AIDS with Disseminated Histoplasmosis

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This report is a description of two Ohio cases of acquired immunodeficiency syndrome (AIDS) and disseminated histoplasmosis, with discussion of diagnosis and treatment of this combination. The patient in case 1 developed disseminated histoplasmosis as the first significant symptomatic medical condition of his life. The patient in case 2 presented with severe pharyngitis, but without signs or symptoms specific to the lungs. Amphotericin B alone does not eradicate histoplasmosis in an AIDS patient. The best therapy at present is a full course of amphotericin B followed by a lifetime regimen of ketoconazole to prevent relapse. Family physicians in the District of Columbia, Texas, Maryland, Louisiana, Missouri, Illinois, Arizona, and Puerto Rico should be particularly vigilant in looking for the combination of these two diseases.

Disseminated histoplasmosis is now recognized as an infectious complication of the acquired immunodeficiency syndrome (AIDS) in areas of the United States endemic for histoplasmosis,[1] in the Caribbean and South America,[2] and in nonendemic areas where it appears sporadically.[3] Although medical reports first documented the existence of AIDS in mid-1981,[4–8] research did not confirm an association between AIDS and disseminated histoplasmosis until late 1983.[9–12] *Histoplasma capsulatum* thrives primarily in the Ohio and Mississippi river valleys, whereas the US epidemic of the human immunodeficiency virus (HIV) was first kindled in the coastal cities of New York and San Francisco. Thus, early victims of AIDS resided in areas of low exposure to *Histoplasma*. This initial geographic separation probably delayed the recognition of an association between the two diseases.[1] In 1985 the Centers for Disease Control revised its case definition of AIDS for national reporting to include disseminated histoplasmosis.[13] The authors describe two Ohio cases of AIDS with disseminated histoplasmosis not previously reported.

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CASE REPORTS

Case 1

K.K., a 31-year-old male hospital custodian, came to the emergency department because of productive cough, emesis, and diarrhea.

Before this illness he had always been in good health, and findings on a pre-employment chest radiograph taken 6 months before admission were normal. During the 3 months prior to admission he suffered a persistent cough and increasing fatigue, which led to fever, chills, vomiting, night sweats, and diarrhea with occasional blood. He had not worked with any biologically hazardous materials until 1 month before admission.

The patient is a resident of Columbus, Ohio. He had no past history of increased susceptibility to infections, immunosuppressive drug therapy, malignant neoplasm, or exposure to tuberculosis, excavation sites, bats, or birds. He denied homosexual activity, transfusions of any kind, and intravenous drug use. He insisted he had only one sexual partner for the previous 6 years, although he later admitted to heterosexual contact with an intravenous drug abuser.

On general examination, the patient was a well-developed, muscular man who appeared obviously ill and weak. His pulse was 128 beats per minute, respirations 24/min, blood pressure 100/60 mmHg, and oral temperature 103.2°F (39.6°C). His skin was hot and dry, but without petechiae or rashes. The nail beds and mucous membranes were pale. There was no palpable lymphadenopathy. Findings on examination of head, eyes, ears, nose, and throat

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were unremarkable. There were few rales audible bilaterally in the lungs. The heart had a rapid rate, but was otherwise normal on examination. Findings on abdominal examination were unremarkable. Rectal examination produced stool that reacted positively for occult blood. Findings on genitourinary and neurological examinations were unremarkable.

A chest radiograph showed a 3-cm cavitary lesion in the posterior segment of the left upper lobe and an extensive micronodular process, described as consistent with miliary tuberculosis. An electrocardiogram showed sinus tachycardia, but was otherwise unremarkable. White blood cell count was 2.7×10^9/L (2,700/mm^3), hemoglobin concentration was 113 g/L (11.3 g/dL), hematocrit was 0.35 (35%), and platelet count was 51×10^9/L (51,000/mm^3). Sodium was 124 mmol/L (124 mEq/L), chloride was 89 mmol/L (89 mEq/L), and the remaining admission laboratory results were unremarkable. The physicians primarily considered the possibilities of mycobacterial infection, fungal infection, and parasitic infestation, feeling that psittacosis, carcinomatosis, and viral pneumonia were less likely. Routine peripheral blood smear showed monocytes containing organisms with the appearance of *Histoplasma*. Smear of the bone marrow likewise showed *Histoplasma* organisms inside granulomas. Multiple cultures yielded *Histoplasma capsulatum*, including two sputum specimens, two peripheral blood specimens, and three bone marrow specimens. An enzyme-linked immunosorbent assay (ELISA) test was positive for HIV antibody, indicating infection with the virus, which the western blot confirmed. At this stage, *Histoplasma* antibody titers for the mycelial and yeast phases were both negative. Fungal precipitins were negative for *Histoplasma*, *Blastomyces*, *Coccidioides*, and *Aspergillus*. All three sputum specimens were negative for *Mycobacterium* by smear and culture. Mycobacterial cultures of the bone marrow specimen and all three urine specimens were negative.

