

CASE REPORT

## Acute disseminated histoplasmosis in an immunocompetent patient\*

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Histoplasmosis is a fungal disease caused by inhalation of *Histoplasma capsulatum* fungus. The disease does not normally affect immunocompetent individuals after a single, transient inhalation exposure. However, longer exposure may cause chronic or disseminated acute pulmonary infection. In immunocompromised patients, the infection is disseminated and severe. We report the case of a 13-year-old immunocompetent patient, presenting with fever, cough and dyspnea for one month. The chest X-ray and computed tomography scan revealed interstitial infiltrate and diffuse micronodules. The patient reported having had close and prolonged contact with birds. He was submitted to an open lung biopsy and the tissue culture was positive for *Histoplasma capsulatum* sp. He was treated with amphotericin B for 28 days, followed by treatment with itraconazole for 6 months, and there was complete resolution of the disease.

**Key words:** Histoplasmosis. Immunocompetence. Birds.

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## INTRODUCTION

Acute disseminated histoplasmosis is a systemic granulomatous disease caused by *Histoplasma capsulatum* and can be misdiagnosed as severe community-acquired pneumonia. This disease is uncommon in immunocompetent individuals and, in most of those patients, evolution is satisfactory. The disease may be self-limited or subclinical. In some cases, depending on length of exposure, delay in diagnosis, and host response, the evolution may be unfavorable<sup>(1)</sup>. We report the case of an immunocompetent patient who presented with the severe form of the disease, probably as a result of prolonged exposure and delayed diagnosis.

## CASE REPORT

A 13-year-old schoolboy presenting with dry cough, daily fever, and progressive dyspnea for one month was admitted to the respiratory intensive care unit. He was treated with antibiotics, but there was no improvement. At admission, the general state of the patient was impaired; he was pale (++/4+), and presented tachypnea (respiratory frequency: 32 breaths/min), tachycardia (heart rate: 130 beats/min), and arterial blood pressure of 120/80 mmHg. He reported frequent exposure to birds in the home (bird breeding) and denied having had contact with tuberculosis patients. Upon auscultation, coarse crackles were heard in the lower two-thirds of both lungs. Abdominal palpation identified splenomegaly and the spleen was palpable to within approximately 10 cm of the left costal margin. Cervical and inguinal lymphadenopathy was present as well. Initial tests revealed anemia (hemoglobin: 7.8 g/dL; hematocrit: 23.3%), leukopenia (2920/mm<sup>3</sup>), thrombocytopenia (135,000/mm<sup>3</sup>) and hypoxemia (arterial oxygen tension: 53 mmHg and arterial oxygen saturation by pulse oximetry: 90% – on 50% oxygen by Venturi mask).

Chest radiography revealed interstitial infiltrate in the lung bases and mediastinal widening that later evolved to diffuse alveolar infiltrate (Figure 1). High-resolution computed tomography scans of the chest (using a window for the mediastinum) revealed diffuse micronodules and mediastinal lymphadenopathy (Figure 2).

Throughout the study, blood and urine cultures, as well as testing for acid-fast bacilli (sputum smear), FR, FAN, anti-extractable nuclear antigen (anti-ENA) antibodies, C3, C4 and anti-HIV were negative. Immunoglobulin test results were normal. Bronchoscopy with transbronchial biopsy revealed macrophages and lymphocytes (but no specific granulomas), inflammatory process, and mucous goblet cell hyperplasia of the respiratory epithelium. Lumbar puncture revealed normal cellularity, and fungi and acid-fast bacilli tests were negative. Microscopic examination of the cerebrospinal fluid tested negative for bacteria. Myelography revealed myeloid and erythroid hyperplasia (1,3:1) and megakaryocytic hypoplasia, with bone marrow response to the infectious process.

The dyspnea became more severe, and the patient was submitted to 100% fraction of inspired oxygen (non-rebreathing mask) and then underwent open-lung biopsy. Histopathological examination revealed fungi consistent with histoplasma, and *Histoplasma capsulatum* sp was isolated through tissue culture (Figure 3).

The patient was initially treated with amphotericin B (total dosage: 2 g) during hospitalization, followed by itraconazole (200 mg per day) for six months as an outpatient. Evolution was satisfactory (radiological resolution) and the patient was asymptomatic.

## DISCUSSION

Pulmonary histoplasmosis is a fungal disease caused by *Histoplasma capsulatum*, and two varieties are known to be human pathogens, namely: *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii*. The disease is endemic in certain regions of Latin America and North America, and there have been cases reported in Europe and Asia. This pattern of distribution may be related to climate, humidity level, and soil characteristics<sup>(1)</sup>. The capsulatum variety is common in soil containing bat or bird feces.

The fungus, in its dimorphic form, was first isolated in 1905, and its pathogenesis was described in lab animals<sup>(2,13)</sup>. In 1932, the first case diagnosed in humans was that of a six-year-old child who died of acute disseminated histoplasmosis<sup>(3,13)</sup>. Immunodeficient individuals are most at risk for developing the disease<sup>(5)</sup>. The disease can be classified as acute, chronic or disseminated, according to clinical evolution<sup>(6)</sup>.

