Pleural Effusion in Michigan Caused by Coccidioides Immitis After Travel to an Endemic Area

Christopher M. Hughes
Paul A. Kvale

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Coccidioidomycosis is an endemic disease in the southwestern United States, but may be seen in nonendemic locations due to patients' travels. Pleural effusions caused by Coccidioides immitis occur in about 7% of adult patients during the primary infection; the effusions are generally "benign" and require no specific therapy (1). Coccidioidomycosis should be considered in the differential diagnosis of pleural effusion occurring in patients with the proper clinical manifestations and a history of travel to an endemic area.

Case Report

This previously healthy 47-year-old white female was initially evaluated by her private physician because of left-sided pleuritic chest pain after returning home to Michigan from Arizona. (She had traveled numerous times to Arizona during the preceding six months.) Her clinical examination, electrocardiogram, and chest roentgenogram (Fig 1) were normal. Two months later the pleuritic chest pain had largely abated, but she complained of a pulling and catching in her left hemithorax with deep inspiration, associated with general malaise and temperature spikes of > 38.3°C (101°F). She denied cough, dyspnea, wheezing, anorexia, chills, night sweats, or skin rashes. She did not smoke, drink alcohol socially, and had no significant medical history. There was no known exposure to asbestos. She had no unusual hobbies or habits. She took no medicines and had no allergies. Physical examination revealed an anxious female in no acute distress. Her temperature was 38.1°C (100.6°F), blood pressure 130/70 mm Hg, heart rate 80 beats/min, and respiration 16 breaths/min and unlabored. The left lower hemithorax was dull to percussion with decreased breath sounds. The remainder of her physical examination was normal; specifically, she had no skin rash. Chest roentgenogram revealed a moderate, left-sided pleural effusion without lymphadenopathy. Computed tomography (CT) studies of the abdomen and thorax were normal except for the pleural effusion; specifically, there was no hilar or mediastinal lymphadenopathy. There was no reaction to PPD and a positive reaction to mumps and candida control skin tests. Complete blood count revealed a hemoglobin of 141 g/L (14.1 g/dL), WBC count of $8.7 \times 10^9/L$ (8,700/μL) with 0.07 (7%) eosinophils on differential. SMAC results were normal. ANA and rheumatoid factor were negative. Thoracentesis revealed straw-colored fluid, protein 53 g/L (5.3 g/dL), lactic dehydrogenase 331 U/L, WBC count $4.2 \times 10^9/L$ (4,160/μL) with 0.72 (72%) lymphocytes, 0.18 (18%) monocytes, 0.09 (9%) eosinophils, 0.01 (1%) basophils, 0.15 (15%) nonhematologic cells, and RBC count 860 x $10^9/L$ (860/μL). Cytology of the pleural fluid was negative for malignancy. Pleural biopsy showed noncaseating granulomata. Routine gram stain, culture and sensitivity, fungal stain, and acid-fast bacillus (AFB) stain were negative for both pleural fluid and biopsies. Fungal and AFB cultures were negative. Bronchoscopy and transbronchial biopsy were nonspecific, and neither AFB nor fungi were recovered. The patient was placed on 300 mg/day of isonicotinoylhydrazine (INH), 600 mg/day of rifampin, and aspirin as needed and was sent to Henry Ford Hospital for consultation.

At our initial evaluation the patient's complaints had largely resolved. She no longer had fever and her chest discomfort had improved, but she still felt fatigued. On physical examination temperature was 37°C (98.6°F), blood pressure 130/70 mm Hg, heart rate 80 beats/min, and respiration 16 breaths/min and unlabored. Again, the only significant physical findings were dullness to percussion and decreased breath sounds in the left lower hemithorax. Chest roentgenogram revealed a left pleural effusion (Fig 2). CT of the thorax revealed no additional abnormalities. A repeat PPD was negative with positive control skin tests. The coccidioidal immunodiffusion titers were positive at 1:16 with full identity of all bands; complement fixation titers were also positive at 1:8. Immunodiffusion titers and complement fixation titers for Aspergillus, blastomycosis, and histoplasmosis were negative. Repeat
fungal and AFB cultures of the pleural fluid and pleural biopsies revealed no growth. INH and rifampin were discontinued, and the patient continued to improve both clinically and by chest roentgenogram (Fig 3). On the advice of a third consultant elsewhere she was placed on 400 mg/day of ketoconazole for the last several months of her course.

