A 77-Year-Old Farmer With Respiratory Failure and Thrombocytopenia*

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A 77-year-old farmer presented with a 3-month history of progressive dyspnea. His symptoms started with anorexia, malaise, fever, and dry cough. He was initially treated with azithromycin and a short course of oral corticosteroids for COPD exacerbation. Two days after finishing the treatment, his symptoms progressed, and he was admitted to a local hospital with respiratory distress, altered mental status, hypotension, and abnormal chest radiograph findings. Bronchoscopy showed normal airways, and the BAL fluid sample revealed lymphocytosis with negative culture results. The patient was treated with doxycycline, ceftriaxone, and corticosteroids for presumed hypersensitivity pneumonitis and showed some improvement. He was subsequently discharged from the hospital while receiving therapy with prednisone, 20 mg. Five days later, he was readmitted to the hospital with worsening malaise, fever, altered mental status, and severe respiratory distress that required mechanical ventilation. He was then transferred to our facility for further management.

His medical history was significant for hypertension and diabetes. He was a lifelong nonsmoker and had worked his whole life as a farmer. He denied the use of alcohol or illegal drugs. The patient lived in Ohio, and no recent travels or contacts with sick persons were reported by the family.

Physical Examination

The patient arrived intubated and receiving mechanical ventilation. His temperature was 97.4°F, BP was 90/68 mm Hg, heart rate was 120 beats/min, respiratory rate was 22 breaths/min, and oxygen saturation was 98% with a fraction of inspired oxygen of 80%. The findings of examinations of the head, eyes, nose, and throat were unremarkable. His neck was supple with no lymphadenopathy. A chest examination revealed bilateral ronchi. The findings of a cardiovascular examination were significant only for tachycardia. His abdomen was soft, nontender, and there was no hepatosplenomegaly. There were no skin lesions or lower-extremity edema.

Laboratory Data

The WBC count was 10,300 cells/μL, with 82% neutrophils, 16% bands, and 1% lymphocytes. The hemoglobin concentration was 8.2 g/dL, and the platelet count was 36,000 cells/μL with rare schistocytes in the peripheral smear and 3.5% reticulocytes. Prothrombin time was 16.3 s, and partial thromboplastin time was 38 s. Electrolytes were normal; creatinine, 2.01 mg/dL; BUN, 58 mg/dL; aspartate aminotransferase, 66 U/L; alanine aminotransferase, 271 U/L; serum lactate dehydrogenase (LDH), 2,769 U/L; lactate, 5.1 mmol/L; total bilirubin, 1 mg/dL; and indirect bilirubin, 0.5 mg/dL. Arterial blood gas analysis performed with an 80% fraction of inspired oxygen revealed the following: pH, 7.089; PaCO₂, 66 mm Hg; PaO₂, 208 mm Hg; HCO₃⁻ concentration, 18 mmol/L; and oxygen saturation, 98%. A chest radiograph (Fig 1) showed bilateral airspace disease to be most dense in the right mid-lung zone.

Hospital Course

A bronchoscopy performed on hospital admission showed diffuse adherent plaques in the bronchi, and samples were send for bacterial, fungal, and viral cultures. The BAL fluid sample showed heavy purulence and blood with 8% alveolar macrophages, 85% neutrophils, and 7% eosinophils. The HIV test was negative. The BAL fluid smear is shown in Figure 2.
What is the diagnosis?

**Figure 1.** A radiograph obtained on hospital admission shows bilateral alveolar lung disease, predominantly involving the right middle zone.

**Figure 2.** A BAL smear (Wright-Giemsa, original ×100) showing alveolar macrophages with numerous intracellular yeast-like organisms 2 to 4 μm in diameter with eccentric chromatin. Notice the pseudocapsule surrounding each organism. A prominent number of erythrocytes are present in the specimen, suggesting diffuse alveolar damage. Image courtesy of Dr. William Becker (Department of Pathology; The Ohio State University; Columbus, OH).
Diagnosis: Disseminated histoplasmosis with severe sepsis

The BAL fluid specimen showed small intracellular yeasts, and the BAL fluid culture was positive for *Histoplasma capsulatum*. The peripheral smear also showed intracellular yeasts, and blood cultures were positive for *H. capsulatum*.

**Discussion**

Disseminated histoplasmosis was first described by Darling during the construction of the Panama Canal in 1905. The disseminated form of the disease usually occurs after a large inoculum of *H. capsulatum* reaches the alveoli. Hematogenous dissemination to other tissues occurs during the first 2 weeks, but progression of the disease is more likely to occur in immunosuppressed individuals, small children, and the elderly. Reactivation of a latent Histoplasma infection years after the first exposure has also been reported.

Our patient lived in the Ohio River basin where *H. capsulatum* is endemic. The endemic distribution of the disease in the Ohio and Mississippi River valleys is thought to be caused by moderate climate, humidity, soil characteristics, and the presence of the bird and bat excrement, which is favorable for the growth of the organism.