Patients suffering from acute pulmonary infection may either be asymptomatic or present with symptoms similar to the flu, such as fever, shivering, dry cough, pleural or substernal chest pain, malaise, myalgia and arthralgia, as well as erythema (multiforme or nodosum)<sup>(7)</sup>. Incubation time and severity of the disease varying depending on the degree of exposure and the immune status of the host<sup>(1)</sup>. In immunocompetent individuals suffering prolonged exposition or delayed diagnosis, both of which may have occurred in the present case, evolution may be unfavorable. Late complications may result from intense immune response of the host, characterized by fibrosis and enlargement of hilar or mediastinal lymph nodes, leading to compression of adjacent structures as well as to secondary complications. Chest X-rays may be normal or may reveal diffuse infiltrates, hilar and mediastinal lymph node enlargement, or diffuse granular opacities<sup>(6)</sup>.

Chronic pulmonary infection may resemble pulmonary tuberculosis. This, together with the difficulty involved in performing mycological tests, may explain the fact that there have been few confirmed cases in Brazil<sup>(8)</sup>. Pathogenesis and evolution are rather complex. Histopathological analyses reveal two basic lesions: interstitial pneumonitis (early lesion) and lesion tissue organization with a majority of giant cells and progressive cavitation (chronic). Symptoms and radiological findings indicate which of the two types (or stages) of the disease is present. Systemic symptoms are more severe during the pneumonitis phase, whereas hemoptysis and progressive dyspnea appear during the cavitation phase, which may progress to respiratory insufficiency<sup>(6)</sup>.

Disseminated histoplasmosis is a less common manifestation of the disease and mainly infects immunodeficient (transplanted or AIDS) patients, as well as the very young or very old<sup>(1)</sup>. The severity of symptoms and histopathology reflect the degree of patient immunocompetence. The most common

signs and symptoms are fever, shivering, indisposition, weight loss, hepatomegaly, splenomegaly, peripheral lymphadenopathy; ulceration of oropharyngeal mucosa (in 25% to 75% of cases); bone marrow alterations (anemia, leukopenia, thrombocytopenia), and electrolyte abnormalities. Some cases of alterations to the heart (endocarditis) and gastrointestinal system (bleeding due to mucosal ulceration), as well as to the central nervous system (chronic lymphocytic meningitis), have been reported<sup>(1,6)</sup>. Chest X-rays may reveal changes due to previous primary infection or to interstitial pneumonitis with hematogenous dissemination.

A diagnosis of pulmonary disease caused by fungi is confirmed through analysis of sputum cultures, tracheal aspirate, bronchoalveolar lavage fluid or biopsy samples<sup>(9)</sup>. Diagnosis can also be made through culture or histopathological analysis of other affected organs, fluids and tissues (blood, bone marrow, liver, lymph nodes, skin or mucosa) using special (Grocott) staining techniques<sup>(5)</sup>, serology, complement fixation or immunodiffusion<sup>(6)</sup>. Open-lung biopsy is a very important diagnostic tool when other less invasive methods do not facilitate diagnosis. Mortality of non-treated, severe cases is 80%, which can be reduced to less than 25% with antifungal therapy<sup>(10,11)</sup>. Many patients diagnosed with acute histoplasmosis do not require specific treatment and will recover spontaneously. However, treatment is recommended for all cases of progressive disseminated histoplasmosis<sup>(11,13)</sup>. Among severe cases, the mortality rate is 50%, even when amphotericin B therapy is administered. However, 98% of mild cases respond to the same treatment<sup>(12)</sup>.

A 6- to 12-month course of antifungal drugs (amphotericin B, itraconazole or ketoconazole) is recommended<sup>(1)</sup>. We present this case because the pathological presentation is rare in immunocompetent individuals, and because we feel it is important to investigate this diagnosis in hard-to-treat cases community-acquired pneumonia.

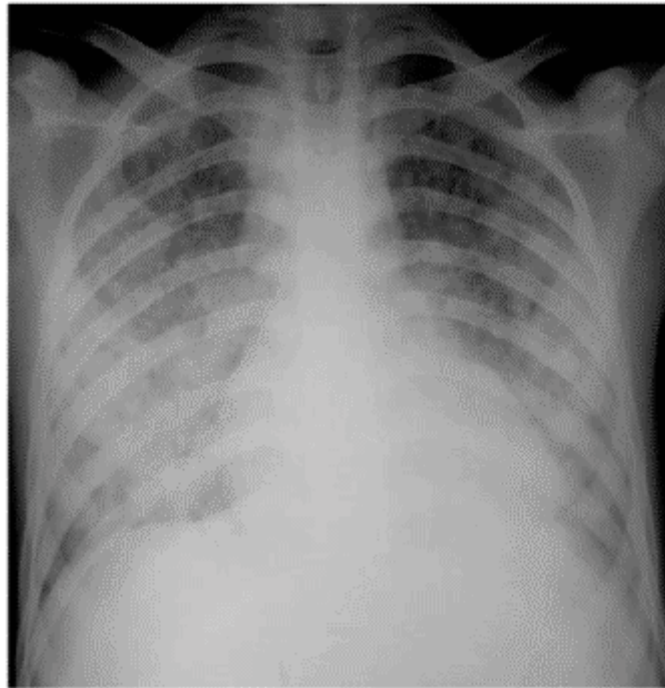


Figure 1. Anterior-posterior chest X-ray revealing interstitial evolution to bilateral opacity and air bronchogram. Mediastinal widening can be seen.

