33-Year-Old Woman With Pleuritic Chest Pain and Nonproductive Cough

CASSIE C. KENNEDY, MD,* AND TIMOTHY R. AKSAMIT, MD†

A 33-year-old Somali woman, who had immigrated to the United States less than 3 years previously, presented to an urgent care center with right shoulder discomfort of 2 weeks' duration that radiated under her right breast. Associated symptoms included nonproductive cough, subjective fever, chills, and fatigue. The patient was a nonsmoker with no occupational or animal exposures. She denied contacts with ill persons. Her medical history was unremarkable, and she was taking no medications. On physical examination, the patient was afebrile with decreased breath sounds within the right lung on auscultation. She had no clubbing, cyanosis, or edema. Results from her heart examination were normal. Chest radiography revealed a small focal consolidation in the right lung base. Radiographic findings were believed to be most consistent with pulmonary infarction or pneumonia. Computed tomography (CT) angiography showed no pulmonary embolism, but pleural thickening and a poorly defined masslike infiltrate were seen. The patient received levofloxacin for presumed community-acquired pneumonia. After 17 days of antibiotic therapy, the patient returned to her primary care physician with no improvement in symptoms. Repeat chest radiography revealed interim development of a right-sided pleural effusion (Figure 1).

The patient was admitted to our inpatient general medicine service for further evaluation and treatment. On admission, the patient had symptoms of fatigue and weight loss. Physical examination revealed decreased breath sounds and dullness to percussion in the right lung base. Abdominal examination was consistent with an approximate 20-week gravid uterus. This previously unsuspected pregnancy was confirmed by β-human chorionic gonadotropin blood test. Complete blood cell count with differential revealed mild anemia. Human immunodeficiency virus (HIV) test results were negative.

*Fellow in Pulmonary and Critical Care Medicine, Mayo School of Graduate Medical Education, Mayo Clinic College of Medicine, Rochester, Minn.
†Adviser to fellow and Consultant in Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, Minn.

See end of article for correct answers to questions.

Individual reprints of this article are not available. Address correspondence to Timothy R. Aksamit MD, Division of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, 200 First St SW, Rochester, MN 55905 (e-mail: aksamit.timothy@mayo.edu).

1. Which <u>one</u> of the following is the <u>most likely</u> diagnosis in this patient?

a. *Influenza A*
b. *Latent tuberculosis infection (LTBI)*
c. *Community-acquired pneumonia*
d. *Active pulmonary tuberculosis (TB)*
e. *Pulmonary embolus*

It would be unlikely for this patient to develop a pleural effusion from influenza A, and the clinical course would be too prolonged. By definition, chest radiography in LTBI would not suggest active mycobacterial TB disease (infiltrate, effusion). The community-acquired pneumonia complication rate is higher in pregnancy (2 cases of 25 had empyema in 1 small series).[1] However, community-acquired pneumonia would not likely progress in a young immunocompetent patient after a full course of levofloxacin, which is expected to have a clinical success rate of up to 96%.[2] Given this patient's recent immigration from a region at high risk of *Mycobacterium tuberculosis* infection, generalized symptoms (weight loss, fatigue, and subjective fever), abnormal findings on chest radiography, and unresponsive course to fluoroquinolone therapy, she was considered to have active pulmonary TB. A significant pulmonary embolus likely would not have been missed on her prior CT angiogram. Computed tomography angiography has a reported likelihood ratio of a negative test of 0.11, which, in a patient such as this with a pretest probability of 30% or less, would make a posttest probability of disease less than 5%.[3]

In the course of the patient's evaluation, a purified protein derivative (PPD) tuberculin skin test (TST) was performed.

2. Which <u>one</u> of the following constitutes <u>positive</u> PPD-TST (Mantoux or PPD) results in this patient?

a. *0-mm induration*
b. *≥5-mm induration*
c. *≥10-mm induration*
d. *≥15-mm induration*
e. *Unable to interpret accurately in pregnancy*

