A Cautionary Tale

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PRESENTATION
A negative test result proved misleading in the case of a 51-year-old woman from Chihuahua, Mexico. During one of her frequent visits to a daughter in the United States, the woman presented with a 2-month history of intermittent hemoptysis, weight loss, and night sweats. She had no history of chest pain, dyspnea on exertion, fever, chills, hematemesis, melena, or epistaxis, and she denied use of tobacco, alcohol, or injectable drugs. However, she had type 2 diabetes mellitus, hypertension, and 12 years earlier, she underwent mastectomy, chemotherapy, and radiotherapy for cancer of the right breast.

Five years before her current admission, the patient was diagnosed with pulmonary tuberculosis based on a positive (30 mm) tuberculin skin test and a radiographic finding of a left apical cavitation (Figure 1). At that time, her husband had confirmed pulmonary tuberculosis, so although her diagnosis was never verified with a culture, she received antitubercular therapy for 4 months.

ASSESSMENT
Physical examination revealed the following: blood pressure, 170/88 mm Hg; heart rate, 88 beats per minute; respiratory rate, 18 breaths per minute; temperature, 99.7°F (37.6°C); and oxygen saturation of 98% on 2 liters oxygen by nasal cannula. Fine rales were audible at both lung bases. A cardiac examination was normal, and she had no hepatosplenomegaly or lymphadenopathy. Laboratory studies disclosed a white blood cell count of 6.9 x 10^3/mm^3, hemoglobin of 10.6 g/dL, platelet count of 288 x 10^3/mm^3, and a creatinine of 1.1 mg/dL. Liver function tests and a coagulation profile were normal. Computed tomography of the chest showed right upper-lobe infiltrate with a thin-walled-cavity (Figure 2), a 2.7 pleural-based scar in the left apex, scattered ground-glass opacities in both lung fields, and mediastinal and right hilar lymphadenopathy.

Mycobacterial and fungal sputum smears were reported negative, as were tests for serum Histoplasma antigen and serum Coccidioides antibody. Chronic granulomatous inflammation was evident with right upper-lobe tissue biopsy guided by computed tomography; again, mycobacterial and fungal smears were negative. Nonetheless, her history suggested recurrent pulmonary tuberculosis, so isoniazid, rifampin, and ethambutol were initiated. Subsequent mycobacterial and fungal cultures of sputum and lung tissue were negative.

DIAGNOSIS
Three months later, the patient developed massive hemoptysis and right upper lobectomy was performed. Fungal stain and culture of the lung tissue showed Coccidioides species (Figure 3). Enzyme immunoassay for Coccidioides IgG was positive, and the complement fixation antibody titer was 1:8. Pulmonary coccidioidomycosis was diagnosed.

Coccidioides species are dimorphic fungi endemic to the southwest regions of the United States, Northern Mexico, and parts of Central and South America. These include C. immitis, the cause of coccidioidomycosis, and C. posadasii, but no clinical laboratory method differentiates between them. In the soil, Coccidioides species exist as mycelia that mature to form the infective arthroconidia. Nearly all infections are the result of inhaling arthroconidia, which become spherules in the lungs. Cutaneous inoculations with extension to regional lymph nodes have been reported but are exceedingly rare. Most patients with coccidioidomycosis live in endemic areas. Clinicians in other locales can encounter the disease in travelers from endemic regions or in former residents who experience reactivation of latent infections.

At least one half to two thirds of all infections are subclinical or sufficiently mild not to prompt medical evaluation. Primary Coccidioides infections most frequently
Figure 1  Five years before the patient’s current admission, a left apical cavity was discovered on a radiograph.

Figure 2  A right upper-lobe infiltrate with a thin-walled-cavity was noted on a computed tomography of the chest.
manifest as community-acquired pneumonia 1 to 3 weeks after exposure.\textsuperscript{6,7} Distinguishing coccidioidomycosis from other etiologies is usually difficult without laboratory confirmation, such as detection of anticoccidioidal antibodies in serum or identification of \textit{Coccidioides} species in sputum or another respiratory specimen.\textsuperscript{8,9} Approximately 5\% to 10\% of infections trigger pulmonary sequelae, usually nodules or cavities.\textsuperscript{9} The latter, which can be present at any stage of the primary infection, are typically solitary, near the pleura, thin-walled, and under 4 cm in diameter.\textsuperscript{1,10,11} Half regress after 2 years without antifungal therapy. In the chronic phase of infection, patients are generally asymptomatic.