Based upon presumptive identification of *Histoplasma* in the first peripheral blood smear, the patient was started on a course of intravenous amphotericin B. His clinical and laboratory values steadily improved and he was discharged on the 15th hospital day on oral ketoconazole for the rest of his life.

Case 2

S.C. is a 54-year-old male Ohioan who was delivered by one of the authors (T.W.). During his teenage years, he discussed his homosexual lifestyle with that physician. Later, while serving a prison term for a drug conviction, he requested AIDS testing when one of his sexual contacts contracted this disease. The ELISA was positive for HIV infection and confirmed by western blot. Total lymphocyte count was 2.4×10^9/L (2400/mm^3), inducer-helper cells (CD 4) were 0.168×10^9/L (168/mm^3, normal = 390 to 1920/mm^3), and suppressor-cytotoxic cells (CD 8) were $2.064 + 10^9$/L (2064/mm^3, normal = 230 to 1320/mm^3). Helper-suppressor T lymphocyte ratio was less than 0.1 (normal range = 0.9 to 2.3). Serologic studies demonstrated chronic hepatitis B virus carrier state. The patient had no symptoms at that time.

Two months before hospitalization he noticed a productive cough. Findings on physical examination were consistent with a mild upper respiratory infection, which was treated symptomatically. Over the next 6 weeks he developed progressive symptoms of severe sore throat, malaise, weakness, fever, lymphadenopathy, hepatosplenomegaly, a tongue lesion, and anemia. One week before admission the patient appeared acutely ill with accelerating symptoms. Alarmed, his family physician considered the probability of various severe infections and pressed for hospital admission, but the patient refused. Biopsy of this nonsmoker's tongue showed hairy leukoplakia.

The patient finally agreed to hospitalization to treat his accelerating symptoms. Physical examination showed him to be in acute distress, pulse 88 beats per minute, respirations 14/min, blood pressure 160/100 mmHg, and temperature 104°F (40°C). The pharynx was erythematous with exudate on the right tonsil. One large nontender cervical lymph node and several smaller tender cervical nodes were palpable. The lungs were clear to auscultation and percussion, and the remainder of the physical examination was unremarkable.

Initial white blood cell count was 4.5×10^9/L (4,500/mm^3), hemoglobin concentration was 107 g/L (10.7 g/dL), hematocrit was 0.30 (30%), mean corpuscular volume was 85 fL, platelet count was 236×10^9/L (236,000/mm^3). Serum lactate dehydrogenase activity was slightly elevated at 4.18 μkat/L (251 U/L, normal = 0 to 220 U/L). Admission chest radiograph showed no cardiopulmonary disease. Throat swab culture yielded α- and γ-hemolytic streptococci, *Hemophilus* species, and *Neisseria* species.

Physicians considered the differential diagnosis to include lymphoma and lymphadenopathy reactive to viral, aerobic bacterial, anaerobic bacterial, mycobacterial, or fungal infections. Appropriate cultures were taken, and intravenous ampicillin-sulbactam was started as empiric therapy for the leading diagnosis of severe bacterial pharyngitis with abscess. The otorhinolaryngology consultant performed multiple needle aspirations of the pharynx, but found no focal collection of pus. Computed tomography of the neck showed anterior and posterior cervical lymphadenopathy without abscess formation. The patient continued to have high fevers and rigors despite antibiotic therapy, raising the possibilities of antimicrobial resistance, occult abscess, and malignancy. Cervical lymph

node and bone marrow biopsies demonstrated granulomatous inflammation; Gomori methenamine silver (GMS) stain revealed intracellular yeast suggestive of *Histoplasma capsulatum* in both specimens. On the ninth hospital day, cultures of bone marrow and lymph node aspirates yielded *Histoplasma capsulatum*. Complement fixation titers did not detect any antibody against *Histoplasma*, but the more sensitive immunodiffusion technique demonstrated an M band of identity for *Histoplasma* antibody.

The empiric antibiotic was discontinued, and amphotericin B was started, producing a remarkable improvement in adenopathy and fever. The patient developed gastrointestinal intolerance after discharge from the hospital, so amphotericin B was changed to ketoconazole and the patient continued to improve clinically.

DISCUSSION

Histoplasma has low virulence in normal patients without massive inhalation exposure, often producing indolent or asymptomatic conditions. The fungus may spread widely via the blood stream and lymphatics, but typically it infects the lungs, liver, lymph nodes, and spleen, often causing telltale calcifications in these areas. In disseminated disease the infection of additional tissues becomes apparent, including bone marrow, oropharynx, gastrointestinal submucosa, adrenal glands, and occasionally brain and heart. Before AIDS, disseminated histoplasmosis had occurred almost exclusively in the very young, the very old, patients with malignancy of the hematopoietic or lymphatic system, or patients taking immunosuppressive drugs.