The PPD-TST evaluates for TB infection but does not differentiate active from latent disease. In the presence of TB infection, the test produces a measurable amount of skin induration at the site of intradermal injection, read between 48 and 72 hours later. A test that results in 0 mm of induration can be either a true negative in the absence of

disease or a false negative in the setting of active disease, LTBI, immunosuppression, or anergy. The size of the PPD-TST induration is interpreted as "positive" depending on the underlying risk of TB infection in the patient (or pretest probability). Results in high-risk patients are positive at 5 mm of induration or greater, in moderate-risk patients at 10 mm or greater, and in low-risk patients at 15 mm or greater.[4] This patient's PPD-TST results would not be positive at 5 mm of induration because she lacked any of the clinical factors that would have placed her at high risk such as HIV infection, immunosuppressive therapy, or a known recent close contact with someone with active pulmonary TB, and her chest x-ray was not consistent with previous TB infection.[4] Immigrants to the United States within the past 5 years from endemic areas (Asia, Africa, Latin America, Eastern Europe, and Russia) such as this patient are considered at moderate risk, and therefore the PPD-TST is positive if there is 10 mm of induration.[4] Other factors that would place a patient at moderate risk include injection drug use; working in high-risk settings such as health care facilities or laboratories that work with TB; or having silicosis, diabetes mellitus, chronic renal failure, hematologic or head, neck, or lung malignancy, or malnutrition.[4] Low-risk patients have none of the previously mentioned conditions. Pregnant patients who are at moderate or high risk of TB infection should undergo PPD-TST[4]; TSTs are regarded as safe[4] and valid[5] in pregnancy. Pregnancy complicated by active pulmonary TB has been shown to result in lower birth weights and increased prematurity and perinatal deaths with worse outcomes in late diagnosis or inadequate treatment.[6] When TB was treated adequately, no difference was reported in duration of gestation between pregnant women with TB and healthy controls.[7]

This patient's PPD-TST result was 14 mm of induration.

3. To minimize further spread of this patient's disease to others during hospitalization, which <u>one</u> of the following is <u>most appropriate</u>?

a. *Hospitalize patient in private room, but respiratory isolation is not necessary until* M tuberculosis *is proved with positive sputum results on acid-fast bacillus (AFB) test or culture*

b. *Hospitalize patient in respiratory isolation for the duration of treatment of active TB infection*

c. *Hospitalize patient in respiratory isolation until results are negative in 3 separate AFB sputum tests*

d. *Hospitalize patient in respiratory isolation until sputum culture results are negative*

e. *Hospitalize patient in respiratory isolation until results of pleural fluid cultures and tests are negative*

The Centers for Disease Control and Prevention offers specific recommendations for patients with suspected or proven active pulmonary TB infection who require hospitalization. Respiratory isolation consists of a negative-pressure room that is ventilated with sufficient air exchanges and appropriately removes air exhaust.[8] Also, the room door should remain closed with signs indicating the type of isolation and the need for health care workers to use personal protective equipment when entering. Patients should wear protective masks when outside their room during respiratory isolation.[8] Placement of patients with suspected active pulmonary TB in a private room is insufficient to prevent the exposure of uninfected personnel to TB through respiratory droplet transmission. Any patient requiring hospitalization with suspected active pulmonary TB should be placed in respiratory isolation until active pulmonary TB is ruled out or they are treated and determined to be of low infectivity risk.[8] Patients do not need to remain in isolation for the duration of treatment. Patients responding to treatment who have 3 consecutive sputum samples with negative results on AFB tests on separate days are considered at low risk of spreading infection[8] and can be removed from respiratory isolation. One does not need to wait until sputum culture results are negative. Patients with LTBI (positive results in PPD-TST in an asymptomatic patient without active pulmonary or extrapulmonary TB) and those with extrapulmonary TB (including pleural TB) infection do not require respiratory isolation.[8] Therefore, pleural fluid tests or cultures are not a factor in determining the length of respiratory isolation.

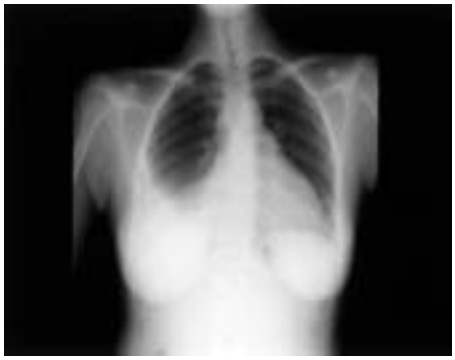

FIGURE 1. Posteroanterior chest radiography shows interim development of right-sided pleural effusion.

This patient was placed in respiratory isolation since she was hospitalized. Sputum AFB tests and cultures were performed. Obstetrics was consulted regarding the pregnancy. The patient underwent thoracentesis for evaluation of the pleural effusion. