

## THE CLINICAL PICTURE

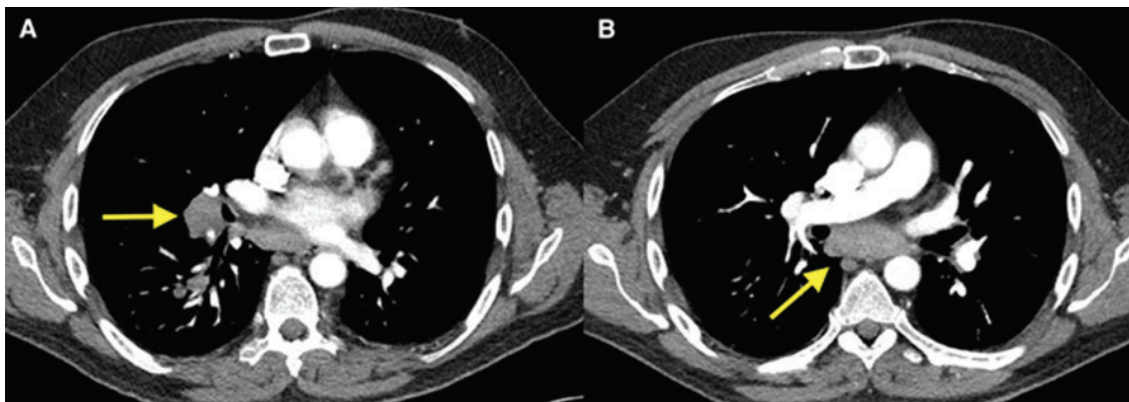
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# Mediastinal granuloma due to histoplasmosis in a patient on infliximab



**Figure 1.** (A) An enlarged lymph node (2.4 cm × 2.0 cm) at the bifurcation of the bronchus intermedius. (B) An enlarged inferior mediastinal lymph node (2.0 cm × 5.4 cm).

**Fewer than 5% of people exposed develop symptomatic disease**

**A** 50-YEAR-OLD MAN with Crohn disease and psoriatic arthritis treated with infliximab and methotrexate presented to a tertiary care hospital with fever, cough, and chest discomfort. The symptoms had first appeared 2 weeks earlier, and he had gone to an urgent care center, where he was prescribed a 5-day course of azithromycin and a corticosteroid, but this had not relieved his symptoms.

He reported no recent travel, exposure to animals, or sick contacts. His temperature was 38.3°C (100.9°F). Results of the physical examination and initial laboratory testing were unremarkable. Chest computed tomography revealed prominent right hilar and mediastinal lymphadenopathy (**Figure 1**).

Bronchoscopy revealed edematous mucosa throughout, with minimal secretion. Specimens for bacterial, acid-fast bacillus, and fungal cultures were obtained from bronchoal-

veolar lavage. Endobronchial lymph node biopsy with ultrasonographic guidance revealed nonnecrotizing granuloma.

Bronchoalveolar lavage cultures showed no growth, but the patient's serum histoplasma antigen was positive at 5.99 ng/dL (reference range: none detected), leading to the diagnosis of mediastinal granuloma due to histoplasmosis with possible dissemination. His immunosuppressant drugs were stopped, and oral itraconazole was started.

At a follow-up visit 2 months later, his serum antigen level had decreased to 0.68 ng/dL, and he had no symptoms whatsoever. At a visit 1 month after that, infliximab and methotrexate were restarted because of an exacerbation of Crohn disease. His oral itraconazole treatment was to be continued for at least 12 months, given the high suspicion for disseminated histoplasmosis while on immunosuppressant therapy.

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### ■ DIFFERENTIAL DIAGNOSIS OF GRANULOMATOUS LUNG DISEASE AND LYMPHADENOPATHY

The differential diagnosis of granulomatous lung disease and lymphadenopathy is broad and includes noninfectious and infectious conditions.<sup>1</sup>

Noninfectious causes include lymphoma, sarcoidosis, inflammatory bowel disease, hypersensitivity pneumonia, side effects of drugs (eg, methotrexate, etanercept), rheumatoid nodules, vasculitis (eg, Churg-Strauss syndrome, granulomatosis with polyangiitis, primary amyloidosis, pneumoconiosis (eg, beryllium, cobalt), and Castleman disease.