In 90% of the patients, the acute infection is unrecognized; many patients are asymptomatic, and others have mild symptoms that resolve before they seek medical attention. It is estimated that 1 of 2,000 patients will develop progressive disseminated histoplasmosis, as noted after the two Indianapolis epidemics. In this epidemic, the two major risk factors for progressive dissemination were immunosuppression and age > 54 years. Our patient received corticosteroids initially for “COPD exacerbation” and then for hypersensitivity pneumonitis. It is likely that this led to a further impairment of cellular immunity and to dissemination of the infection.

ARDS, vascular collapse, coagulopathy, thrombocytopenia, and elevated concentrations of LDH and liver enzymes are part of the sepsis syndrome caused by disseminated histoplasmosis. In AIDS patients, the presence of thrombocytopenia and elevated LDH concentration has been associated with dissemination. In one retrospective study, LDH levels of > 600 UI/L favored the diagnosis of disseminated histoplasmosis over *Pneumocystis carinii* pneumonia. Ferritin levels of > 10,000 IU/L were also strongly suggestive of histoplasmosis. The elevated LDH and ferritin levels in patients with disseminated histoplasmosis are likely secondary to reactive hemophagocytosis, as has been observed by some investigators. CNS involvement occurred in up to 20% of the cases, and the adrenal glands were affected in 80% of the patients, with overt Addison disease in < 10% of patients. No similar studies have been done in non-AIDS patients.

The isolation of the organism from body fluids or tissues is required to establish the diagnosis. In patients with the disseminated form of the disease, bone marrow biopsy and culture offer the highest yield (50 to 75%) followed by blood cultures (50 to 70%). Urinary antigen testing, although it cannot ascertain the diagnosis of disseminated histoplasmosis, is useful for monitoring treatment response, as the concentrations will decrease with therapy and increase with lack of response to treatment and recurrence of the disease.

Treatment for acute disseminated histoplasmosis should be instituted as soon as the disease is suspected. Therapy with amphotericin B, 0.7 to 1.0 mg/kg/d, is recommended in severely ill patients. Experience with the lipid formulations is limited, but it seems that they are effective at a dosage of 3 to 5 mg/kg/d. A response rate of 62 to 92% in non-AIDS patients has been reported for treatment amphotericin. Therapy with itraconazole can be substituted at a dosage of 400 mg/d once the patient is stable, no longer requiring hemodynamic or respiratory support, and should be continued for 6 months. Amphotericin can also be used for treatment during the full course of the disease, with a total dose of 35 mg/kg for 2 to 4 months. Some experts recommend continuing treatment until testing for the urinary antigen becomes negative. In patients with AIDS, treatment with itraconazole, 200 mg/d, should be continued for life.

**Follow-up**

The respiratory symptoms reported by our patient 3 months before hospital admission were likely acute pulmonary histoplasmosis, which was complicated by corticosteroid therapy. The finding of small intracellular yeasts and the BAL fluid cultures that were positive for *H. capsulatum* confirmed the diagnosis. The BAL fluid in fungal disease typically shows lymphocyte predominance, which was observed in the findings from our patient’s first bronchoscopy. However, fluid from the subsequent BAL was neutrophil predominant, which, we suspect, was from the diffuse alveolar damage. The patient received treatment with a lipid formulation of amphotericin. After 1 week, he no longer required ventilatory and hemodynamic support. After receiving amphotericin therapy for 4 weeks, his treatment was switched to itraconazole for 6 months. His renal function did not improve, and he still requires regular hemodialysis.
Clinical Pearls

1. Disseminated histoplasmosis should be considered in patients presenting with sepsis who live in endemic areas such as the Ohio and Mississippi river valleys, and in travelers from Central and South America.

2. Besides AIDS patients, immunosuppressed persons, the elderly, and children < 2 years of age are at risk for disseminated histoplasmosis.

3. Histoplasmosis may present subacutely and may be preceded by respiratory symptoms. Dissemination is suggested by hypotension, fever, respiratory and renal failure, coagulopathy, thrombocytopenia, and elevated LDH and ferritin levels.

4. Meningitis and adrenal insufficiency can also occur in patients with disseminated histoplasmosis.

5. Bone marrow and blood cultures have the highest sensitivity in diagnosing disseminated histoplasmosis.

6. The treatment of choice is amphotericin. Itraconazole may be substituted once the patient is stable. In immunocompetent patients, the treatment should continue for 6 months or until the urinary antigen level is negative.

Suggested Readings


Corcoran GR, Al-Abdely H, Flanders CD, et al. Markedly elevated serum lactate dehydrogenase levels are a clue to the diagnosis of disseminated histoplasmosis in patients with AIDS. Clin Infect Dis 1997; 24:942–944


Kumar N, Jain S, Singh NH. Disseminated histoplasmosis with reactive hemophagocytosis: aspiration cytology findings in two cases. Diagn Cytopathol 2000; 23:422–424

