

# Disseminated Histoplasmosis In Patients With The Human Immunodeficiency Virus (HIV) In A Nonendemic Area In New York

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## Abstract

Disseminated Histoplasmosis is a serious opportunistic infection in patients with AIDS. We report our experience in a nonendemic area where ten such patients were diagnosed with histoplasmosis. The clinical presentations, diagnostic challenges and outcome are reviewed. Disseminated histoplasmosis can simulate other opportunistic infections and should be considered in the AIDS patient presenting with a low CD4 count, febrile illness, elevated ferritin and LDH levels, thrombocytopenia, history of travel or residence in an endemic area. Greater awareness of this entity is needed, especially in those critically ill patients where the diagnosis can be easily missed if unsuspected and is fatal if not treated.

## INTRODUCTION

Histoplasmosis is prevalent in the Ohio and Mississippi River valleys of North America, and certain areas of Latin America, the Caribbean, Africa, and Asia. The mold form of the organism grows in soil that has been enriched with bird or bat droppings, and infects humans when the soil is disturbed and microconidia enter the airways and cause pneumonitis and mediastinal adenitis, the outcome of which depends upon the size of the inoculum, the immune status and underlying health of the host, and perhaps host genetic factors and fungal virulence characteristics.

Patients with the acquired immunodeficiency syndrome (AIDS) with active *Histoplasma capsulatum* infection tend to present with a severe illness characterized marked by disseminated disease. Urban centers within hyper-endemic areas such as Indianapolis, Indiana, and Kansas City, Missouri, have reported an incidence of histoplasmosis in patients with AIDS as high as 26% compared with less than 1% for in non-endemic areas (1,2).

The Purpose of the study was to evaluate the incidence and presentation of pulmonary histoplasmosis in AIDS patients in a non-endemic inner-city hospital in New York and compare with the presentation as reported in other non-endemic areas.

## METHODS

This was a retrospective review of the medical records, mycology laboratory results and chest roentgenograms (CXR) of all the HIV infected patients with laboratory proven Histoplasmosis. The study period included 1993 to 1997. This study was considered exempt by the Institutional Board Review at our institution.

## CRITERIA FOR DIAGNOSIS

Disseminated histoplasmosis was defined by the presence of extrapulmonary *Histoplasma capsulatum* detected by culture, peripheral blood smear, or histopathologic examination in association with an acute illness.

The diagnosis of AIDS was defined according to the case definition established by the Center for Disease Control (3).

We defined presentation as acute if the symptoms were present for 2 weeks or less, sub-acute between 2 to 6 weeks of symptoms and chronic if more than 6 weeks of symptoms (4).

## RESULTS

During the study period, 4376 HIV infected patients were admitted to our institution. Ten of these patients (0.2%) were diagnosed with pulmonary histoplasmosis. All the patients had disseminated disease.

The ten patients were New York residents. There were six

males and four females with a median age of 42 years (range 29-55). The racial composition of the group consisted of 8 Hispanic (80%) and 2 African-American (20%). Six of the ten patients were born in an endemic area (Puerto Rico), one patient was incarcerated in New York area and another had traveled to the Caribbean. The median time interval since last known travel or exposure to an endemic area was four years (range 2 to 6 years)

The risk factors for HIV disease were intravenous drug use in six patients, sexual exposure in two and unknown in two. All the patients had AIDS with a mean CD4 count of 44 mm<sup>3</sup>.

**CLINICAL PRESENTATION**

The most common presentation of the patients was fever, cough, dyspnea and weight loss. Table 1 show the clinical and laboratory presentation. Our results are compared with another study reported in AIDS patients from a non-endemic area in San Francisco, California (5). The patients we report appear to have more pulmonary manifestations and less of GI symptoms and Hepatosplenomegaly. Serum ferritin was measured in three patients and in all of them was elevated, mean value being 13817 (range 3890 to 24047 ng/ml)

Ninety percent of patients had respiratory symptoms at the time of admission; six of them had a sub-acute presentation and two had chronic, more than six weeks of respiratory and constitutional symptoms. Acute presentation was seen in two patients, one of them presented with septic shock and ARDS. Opportunistic or chronic infections were common in our patients; six were undergoing treatment for various diseases, (pulmonary tuberculosis 1, Cryptococcus meningitis 1, CMV retinitis 1, HIV dementia 1, CNS Toxoplasmosis 1).