There is concern that tumor necrosis factor antagonists may increase the risk of lymphoma, but a 2017 study found no evidence of this.<sup>2</sup>

Infectious conditions associated with granulomatous lung disease include tuberculosis, nontuberculous mycobacterial infection, fungal infection (eg, *Cryptococcus*, *Coccidioides*, *Histoplasma*, *Blastomyces*), brucellosis, tularemia (respiratory type B), parasitic infection (eg, *Toxocara*, *Leishmania*, *Echinococcus*, *Schistosoma*), and Whipple disease.

### ■ HISTOPLASMOSIS

Histoplasmosis, caused by infection with *Histoplasma capsulatum*, is the most prevalent endemic mycotic disease in the United States.<sup>3</sup> The fungus is commonly found in the Ohio and Mississippi River valleys in the United States, and also in Central and South America and Asia.

Risk factors for histoplasmosis include living in or traveling to an endemic area, exposure to aerosolized soil that contains spores, and exposure to bats or birds and their droppings.<sup>4</sup>

Fewer than 5% of exposed individuals develop symptoms, which include fever, chills, headache, myalgia, anorexia, cough, and chest pain.<sup>5</sup> Patients may experience symptoms shortly after exposure or may remain free of symptoms for years, with intermittent relapses of symptoms.<sup>6</sup> Hilar or mediastinal lymphadenopathy is common in acute pulmonary histoplasmosis.<sup>7</sup>

The risk of disseminated histoplasmosis is greater in patients with reduced cell-mediated immunity, such as in human immunodeficiency

virus infection, acquired immunodeficiency syndrome, solid-organ or bone marrow transplant, hematologic malignancies, immunosuppression (corticosteroids, disease-modifying antirheumatic drugs, and tumor necrosis factor antagonists), and congenital T-cell deficiencies.<sup>8</sup>

In a retrospective study, infliximab was the tumor necrosis factor antagonist most commonly associated with histoplasmosis.<sup>9</sup> In a study of patients with rheumatoid arthritis, the disease-modifying drug most commonly associated was methotrexate.<sup>10</sup>

### ■ GOLD STANDARD FOR DIAGNOSIS

Isolation of *H capsulatum* from clinical specimens remains the gold standard for confirmation of histoplasmosis. The sensitivity of culture to detect *H capsulatum* depends on the clinical manifestations: it is 74% in patients with disseminated histoplasmosis, but only 42% in patients with acute pulmonary histoplasmosis.<sup>11</sup> The serum histoplasma antigen test has a sensitivity of 91.8% in disseminated histoplasmosis, 87.5% in chronic pulmonary histoplasmosis, and 83% in acute pulmonary histoplasmosis.<sup>12</sup>

Urine testing for histoplasma antigen has generally proven to be slightly more sensitive than serum testing in all manifestations of histoplasmosis.<sup>13</sup> Combining urine and serum testing increases the likelihood of antigen detection.

### ■ TREATMENT

Asymptomatic patients with mediastinal histoplasmosis do not require treatment. (Note: in some cases, lymphadenopathy is found incidentally, and biopsy is done to rule out malignancy.)

Standard treatment of symptomatic mediastinal histoplasmosis is oral itraconazole 200 mg, 3 times daily for 3 days, followed by 200 mg orally once or twice daily for 6 to 12 weeks.<sup>14</sup>

Although stopping immunosuppressant drugs is considered the standard of care in treating histoplasmosis in immunocompromised patients, there are no guidelines on when to resume them. However, a retrospective study of 98 cases of histoplasmosis in pa-

Combining urine and serum testing increases the likelihood of antigen detection

tients on tumor necrosis factor antagonists found that resuming immunosuppressants might be safe with close monitoring during the course of antifungal therapy.<sup>9</sup> The role of long-term suppressive therapy with antifungal agents in patients on chronic immunosuppressive therapy is still unknown and needs further study.

■ TAKE-HOME MESSAGES

- Histoplasmosis is the most prevalent endemic mycotic disease in the United States, and mediastinal lymphadenopathy is commonly seen in acute pulmonary histoplasmosis.

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- Histoplasmosis should be included in the differential diagnosis of granulomatous lung disease in patients from an endemic area or with a history of travel to an endemic area.
- Immunosuppressive agents such as tumor necrosis factor antagonists and disease-modifying antirheumatic drugs can predispose to invasive fungal infection, including histoplasmosis.
- While isolation of *H capsulatum* from culture remains the gold standard for the diagnosis of histoplasmosis, the histoplasma antigen tests (serum and urine) is more sensitive than culture. ■

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