

Disseminated Histoplasmosis in Patients with AIDS in Panama: A Review of 104 Cases

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We identified the incidence and primary clinical characteristics of histoplasmosis in patients with acquired immunodeficiency syndrome (AIDS) in our hospital. Disseminated histoplasmosis is a common and severe disease among patients with AIDS in Panama and should be suspected for patients with a CD4 cell count of <100 cells/ μ L, fever, respiratory symptoms, weight loss, and diarrhea.

Samuel Darling [1] reported the first case of histoplasmosis in a human, in December 1905 in Panama. The conditions that favor the growth of *Histoplasma capsulatum*, a dimorphic fungi, in soil are a mean temperature of 22°C–29°C, an annual precipitation of 35–50 in, and a relative humidity of 67%–87%. These conditions usually are found in Panama, and several studies of histoplasmin skin-test reactivity have shown high prevalence rates, confirming that Panama is an endemic region for histoplasmosis [2–4]. Nevertheless, any form of histoplasmosis was seldom diagnosed among Panamanians before the spread of AIDS [3]. Currently, Panama has an estimated prevalence rate of AIDS of 1.5% [5], and disseminated histoplasmosis (DH) is a common diagnosis for admission to the AIDS ward of our hospital (Arnulfo Arias Madrid Hospital, Panama City); moreover, DH is often the AIDS-defining illness in our patients. To assess the incidence, primary clinical characteristics, methods for diagnosis, treatment, and outcome of this disease in Panama, we performed a retrospective study of patients with AIDS who had received a diagnosis of histoplasmosis from January 1997 through December 2003 in our hospital. We compared our results with the available literature on this topic.

Patients and methods. Histoplasmosis was defined by a

culture positive for *H. capsulatum* or a histopathologic finding of organisms consistent with *H. capsulatum*. DH was defined by the identification of the fungus in specimens of blood or bone marrow and was associated with systemic symptoms.

Case patients were >15 years of age and were those patients at Arnulfo Arias Madrid Hospital who had a serologic test positive for HIV-1 infection and laboratory evidence of newly diagnosed histoplasmosis, as described above, during the period from January 1997 through December 2003. We reviewed the medical records of patients with HIV infection or AIDS who had a diagnosis of histoplasmosis at discharge and/or a mycology laboratory report of growth of *H. capsulatum* and who were hospitalized from January 1997 through December 2003. Information was collected on demographic characteristics; risk factors for HIV infection; date of diagnosis of HIV infection; date of diagnosis of histoplasmosis; clinical manifestations; laboratory and radiographic findings at the time of admission to the AIDS ward; CD4 cell count and viral load, when available; results of microbiologic or other diagnostic studies; and anti-fungal therapy, its side effects, and its outcome.

Results. Between January 1997 and December 2003 at our hospital, 182 patients with HIV infection or AIDS had cultures positive for *H. capsulatum*. During the study period, 2379 patients were admitted to the hospital's AIDS ward; thus, histoplasmosis represented 7.65% of admissions (table 1). Of these 182 patients, we found and reviewed the medical records for 104. Table 2 summarizes the demographic characteristics of the 104 patients.

The most common clinical findings are compiled in table 3. Radiographic findings were recorded for only 54 patients, and 41 had abnormal results. The most common abnormalities reported were bilateral reticulonodular infiltrates (26 [48%] of the 54 patients).

Other opportunistic infections were diagnosed in 27 patients (26%) prior to or concomitant with the diagnosis of histoplasmosis. Tuberculosis was the most common associated infection (16 patients [15.4%]). Other coexisting opportunistic conditions were toxoplasmosis and Kaposi sarcoma, which were diagnosed in 4 and 3 patients, respectively. Only 14 (13.5%) of the 104 patients were receiving antiretroviral therapy at the onset of symptoms of histoplasmosis; 3 patients were receiving monotherapy or bitherapy, and the rest had been receiving HAART for the previous 3–6 months.

The diagnostic tests that showed positivity were as follows: blood culture, 67.3%; bone marrow culture, 51%; and histopathology of a bone marrow biopsy, 24%. Results of biopsies

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Table 1. Cases of histoplasmosis in patients with AIDS who were hospitalized from 1997 to 2003 in the AIDS ward of Arnulfo Arias Madrid Hospital, Panama City.

Year	No. of patients hospitalized ^a	No. (%) of patients with histoplasmosis ^b
1997	337	13 (3.86)
1998	326	29 (8.89)
1999	366	31 (8.47)
2000	372	47 (12.63)
2001	371	26 (7.0)
2002	310	18 (5.8)
2003	297	18 (6.0)
Total	2379	182 (7.65)

^a Includes all patients admitted to the AIDS ward for any reason.

^b Includes all patients with a culture-proven diagnosis of histoplasmosis, whether or not the patients' medical records were reviewed for the present study.

of skin and lymph nodes were found to be positive for 6 and 4 patients, respectively. Results of biopsies of 2 mucosal lesions (from the tongue and colon) also were positive. Those who had positive biopsy results also had positive results of either blood or bone marrow cultures. *H. capsulatum* was also found in 3 bone marrow smears and 2 buffy-coat smears.

Of the 104 patients, 100 (96%) received amphotericin B deoxycholate induction therapy, 1 received itraconazole, and 3 died without receiving antifungal therapy. Most of the patients received ~1 g amphotericin B and then were switched to oral itraconazole. Forty patients showed adverse effects related to therapy with amphotericin B: the most common effects were hypokalemia (20 [50%] of 40 patients) and an increase in creatinine level (17 [42.5%] of 40 patients).

On the basis of data for 57 patients, the mean time to defervescence was calculated to be 2.9 days (range, 1–10 days). The median duration of hospitalization was 18.8 days (range, 3–60 days).

The mortality rate was 12.5% (13 of 104 patients). Ten patients died <30 days after admission to the hospital. Two patients died because of a relapse of histoplasmosis, at 1 and 3 years after the first episode, respectively. The other patient died 2 months after admission. Only 6 (5.8%) of the 104 patients had a relapse of histoplasmosis during the study period.

Discussion. In endemic areas, the incidence of histoplasmosis among patients with AIDS is 5%–20% [6, 7]. The percentage of patients with histoplasmosis in the AIDS ward of our hospital during the study period was 7.65%. There was an increase in the number of cases of histoplasmosis during 1998–2001, and this increase reached its peak in 2000, with an incidence of 12.63%. Studies based on histoplasmin reactivity that were done in the 1950s, 1960s, and 1970s [2–4] found a

prevalence of 48%–54% in Panama. During the deep state of immunosuppression that is the hallmark of AIDS, the development of histoplasmosis could be due to primary infection, reinfection, or reactivation, in an endemic area [6, 8, 9] such as Panama.

In terms of age, sex, type of presentation of histoplasmosis (i.e., disseminated), CD4 cell count, clinical manifestations, abnormal results of laboratory and radiographic tests, response to treatment, outcome, and mortality rate, our findings correlated with those of previous reports [10–17]. All of our patients with histoplasmosis had acquired HIV infection through sexual intercourse, and most of them had been infected through heterosexual contact. This pattern was not unexpected, because it reflects the main pattern of transmission of HIV infection in Panama [18]. This finding differs from those of reports in which men who have sex with men and injection drug users are the predominant patient groups [11, 12].

Skin lesions were found in only a few cases, which is similar to the results of studies of patients from the Ohio and Mississippi River valleys [8] but different from the results of reports from other Latin American countries, where skin lesions are a prominent and frequent manifestation [19–21].

According to the literature, the highest yield in terms of positivity for histoplasmosis is usually obtained from bone marrow culture (>75% of cases) or blood culture (50%–70% of cases) [1, 6, 8]. In our study, 67.3% of patients had positive blood cultures, but only 51% of patients had positive bone marrow cultures. Blood and bone marrow cultures were done in accordance with the conventional procedures. The lysis-centrifugation method, considered to be optimal for the isolation of fungal pathogens [6], was not available at our hospital.