AIDS can make the clinical diagnosis of disseminated histoplasmosis difficult in several ways. For example, disseminated histoplasmosis may occur unexpectedly as the first manifestation of AIDS in a patient with previously unrecognized HIV infection.[14] The first patient's fungal infection had disseminated alarmingly to lungs, gastrointestinal tract, and bone marrow. Such dissemination usually occurs only in patients with compromised cellular immunity, but this patient initially appeared previously healthy. The physicians then considered the diagnosis of AIDS and confirmed HIV infection by testing. In contrast, the second patient, who had known infection with HIV, developed a severe illness with rapidly accelerating symptoms, raising the red flag of overt immunosuppression.

Second, the combination of AIDS and disseminated histoplasmosis can present with nonspecific signs and symptoms, such as fever, weight loss, and splenomegaly.[8] It may also mimic miliary tuberculosis,[3] as the first case illustrates.

TABLE 1. KEY SIGNS AND SYMPTOMS OF DISSEMINATED HISTOPLASMOSIS IN 41 PATIENTS WITH ACQUIRED IMMUNE DEFICIENCY SYNDROME*

Clinical Feature	Number	Percent
Fever	34	83
Weight loss	20	49
Anemia†	18	44
Splenomegaly	18	44
Lymphadenopathy	17	41
Hepatomegaly	17	41
Reticulonodular, diffuse interstitial infiltrates	17	41
Normal chest roentgenogram	10	24
Alveolar infiltrates	7	17
Rales or rhonchi	6	15
Dyspnea	6	15
Cough	6	15
Abdominal pain	5	12
Diarrhea	5	12
Thrombocytopenia	4	10
Rash	4	10
Encephalopathy	3	7
Renal failure	3	7
Disseminated intravascular coagulation	3	7
Hypotension	3	7
Malaise	3	7
Leukopenia	2	5
Hypoxia	2	5
Night sweats	2	5
Pancreatitis	1	2

** Compiled from Taylor et al,[11] Wheat et al,[9] Huang et al,[3] Mandell et al,[2] Bonner et al,[17] and Johnson et al[14]*
† Hemoglobin, hematocrit not reported in 22 of 41 cases

Third, the clinical features may create a confusing picture, since multiple opportunistic infections in the same AIDS patient are common.[14]

The clinician may initially discount the possibility of disseminated histoplasmosis in a patient known to have AIDS, particularly if the lungs appear uninvolved, as in the second case. Signs and symptoms focused on the pharynx and neck with no specific evidence of lung involvement. Thus, clinicians should add disseminated histoplasmosis to the list of diagnoses considered in an AIDS patient who has lived in an area endemic for histoplasmosis and who appears septic with pharyngitis. When dealing either with AIDS or with disseminated histoplasmosis, the clinician should maintain a heightened index of suspicion for the other diagnosis as a coexisting condition.

The clinical features of disseminated histoplasmosis in AIDS patients as previously reported in the literature are summarized in Table 1. (This compilation was cross-checked to avoid counting individual patients more than once. A patient who was treated with prednisone therapy

was excluded because she did not have AIDS.[2]) The clinical features of the two patients presented above are comparable to those listed in Table 1, except for the severe pharyngitis in case 2. Oropharyngeal ulcers do occur commonly in disseminated histoplasmosis without AIDS and are the hallmark of mild chronic disease of the adult type.[15] The occurrence of these ulcers increases with chronicity of the infection.

All the findings of disseminated histoplasmosis with AIDS listed in Table 1 also occur in disseminated histoplasmosis without AIDS as described in the exhaustive review by Goodwin et al.[16] The frequencies of anemia, cough, diarrhea, thrombocytopenia, malaise, and leukopenia seem to be significantly lower in AIDS patients than in non-AIDS patients, but some values in Table 1 probably underestimate the true frequencies in AIDS patients, since not all features were described in every patient.

The methods for laboratory diagnosis of these patients have some pitfalls, but they also have some peculiar advantages. Wheat et al[9] place great value on *Histoplasma* complement-fixation titers, a view not shared by some other authors.[2,14] Suffice it to say that serologic testing may give negative results despite fungal dissemination. Likewise, chest radiograph results at admission may be normal despite dissemination of the fungus,[14] as illustrated by the second case.