**Discussion**

Coccidioidomycosis is caused by a tissue dimorphic soil fungus endemic in the desert of southwestern United States, particularly the San Joaquin Valley of California, Arizona, and New Mexico (2). Approximately 50,000 persons are infected each year, and in susceptible populations about 0.4% per year seek medical help for their infections (3). Less than half of the patients with primary pulmonary coccidioidomycosis are symptomatic. The most common manifestation is a febrile pulmonary illness much like influenza. The most common symptoms associated with primary pulmonary infection are cough, fever, and chest pain, seen in 70% to 90% of patients (3). Cough is usually associated with small amounts of sputum which may be streaked with blood. Night sweats may accompany the fever. The chest pain (82% of patients) is usually pleuritic. Fatigue and lethargy may be profound. Other, less common symptoms seen with the primary infection are headache, sore throat, diffuse muscle aches, and loss of appetite (3).

Over one-third of the patients have peripheral eosinophilia and one-half have erythema nodosum or erythema multiforme (4). Erythema nodosum is especially common in women. Our patient denied any form of skin rash, which may have given other physicians a better clue to the correct diagnosis earlier. Erythema multiforme and toxic erythema (a diffuse maculopapular eruption) are additional dermatologic manifestations commonly seen with primary coccidioidal pulmonary infections. Typical "valley fever" consists of erythema nodosum or erythema multiforme plus arthralgias or arthritis and sometimes mild conjunctivitis.

Most patients with primary coccidioidomycosis have abnormal chest roentgenograms. Alveolar infiltrates are the most common, usually seen in one segment or lobe, extending to the visceral pleura in all cases (1). Atelectasis is also common. Hilar adenopathy is seen in 20% of cases, usually ipsilateral to the infiltrate. Again, these clues to the diagnosis were lacking in our patient, perhaps because of the fortuitous timing when chest roentgenograms were obtained. Although small pleural effusions may be seen in 20% of patients, larger pleural effusions are seen in only 2% to 6% of patients (3). The effusions are unilateral and represent a parapneumonic process rather than an extrathoracic dissemination. Davies (2) states that sterile pleural effusions and pleurisy occur in 5% to 10% of cases and likely represent hypersensitivity rather than infection. Pleural effusions may also occur in the chronic form of coccidioidomycosis, but often represent empyema with or without bronchopleural fistula contributing to an increased acute and chronic morbidity (4).

Serologic studies are extremely important in establishing a definitive diagnosis, particularly in the absence of recovery of
the organism on cultures or stains of body fluids or tissues. The coccidioidin skin test is usually positive and serum complement fixation titers are elevated (> 1:16) (4). In our patient the immunodiffusion test was positive with full identity to all coccidioidin bands at a titer of 1:16 during the time she presented to us. Follow-up serology was not possible since she chose to go elsewhere for continuing care. The immunodiffusion test we employed largely measures IgG precipitating antibodies, with the patient's serum being matched with a known positive control to *Coccidioides immitis*. The antigen is an “F” antigen, which is a mycelial filtrate and predominantly measures IgG antibody. The serum was sent to the Michigan Department of Public Health, where a complement fixation test was also positive at a titer of 1:8. This is significant because the complement fixation test essentially uses the same antigen that we use (the “F” antigen) in the immunodiffusion test. The complement fixation test is more sensitive, but less specific. Our patient's serum was negative for *Aspergillus*, blastomycosis, and histoplasmosis on immunodiffusion testing, and negative to blastomycosis and histoplasmosis at the Michigan Department of Public Health for complement fixation antibodies. There is much less cross-reactivity with the immunodiffusion test since we can monitor the bands of identity. With full identity, such as was demonstrated in our laboratory, we can confidently conclude that the patient had a positive serologic test for coccidioidomycosis. “TP” antibody (an IgM antibody) was not tested in our laboratory.

The pleural fluid findings in our patient were those of any nonspecific granulomatous pleuritis. Although *Coccidioides immitis* is often recovered from pleural biopsy (and less frequently from pleural fluid), we were unable to recover these organisms from our patient. However, the serologic studies discussed allow for a confident diagnosis of the pleural effusion caused by infection with *Coccidioides immitis*.

The course of primary pulmonary coccidioidomycosis is typically benign, and symptoms resolve without specific therapy unless dissemination or relapse occurs. Even when pleural effusions accompany the primary infection, treatment is rarely necessary; fluid resolution is slow, often taking one to eight weeks (1). Our patient received ketoconazole therapy from a third consultant, a recommendation with which we did not concur. Whether or not the addition of ketoconazole to her management approach helped resolve her pleural effusion more rapidly is conjectural. In a study of a large series of patients with pleural effusions, results showed that the effusions almost always resolved spontaneously without the addition of specific antifungal treatment (1). When the course suggests more complicated disease (eg, persistent effusion with rising complement fixation titers and a negative coccidioidal skin test), systemic amphotericin B should be employed. The utility of ketoconazole in the setting of a pleural effusion accompanying primary pulmonary coccidioidomycosis has not yet been determined.

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**References**