Fever, Weight Loss, and Lung Nodules in a 54-Year-Old Woman with Sarcoidosis

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Diagnosis: Sarcoidosis

Chief Complaints
The patient had been in her usual state of health until a month ago. At that time, she developed a constellation of symptoms including low-grade fever with chills, night sweats, tachycardia, tremor, abdominal cramping, vomiting, and a 20-pound weight loss. She reported that she had the flu 3 months prior.

Past Medical History
Patient was diagnosed with hypertension and sarcoidosis 14 years ago. She was on off corticosteroid therapy depending on the activity of her sarcoidosis until 9 months prior when activation of her sarcoidosis caused her to initiate and continue prednisone therapy to the present.

Family History
Active sarcoidosis in a younger sister and lung cancer in her father.

History of Medications
Her current medications included Pantoprazole, prednisone, potassium chloride, fluticasone, and hydrochlorothiazide. She had been taking risedronate; however, this medication caused a drug reaction and she stopped taking it.

Physical Examination
Vital signs: temperature, 38.6°C; pulse, 100 beats/min; blood pressure (systolic/diastolic), 94/58 mmHg. Maculopapular rash on upper and lower extremities, multifocal 1/6 systolic murmur, and decreased breath sounds on the right side.

Radiologic Findings
Chest x-ray revealed patchy opacities in the right middle, right upper, and left upper lung lobes along with pleural scarring consistent with sarcoidosis. Computed tomography (CT) of the thorax revealed air-space disease with pleural and parenchymal scarring involving the right middle, right lower, and left upper lung lobes and nodules less than 1 cm in the right middle and right lower lobes.

Principal Laboratory Findings
(Table 1) and (Image 1).

Questions:
1. What are this patient’s most striking clinical and laboratory findings?
2. How do you explain this patient’s most striking clinical and laboratory findings?
3. What is this patient’s most likely diagnosis?
4. What are the epidemiologic characteristics and pathogenesis of this patient’s disease?
5. What are the forms of presentation of this patient’s disease?
6. What laboratory methods are available to isolate the organism responsible for this patient’s disease?
7. How is this patient’s disease treated?

Possible Answers:
1. Low-grade fever with chills, night sweats, tachycardia, tremor, abdominal cramping, vomiting, and a 20-pound weight loss; chest x-ray and CT findings consistent with interstitial, patchy airway disease with lung nodules; decreased white blood cell count, microcytic-hypochromic anemia with pancytopenia; mildly increased liver enzymes (AST and ALT); positive urine histoplasma antigen, serum histoplasmin antibody, and bone marrow and blood cultures for Histoplasma capsulatum (Table 1 and Image 1).

2. Our patient’s clinical, radiographic, and laboratory findings are consistent with infection with H. capsulatum.

3. Most likely diagnosis: disseminated histoplasmosis due to fungal infection with H. capsulatum. Histoplasma capsulatum is a dimorphic fungus, which exists in mycelial form in soil, especially soil contaminated with bird droppings. Spores produced by mycelia are disseminated by wind and can be inhaled by humans. The spores mature into an intracellular budding yeast form that produces infection in humans after localizing primarily in histiocytes and macrophages.1 The yeast forms of H. capsulatum are approximately 3 microns in diameter and can be confused with Leishmania donovani organisms; however, they lack the characteristic stub-like kinetoplast arising from the nucleus in Leishmania species.

4. Histoplasma capsulatum is endemic in the Ohio and Mississippi River valleys of the central United States and primarily affects 2% to 5% of people living in these regions.2,3 When spores produced by mycelia of H. capsulatum are airborne and subsequently inhaled by human beings, they mature into yeast forms at body temperatures. The yeast forms are ingested by macrophages and histiocytes in the reticuloendothelial system (bone marrow, spleen, and liver), where they multiply and are carried to the hilar lymph nodes.1 Dissemination to other organs occurs via the bloodstream, where they are again ingested by macrophages and histiocytes.