Histoplasma capsulatum can be identified on GMS stain of a variety of tissues, including bone marrow, lymph node, skin lesion biopsy, liver biopsy, and transbronchial lung biopsy specimens.[14,17] Liver biopsy may prove particularly fruitful in those patients with elevations of serum liver enzymes.[2] The fungus can be cultured from all these tissues, plus sputum, blood, and feces, although it may take many weeks to grow in some cases. In non-AIDS patients with moderate to severe disseminated histoplasmosis of the adult type, urine culture often yields the organism even in the face of a normal urinalysis.[15] Fortunately for the first patient, physicians received the initial clue to the diagnosis very early in the hospital course. An alert technician recognized the organism on routine Wright's stain of the admission peripheral blood smear, allowing the start of presumptive therapy weeks before culture results were reported. Other authors have also reported this finding.[9,17] A GMS stain of the buffy coat may give increased yield for the detection of *Histoplasma*.[15]

Before the availability of HIV antibody assays, physicians had some difficulty in diagnosing HIV infection concurrently with disseminated histoplasmosis, since the latter itself can cause immunologic alterations similar to those found in HIV infection. In particular, disseminated histoplasmosis, among other infections, can reverse the normal helper-suppressor T cell ratio.[1] The ELISA for HIV antibody and western blot assay for viral antigen-specific antibody have eliminated this problem.

Disseminated histoplasmosis had occurred almost exclusively in infants, the elderly, patients with hematologic malignancy, and immunosuppressed patients. Compared with these patient populations, AIDS patients who contract disseminated histoplasmosis suffer greater mortality and morbidity, often developing hypotension, coagulopathy, hypoxia, renal failure, encephalopathy, and hepatic insufficiency.[1]

Amphotericin B is still the drug of choice for this opportunistic fungal infection with AIDS. The patient should defervesce and improve clinically within the first several days of therapy. Despite apparently complete clinical response, however, amphotericin B does not eradicate histoplasmosis in the AIDS patient,[1,9,17] even at a total dose of 2.0 to 2.5 g. This patient will commonly relapse with disseminated histoplasmosis some time after cessation of therapy. In contradistinction, non-AIDS patients rarely relapse after completing a course of amphotericin B.[15] Thus, the coexistence of HIV infection requires continued suppressive antifungal therapy.

Ketoconazole, while generally ineffective as primary treatment, has been found effective in preventing relapses after amphotericin B therapy in patients with AIDS.[17] Present experience indicates the AIDS patient must continue ketoconazole therapy indefinitely.

Researchers are currently investigating two new antifungal agents, fluconazole and intraconazole. These drugs may be available from the Food and Drug Administration under compassionate use for those patients unable to tolerate amphotericin B, typically because of renal toxicity.

CONCLUSIONS

Healed primary lesions of untreated histoplasmosis may still contain many viable organisms,[15] which can launch new episodes of infection as HIV erodes the host's immune defenses. Since disseminated histoplasmosis incurs high morbidity and mortality in AIDS patients, it would be valuable to be able to identify a subset of AIDS patients who are at risk for active fungal infection and to treat before the stage of life-threatening dissemination.

This approach raises several questions. Does disseminated histoplasmosis occur in AIDS patients by reactivation, primary infection, or both? If by reactivation, which tests detect dormant *Histoplasma* infection with high sensitivity in AIDS patients? Present tests of *Histoplasma* exposure rely on immune response, but HIV cripples the immune system. Would concomitant infection with HIV cause a large fraction of false-negative results?

If testing could identify the subset of patients at risk, could some intervention prevent recrudescent histoplasmosis or reinfection, or at least prevent disseminated histo-

TABLE 2. STATES WITH THE HIGHEST COMBINED RISK OF AIDS AND HISTOPLASMOSIS

State	Incidence of AIDS Per Million*	Percent Positive for Histoplasmosis†	Number Per Million at Combined Risk
District of Columbia	1427	21.2	302.5
Texas	176	32.4	57.0
Maryland	174	22.6	39.3
Louisiana	134	27.1	36.3
Puerto Rico	123	?	?
Missouri	66	53.4	35.2
Illinois	103	29.1	30.0
Arizona	89	28.7	25.5
California	372	5.7	21.2
Oklahoma	51	39.1	19.9
Indiana	38	49.4	18.7
Arkansas	32	57.8	18.5
Tennessee	28	65.1	18.2
New York	693	2.6	18.0
Kentucky	26	69.3	18.0
Virginia	88	19.3	17.0
Delaware	93	16.0	14.9

* *From MMWR*[18]
† *From Edwards et al*[19]

plasmosis? Perhaps oral antifungal therapy might be efficacious here.

Does disseminated histoplasmosis affect a significant portion of the AIDS population? Geographic location certainly influences the answer to this question. As the prevalence of HIV infection increases in the central United States, family physicians may expect an increasing number of AIDS cases presenting with disseminated histoplasmosis. This alert applies particularly to states having a relatively high prevalence of both AIDS and histoplasmosis: the District of Columbia, Texas, Maryland, Louisiana, Missouri, Illinois, Arizona, and probably Puerto Rico (Table 2).

Each of these questions will require further investigation before primary care physicians can determine the best strategy for preventing opportunistic histoplasmosis in patients with AIDS.

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