Initial chest roentgenogram (CXR) findings are noted in Table 2 and compared with another study (5). Although majority of our patients had abnormal CXR findings, four of the cases were admitted with normal CXR and three of them subsequently developed lung infiltrates while in the hospital. We did not find any clinical correlation between acuteness of presentation and radiographic findings. Mediastinal adenopathy was not a feature in our group, only one patient had bilateral disease and mediastinal, hilar adenopathy.

**DIAGNOSIS AND OUTCOME**

The diagnosis of Histoplasmosis in our patients was made mainly by tissue diagnosis of lung, lymph nodes or bone

marrow. Only 30% of our cases had a positive blood cultures or positive smears for *H. capsulatum* Table 3. In one patient, although bronchoscopic biopsy was negative, the lymph node biopsy was positive for histoplasma. In yet another patient, although lymph node biopsy was negative, the bone marrow yielded the diagnosis. Treatment with Amphotericin B was initiated in six patients; the other four either died before treatment could be started or did not have a pre mortem diagnosis. One patient had concomitant pulmonary PCP and Histoplasmosis. 60% of the patients died during the initial hospital admission for Histoplasmosis, four patients were discharged home on Iatroconazole, with one of them dying later due to Histoplasmosis. Four patients had necropsy done; pulmonary involvement was seen in all of them Table 4.

**Figure 1**

Table 1: Clinical and laboratory presentation of patients with Histoplasmosis

Clinical presentation	No. (%)	Fredericks et al 1997 No. (%)
Symptoms and Signs		
Fever	10 (100%)	43 (93%)
Respiratory	9 (90%)	31 (67%)
Weight loss (>10 pound)	6 (60%)	-
Gastrointestinal	3(30%)	30 (65%)
Constitutional (weakness)	3(30%)	-
Hepatomegaly	2(20%)	22 (48%)
Hemoptysis	2(20%)	-
Rash (maculopapular)	2(20%)	14 (30%)
Splenomegaly	1(10%)	28 (61%)
Lymphadenopathy	3(30%)	26 (57%)
Laboratory		
Leucopenia (White blood cells<4,000)	9 (90%)	33 (71%)
Thrombocytopenia (Platelets<100,000)	4 (40%)	29 (63%)
Anemia (Hemoglobin<10g/dl)	3 (30%)	43 (93%)
Serum LDH (> 300U/L)	8 (80%)	-

**Figure 2**

Table 2: Initial Radiographic findings compared with another study from a non-endemic area for Histoplasmosis

CXR Findings	No. (%)	Fredericks et al 1997 No. (%)
Normal	4 (40%)	9 (20%)
Abnormal	6 (60%)	37 (80%)
Focal alveolar infiltrate	1 (10%)	6 (13%)
Diffuse alveolar-interstitial infiltrate	4 (40%)	27 (59%)
Bilateral nodular infiltrate	1 (10%)	-

**Figure 3**

Table 3: Microbiology Results for *H. capsulatum*

Test	No. patients positive/No. tested	%
Peripheral blood smear/Cultures	3/10	30 %
FOB biopsy/culture	3/ 4	75 %
Lymph node biopsy	2/3	67 %
Bone marrow biopsy/culture	1/2	50 %
Post mortem necropsy diagnosis	4/4	100%

**Figure 4**

Table 4: Clinical Presentation, Diagnosis and Outcome of the patients

Patient	Presentation	CXR	Positive Diagnostic tests	Outcome after diagnosis
1	Acute	Bilateral Interstitial/Alveolar	FOB BX culture Blood cultures	Survived 11 months, died etiology unknown
2	Acute	RML infiltrate	Necropsy	Expired
3	Sub-acute	Diffuse nodular + Mediastinal LN	FOB BX culture	Alive to discharge, lost for follow up
4	Sub-acute	Normal	Blood cultures/ smears	Expired
5	Sub-acute	Bilateral Interstitial/Alveolar	Bone marrow biopsy	Expired
6	Sub-acute	Bilateral Interstitial/Alveolar	Necropsy	Expired
7	Sub-acute	Normal	Blood cultures/ smears Necropsy	Expired
8	Sub-acute	normal	Cervical LN/ Bone marrow biopsy	Survived 10 months, died of histoplasmosis
9	Chronic	Bilateral Interstitial/Alveolar	Cervical LN FOB BX culture	Survived 10 months, lost for follow up
10	Chronic	Normal	Necropsy	Expired