Table 2. Characteristics of and CD4 cell counts for 104 patients with histoplasmosis and AIDS, at Arnulfo Arias Madrid Hospital, Panama City.

Characteristic	Value
Age, median years (range)	36.7 (20–66)
Male sex	88 (84.6)
Risk factor for HIV infection	
Heterosexual	61 (58.6)
MSM	29 (27.9)
Bisexual	4 (3.8)
Unknown	10 (9.6)
CD4 cell count ^a	
Median cells/ μ L (range)	64.9 (2–428)
<100 cells/ μ L	73 (80)
DH diagnosis	104 (100)
DH as AIDS-defining illness	71 (68.3)

NOTE. Data are no. (%) of patients, unless indicated otherwise. DH, disseminated histoplasmosis; MSM, men who have sex with men.

^a Available for 91 patients.

Table 3. Presenting symptoms and results of physical or laboratory tests for 104 patients with histoplasmosis and AIDS, at Arnulfo Arias Madrid Hospital, Panama City.

Symptom or finding	No. (%) of patients (n = 104)
Fever	96 (92)
Respiratory symptoms	66 (63.5)
Weight loss	65 (62.5)
Diarrhea	52 (50)
Hepatomegaly and/or splenomegaly	44 (42.3)
Elevated transaminase levels (3–10 × ULN) ^a	50 (48)
Elevated LDH level (>3 × ULN) ^b	77 (74)
Pancytopenia	36 (34.6)
Adenopathy	20 (19.2)
Skin lesions	18 (17.3)

NOTE. LDH, lactic dehydrogenase; ULN, upper limit of normal.

^a Normal level for aspartate amino transferase and alanine amino transferase, 8–20 IU/L.

^b Normal level, 60–120 IU/L.

Patients with histoplasmosis and AIDS are often concurrently infected with other opportunistic pathogens, which indicates the need for a careful search for coinfections. We found that 27 patients had other opportunistic infections. Tuberculosis was the most common illness, which is important to note because many cases of histoplasmosis are initially misdiagnosed as disseminated mycobacterial infection [22].

Relapse occurs in 10%–20% of patients with DH and in as many as 80% of patients with AIDS [6]. For most of our patients, the outcome was good, with only 5.8% experiencing a relapse.

The Arnulfo Arias Madrid Hospital is a 1000-bed, tertiary-level health care facility in the social security system, in Panama City. The AIDS ward has 21 beds. HAART was introduced at the hospital in October 1999. The present study covered a few years previous to and several years after the start of HAART. The remarkable decline in the incidence rates of histoplasmosis and other opportunistic infections that has been seen in developed countries [23, 24] after the introduction of HAART has not happened in Panama. Histoplasmosis remains a common and severe infection among patients with AIDS in our hospital, because it is often the first manifestation of the disease. This pattern reflects that of the AIDS epidemic in Panama: HIV-infected people seek medical attention during the advanced stages of the disease, when they have ≥ 1 life-threatening opportunistic infections to fight before HAART can be effective.

There are no accurate records of opportunistic infections among patients with AIDS in Panama; therefore, true incidence rates are unknown. To our knowledge, the present study is the largest review of cases of histoplasmosis in patients with AIDS in Panama and gives us a picture of the incidence of this disease.

This study may serve as a point of reference for further prospective investigations that evaluate epidemiologic aspects and long-term follow-up for these patients in the era of HAART. Likewise, the high incidence of histoplasmosis among patients with AIDS and the severity of the disease validate the need for a faster and more sensitive diagnostic method (e.g., the urinary antigen test available only at the Histoplasmosis Reference Laboratory in Indianapolis, Indiana) and/or a strategy for optimizing the technology currently used (i.e., lysis-centrifugation method used with blood cultures).

In summary, DH should be suspected in any HIV-infected patient in Panama who presents with fever, respiratory symptoms, weight loss, diarrhea, and a CD4 cell count of <100 cells/ μ L. Furthermore, HIV infection should be suspected in any patient with these symptoms, because DH is often the first manifestation of AIDS.

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