5. Histoplasmosis can present as a variety of clinical syndromes, including most commonly as asymptomatic infection, acute pulmonary histoplasmosis, chronic pulmonary histoplasmosis, disseminated histoplasmosis, and much less commonly as central nervous system (CNS) histoplasmosis and mediastinal fibrosis.1,11 Asymptomatic infection with H. capsulatum occurs primarily in immunocompetent individuals and is clinically insignificant.11,12 Such individuals do not have any symptoms except for hilar and mediastinal lymphadenopathy and isolated pulmonary nodules on chest x-ray. Acute pulmonary histoplasmosis, on the other hand, can produce constitutional symptoms like malaise, night sweats along with fever, non-productive cough, and weight loss. Chest x-ray reveals patchy interstitial
and parenchymal infiltrates and hilar and mediastinal lymphadenopathy. The severity of clinical presentation is dependent on the degree of exposure. Inhalation of a large number of *H. capsulatum* spores produces symptomatic disease with flu-like symptoms and patchy interstitial and parenchymal infiltrates and/or nodules on chest x-ray. The disease is usually self-limited, although a few patients may develop complications like pericarditis, arthritis, or mediastinal granulomas. Chronic pulmonary histoplasmosis occurs in the background of a pre-existing chronic lung disease. Males are affected more than females and whites more than blacks. Patients with this disease may present with fever, night sweats, weight loss, and fatigue. Typically, chest x-rays will reveal patchy air-space disease, pleural scarring, and emphysematous lung tissue changes. Disseminated histoplasmosis occurs predominantly in immunocompromised individuals; however, healthy, immunocompetent individuals can get infected. Immunocompromised individuals highly susceptible to infection with *H. capsulatum* include patients with acquired immunodeficiency syndrome (AIDS) and those on prolonged steroid, chemo, or immunosuppression therapy. Individuals with disseminated histoplasmosis present with a variety of clinical signs and symptoms depending upon the organ system involved. The most commonly affected organs are the lymph nodes, bone marrow, gastrointestinal tract, skin, adrenal glands, genitourinary tract, and CNS. The clinical manifestations of disseminated histoplasmosis include lymphadenitis, pan- cytopenia, bowel and bladder ulcerations, hepatosplenomegaly, cerebritis, meningitis, and mass-like lesions. Constitutional symptoms of disseminated histoplasmosis include fever, weight loss, malaise, and headache, while radiographic findings include diffuse or patchy interstitial lung infiltrates, airway disease, and bilateral lung nodules.

6. Laboratory detection of histoplasma can be accomplished by hematoxylin and eosin (H&E) tissue staining, culture, serology, and fungal stains. Intracellular yeast forms can be readily detected in H&E-stained tissue from individuals with the nongranulomatous form of disseminated histoplasmosis. In individuals with the granulomatous form of this disease, it is more difficult to visualize the fungus. The yeast forms appear as small oval structures with a single eccentrically located nucleus and perinuclear clearing, often situated inside histiocytes in clusters or individually. With fungal stains they appear within histiocytes as small, uniform, 1 to 3 \( \mu \)m oval yeast forms with a distinct cell wall and an eccentric nucleus. Gomori methenamine silver (GMS) stain is the most useful stain for the identification of histoplasma. In the disseminated form, bone marrow staining with GMS detects the fungus in as many as 75% of cases. Other stains that can be used are periodic acid–Schiff (PAS) and Giemsa. Isolation of *H. capsulatum* by culture is currently considered the gold standard for definitive diagnosis. The diagnostic sensitivity of cultures in the disseminated form of the disease is as high as 80%. Cultures are time consuming, however, and can take 2 to 4 weeks of incubation for growth of this fungus to occur. Serologic methods for the diagnosis of histoplasma infection are primarily based on immunodiffusion and complement fixation to detect antibodies against *H. capsulatum*. These methods are not very sensitive, however, in patients with the dis-
seminated form of disease especially in immunocompromised patients (e.g., those with AIDS) due to the low antibody titers in these patients. A novel test for the detection of histoplasma antigens in serum by enzyme-linked immunosorbent assay (ELISA) is 72% sensitive and 98% specific in identifying affected individuals in endemic areas. Moreover, antigen detection in urine is more diagnostically sensitive in identifying affected individuals than antigen detection in other body fluids; however, the highest diagnostic sensitivity occurs when both serum and urine are tested for histoplasma antigens.

7. Current recommendations for the management of disseminated histoplasmosis in immunocompromised individuals differ for those with AIDS and those without AIDS. For patients with AIDS and disseminated histoplasmosis, current treatment recommendations are amphotericin B for 3 to 4 months followed by itraconazole for life in the case of severe disease. Treatment with itraconazole for life is suggested for milder forms of disseminated disease. For severe disseminated histoplasmosis in non-AIDS patients, the current recommendation is amphotericin B for 3 to 4 months followed by itraconazole for 16 to 18 months. In non-AIDS patients with milder disseminated disease, itraconazole alone for 16 to 18 months is recommended.

**Keywords**

_Histoplasma capsulatum_, disseminated histoplasmosis, immunocompetent, immunocompromised, histoplasmin