Key Points:

1) Histoplasmosis is typically asymptomatic or self-limiting, but may develop into acute pulmonary infections or severe and progressive disseminated disease in individuals with T-cell deficiencies.

2) Transmission occurs when fungal spores are inhaled into the lungs from disturbed soil in endemic regions, change into the yeast form, and grow within macrophages. The macrophages can disseminate the infection through lymphatics and blood.

3) Immunocompetent individuals have T cells that can activate macrophages to kill the organism with IL-12 and IFN-gamma before disease progression.

4) Failure to activate macrophages, such as in the case of T cell deficiency in patients with AIDS, can lead to severe infection and disseminated histoplasmosis.

5) Histoplasmosis can also occur outside of endemic regions as a reactivation of a latent infection acquired from previous travel or residence.

6) Progressive disseminated histoplasmosis is characterized by fever, night sweats, and weight loss. Physical exam is notable for hepatosplenomegaly and adenopathy. Laboratory data is notable for pancytopenia and elevated lactate dehydrogenase.

Histoplasmosis is the most prevalent endemic mycosis in the United States (2). Most infections are asymptomatic or self-limiting, but some individuals—particularly those with T-cell deficiencies—may develop acute pulmonary infections or severe and progressive disseminated infection (1, 2). Histoplasmosis is the AIDS-defining illness in up to 50 percent of affected patients (1).

EPIDEMIOLOGY

Found in temperate areas, histoplasma is endemic to the Mississippi, Ohio, and St. Lawrence River valleys, the Caribbean, southern Mexico, and parts of Central and South America, Africa, and Asia (1). High concentrations of histoplasma spores can be found in soil contaminated with bird or bat droppings, which can then be transmitted via inhalation (1).

Risk factors for disseminated histoplasmosis include AIDS, other immunodeficiency or immunosuppressive disorders, medications such as TNF-alpha inhibitors for arthritis or immunosuppressive drugs for transplant patients, and extremes of age (2, 4).

Histoplasmosis is the most common endemic mycosis in AIDS patients (1). Progressive disseminated disease usually occurs shortly after initial infection. Disseminated infection can occur in patients who live outside of endemic areas, but these instances are likely caused by reactivation of a latent infection that was previously acquired through travel or residence in the endemic areas (1).

CLINICAL MANIFESTATIONS

Histoplasmosis can present as a mild self-limiting pulmonary illness in immunocompetent individuals. The clinical manifestations of disseminated histoplasmosis vary based on host
immunodeficiency and degree of exposure to the fungus (2). In progressive disseminated histoplasmosis, common symptoms include fever, night sweats, fatigue, weight loss, nausea, vomiting, and dyspnea (1).

**Physical exam:** Physical exams may be notable for hepatosplenomegaly and adenopathy. Approximately 40 to 50 percent of AIDS patients with disseminated histoplasmosis have pulmonary involvement; isolated pulmonary involvement without dissemination occurs in less than 5 percent of cases (1). In severe infection, a sepsis-like syndrome manifested by shock, respiratory distress, and multi-organ failure or meningitis may be seen (1, 2). Mortality in these instances may be as high as 50 percent despite therapy (1, 2).

**Laboratory results:** Laboratory results may be notable for pancytopenia due to bone marrow involvement with histoplasmosis (Figure 1). Elevated levels of aminotransferases, lactate dehydrogenase, and ferritin are common (1). Elevated creatinine level is a poor prognostic factor (1).

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**Imaging studies:** Diffuse interstitial infiltrates, which may be misdiagnosed as pneumocytosis or tuberculosis, are common radiographic findings (Figure 2). Focal infiltrates are rare. Imaging studies may also reveal pleural effusions, mediastinal adenopathy, cavitary disease, and calcified granulomas (1). Progression to an acute respiratory distress syndrome-like disease may occur (1).

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Figure 1. Bone marrow biopsy in disseminated histoplasmosis (2)

![Bone marrow biopsy](image1)

Figure 2. Histoplasmosis in HIV patient (1)

![Histoplasmosis in HIV patient](image2)
**PATHOPHYSIOLOGY**

Figure 3. Biology of Histoplasmosis (5)

*Histoplasma capsulatum* is a thermally dimorphic fungus, existing as a mold in the environment and as yeast when inhaled into the lungs at a body temperature of 37°C (1, 2). Macrophages are initially able to ingest, but not kill the fungi (Figure 3). Before specific immunity has developed, macrophages can spread the infection to adjacent lymph nodes and the reticuloendothelial system through blood and lymphatics, disseminating the infection in a manner similar to tuberculosis (2, 4).

Macrophages become engorged with yeasts, supporting the intracellular proliferation of *H. capsulatum* (Figure 4). Cellular immunity typically occurs 10 to 14 days after exposure, when T cells activate macrophages to develop fungicidal cytokines such as IL-12 and IFN-gamma (2, 4). Thus, T cells play a predominant role in the recovery from histoplasmosis because they activate macrophages to kill Histoplasma and halt disease progression (2). Immunocompetent individuals have the defense mechanisms to self-limit acute histoplasmosis (1, 2).

Failure to activate macrophages in immunocompromised individuals, such as those with AIDS, may lead to the development of severe infection and progressive disseminated histoplasmosis (2). Reactivation of latent histoplasmosis can also occur in immunocompromised patients who left the endemic area years before, which can also develop into disseminated histoplasmosis (1, 2).
RELEVANCE TO CASE

Jim Cornell is a 45 year old man with a history of an untreated HIV infection who presented to the ED with “flu-like” symptoms of fever, night sweats, a productive cough with greenish yellowish sputum, and 20 pound weight loss over the past two months. He’s febrile at 101°F and cachectic. His blood pressure is at the lower end of normal at 105/62, pulse at the higher end of normal at 100, and respiratory rate at 16. His oxygen saturation at room air is at the lower end of normal at 96%, but he is not in acute distress. His physical exam is notable for pale sclerae, oral thrush, bilateral crackles at bases of the lungs, and hepatosplenomegaly. His laboratory results are remarkable for pancytopenia, elevated BUN to creatinine suggesting dehydration, elevated aminotransferases and LDH. His chest x-ray shows bilateral lower lobe infiltrates and calcified mediastinal nodes. His social history is notable for residence in Bloomington, Indiana 8 years before San Diego.

Given the laboratory results (pancytopenia, elevated aminotransferases and LDH), chest x-ray (bilateral lower lobe infiltrates with calcified granulomas), social history (HIV infection, previous residence in Bloomington, Indiana), and clinical presentations (fever, fatigue, night sweats, weight loss, pulmonary involvement), Mr. Cornell likely suffered from a reactivation of a latent infection of *Histoplasma capsulatum* that he acquired from his previous residence, which then developed into progressive disseminated histoplasmosis. It would be helpful to confirm the diagnosis through
PBL Case: Really Bad Flu

microscopy and culture of the blood or respiratory samples to visualize budding yeast cells. Fortunately, he has not yet developed sepsis or multi-organ failure, which has a high mortality rate. It would be critical to treat him with the appropriate antifungal therapy to prevent progression of the disease.

References

1. Baddley, J W, MD; Epidemiology and clinical manifestations of histoplasmosis in HIV-infected patients ©2014. UpToDate.
2. Wheat, J, MD, Kauffman, C A, MD; Pathogenesis and clinical manifestations of disseminated histoplasmosis ©2014. UpToDate.