate specimens, peripheral blood smear, lymph node biopsy specimens, bronchial alveolar lavage fluid sample, transbronchial biopsy material and biopsy samples of cutaneous lesions are usually diagnostic. Culture of bone marrow and blood have been positive in up to 90% of cases². All the three patients were easily diagnosed by direct microscopic examination of collected biopsy specimens. The morphologic appearance of *H. capsulatum* in tissue specimens is fairly typical to most pathologists and haematologists.

The detection of *Histoplasma* polysaccharide antigens in body fluids by radioimmunoassay or enzyme immunoassay using polyclonal antibodies permit the rapid diagnosis of patients with disseminated

histoplasmosis. Antigen can be detected in the urine and serum in 95% and 86% respectively, and in bronchoalveolar lavage fluid and CSF in cases with pulmonary and meningeal involvement in 70% and 67% of cases respectively⁴. The specificity is greater than 98%. In contrast, serologic tests for *H. capsulatum* antibodies lacks both sensitivity and specificity and false-positive results are common due to cross reactivity with other fungi. It also lacks the ability to distinguish between prior and active infection.

Untreated disseminated histoplasmosis is fatal in patients with HIV infection. Intravenous amphotericin B is the treatment of choice for patients with moderate to severe disseminated disease. Remission can be obtained in 80% of patients². A liposomal formulation of amphotericin B with higher therapeutic efficacy and lower toxicity has been approved for those patients who cannot tolerate conventional amphotericin B. Itraconazole is a viable alternative for the treatment of mild disseminated histoplasmosis in AIDS patients³. Clinical improvement occurred in 85% of patients and the median time to resolution of fungemia was one week.

Similar to most opportunistic infections in AIDS, life long suppressive therapy is recommended following successful treatment of disseminated histoplasmosis because relapse rates of 50 to 90% have been reported in those patients who did not receive maintenance therapy. Amphotericin B, 50 - 80mg weekly, has resulted in greater than 90% survival of 14 months. Unfortunately regular administration of amphotericin B is problematic due to the need of an intravenous access route. In a prospective trial³, relapse occurred in only 5% of 42 patients who were placed on itraconazole 200mg twice daily for maintenance therapy. Primary prophylaxis against histoplasmosis is under consideration in high endemic areas. The current public health recommendation for HIV infected patients is to avoid exposure sites and protective isolation is not necessary as the disease is not contagious.

Addendum

Patients in Case 2 and Case 3 have since died from severe opportunistic infections.

References

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