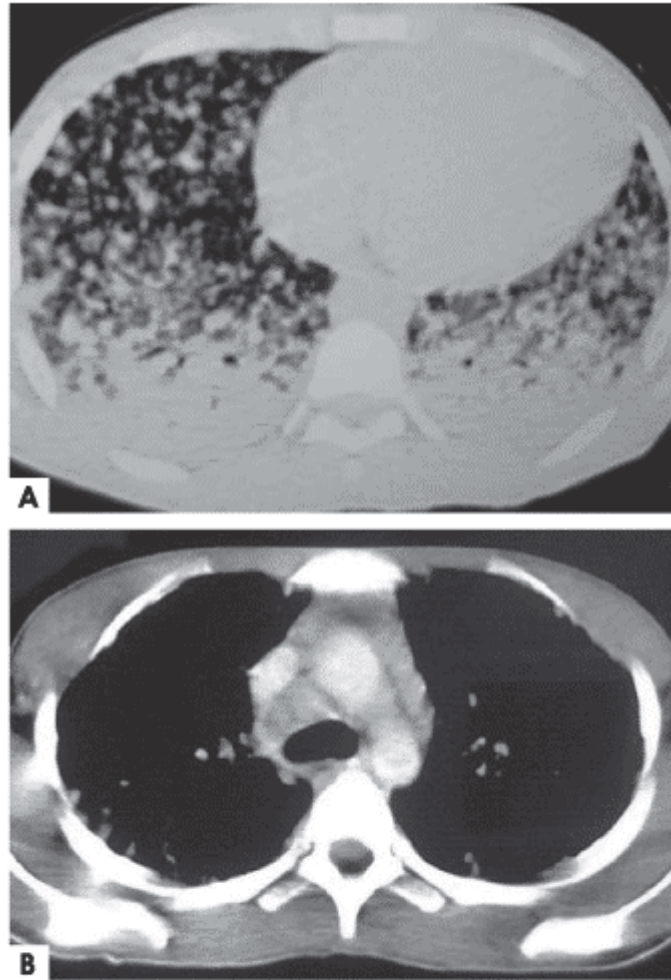


Figure 2. a) Chest computed tomography scan revealing diffuse micronodules and posterior consolidation in the lung bases; b) Enlarged paratracheal lymph nodes in the aortopulmonary window.

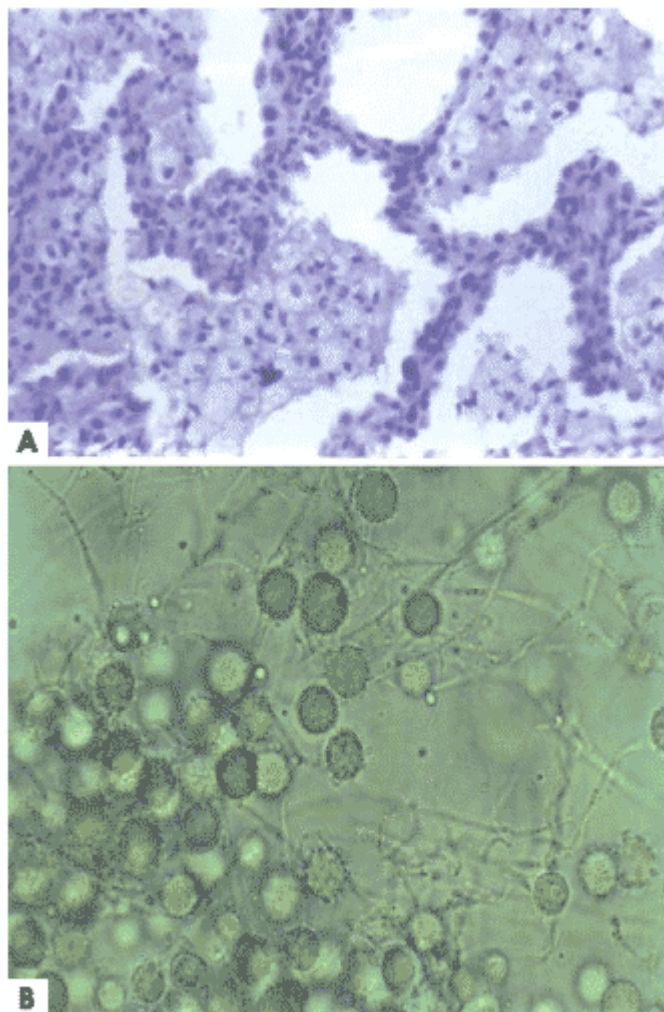


Figure 3. a) Histology: Histoplasma yeast-laden macrophages within the alveoli (hematoxylin-eosin; x400); b) Microbiology (culture): micromorphology of *Histoplasma capsulatum* with numerous nipple-shaped macroconidia.

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