Some patients develop a chronic fibrosing pneumatic process characterized by infiltrates and cavitations that commonly involve more than 1 lobe.\textsuperscript{1,12} Lesions might cause local or systemic symptoms, such as night sweats and weight loss.\textsuperscript{1} This form of infection is not common among persons with T-cell deficiencies but seems to be associated with diabetes or preexisting pulmonary fibrosis.

Direct examination of sputum and other respiratory specimens may reveal the diagnostic spherules of \textit{Coccidioides}, particularly in patients who produce copious sputum or who have multilobar infiltrates.\textsuperscript{11} Bronchoscopy is normally performed in immunosuppressed or severely ill patients, especially if they have diffuse infiltrates. In one study of 30 patients with an abnormal x-ray and a culture or histology indicative of coccidioidomycosis, bronchoscopy yielded the diagnosis in 69\% of cases (after patients with solitary pulmonary nodules were excluded from analysis).\textsuperscript{13} Only 32\% of prebronchoscopy sputum samples produced a positive culture.

Serology is the most common method of diagnosis in primary coccidioidal infections. Even minimally reactive results are often diagnostically important, and a negative serologic test never excludes coccidioidal infection. Repeating serology 1 or more times over 2 months increases the sensitivity of serologic diagnosis, especially for recently acquired infections.\textsuperscript{1}

The differential diagnosis for focal or multifocal cavitary lung diseases includes neoplasms such as bronchogenic carcinomas and lymphomas, pulmonary infarct, septic embolism, immunologic disorders such as Wegener’s granulomatosis and rheumatoid nodules, and infection (see Table).\textsuperscript{14} In cavitary lung disease caused by \textit{Mycobacterium tuberculosis}, sputum smears are likely to be positive for acid-fast bacilli. In a study of 977 patients with culture-proven pulmonary tuberculosis, sputum smears were positive for acid-fast bacilli in 20\% to 40\% of patients with minimal disease, 60\% to 70\% of patients with moderately severe disease, and 90\% to 95\% of patients with advanced cavitary disease.\textsuperscript{15} Among 155 patients with tuberculosis, positive smears were found in 98\% of patients with cavitary disease compared with 70\% of patients with noncavitary disease.\textsuperscript{16}

Patients can have coexisting pulmonary tuberculosis and coccidioidomycosis.\textsuperscript{17,18} A review of 43 such cases noted that simultaneous onset occurred in less than one third of them.\textsuperscript{18} Symptoms of each disease usually emerged sequentially.

### MANAGEMENT

Our patient’s antitubercular therapy was replaced by itraconazole, which produced a good clinical response. While multiple diagnostic tests for presumed pulmonary tuberculosis were negative, other tests also failed to reveal her diagnosis before surgery. We postulate that she initially had culture-negative pulmonary tuberculosis based on her exposure history, tuberculin skin test conversion, and the left apical cavity, which subsequently healed.

This case highlights 3 important clinical points when evaluating cavitary lung disease. First, pulmonary coccidioidomycosis cannot be excluded with negative serological tests or cultures. In addition, tuberculosis is an unlikely cause for cavitary lung disease if sputum smears for acid-fast bacilli are negative. Finally, pulmonary tuberculosis and coccidioidomycosis can coincide in patients at risk.

![Figure 3](image_url)  
**Figure 3** Fungal stain and culture of lung tissue removed during lobectomy revealed the causative organism.

### Table 1  Infectious Causes of Focal or Multifocal Cavitary Lung Disease

<table>
<thead>
<tr>
<th>Bacterial Sources</th>
<th>Fungal Sources</th>
<th>Parasitic Sources</th>
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<tbody>
<tr>
<td>Actinomycosis</td>
<td>Aspergillosis</td>
<td>Amebiasis</td>
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<td>Anaerobic bacteria</td>
<td>Blastomycosis</td>
<td>Hydatid disease</td>
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<td>Gram-negative bacteria</td>
<td>Coccidioidomycosis</td>
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References