**DISCUSSION**

This retrospective case series of 10 patients presents the most common manifestations and diagnostic challenges of pulmonary and disseminated histoplasmosis in AIDS patients. During 1993 to 1997 we identified 10 patients with pulmonary and disseminated Histoplasmosis in our hospital in the South Bronx. This represents 0.2% of all patients admitted with AIDS .Our incidence is strikingly low as compared with the two earlier reports of histoplasmosis in New York which suggest a higher rate in our area, Salzman et al. reported 18 of 890 patients (2 %) with histoplasmosis from two New York City hospitals and Morse et al found 15 out of 600 (2.5%) prison employees to be infected. (6,7). The population served in the South Bronx is predominantly Hispanics and African- American and we would expect to have higher rates of Histoplasmosis. Histoplasmosis is a serious opportunistic infection in patients with AIDS, often presenting as the first manifestation of the syndrome. Most infections occurring in the endemic regions are caused by exogenous exposure, while those occurring in nonendemic areas may represent endogenous reactivation of latent foci of infection or exogenous exposure to microfoci located within those nonendemic regions. Eight of our patients were exposed to endemic areas several years prior to the diagnosis, so we support the statement that reactivation histoplasmosis is the most tenable explanation for most of the cases in our report. The low incidence and therefore the low suspicion of histoplasmosis in AIDS patients residing in nonendemic areas may delay its diagnosis, especially when other concurrent or chronic infections are present. Many of the laboratory and radiological abnormalities can be explained by chronic conditions or medications.

In contrast to the study done by Fredericks et al (5) most of our patients presented with fever, respiratory symptoms and

leukopenia, and we had fewer cases with splenomegaly or lymphadenopathy. As reported by others, serum LDH and ferritin were elevated in our patients. In patients with AIDS, the combination of fever, cytopenia, elevated serum LDH level (> 1,000 IU/L), and/or hyperferritinemia (ferritin level of > 10,000 ng/mL) is a clue to the diagnosis of reactive hemophagocytic syndrome and disseminated histoplasmosis (8,9,10,11)

The radiological presentation in our group is similar to the one reported in other studies (1,12). Chest radiographs were abnormal in up to 60 % of cases and diffuse infiltrates were seen in 40% of cases. Nodular opacities were uncommon in our study, even though this has been one of the common radiological presentations. (4, 12) In comparison to other studies, we had a higher number of patients presenting with a normal CXR, 40% compared with the reported 20 to 27% of normal CXR. (5, 6, 12)

Diffuse infiltrates, in the absence of a history of probable high-inoculum exposure, strongly suggests progressive disseminated disease even in the absence of systemic and laboratory abnormalities. In a comparison of the radiographic findings in progressive disseminated versus subacute pulmonary histoplasmosis, diffuse infiltrates were not observed radiologically in the subacute pulmonary cases (13)

The immunocompromised host with pulmonary histoplasmosis usually has concurrent disseminated disease, even though it may not be apparent clinically. Evidence for dissemination includes hepatosplenomegaly, extrapulmonary lymphadenopathy, mucosal or skin lesions, anemia, leukopenia, thrombocytopenia, or elevated hepatic enzymes.

**CONCLUSIONS**

In summary, histoplasmosis is a serious and often fatal opportunistic infection in patients with AIDS, which can occur in nonendemic areas representing endogenous reactivation of latent foci of infection or exogenous exposure to microfoci located within those nonendemic regions. Cases of Histoplasmosis have also been described during the course of immune reconstitution inflammatory syndrome following initiation of ART.

Disseminated histoplasmosis should be considered in any AIDS patient with a low CD4 lymphocyte count, a febrile illness, an elevated ferritin and LDH levels, cytopenia, history of travel or residence in an endemic area. As in some

of our cases biopsies need to be taken from multiple sites to confirm the diagnosis. Greater awareness of this disease is needed, especially in those critically ill patients where the diagnosis can be easily missed if not suspected. With the availability of Urine and plasma histoplasma antigen studies, diagnosis can be made rapidly if there is a clinical suspicion. In those patients with HIV infection, antigen is detected in urine in 95% of cases of disseminated histoplasmosis and serum in 85 % (14). Other available body fluids can be tested too.

A prompt search for the diagnosis should be undertaken, and early empiric initiation of antifungal therapy may be warranted in some cases. Survival benefits have been reported with the prompt institution of antifungal therapy and maintenance therapy.

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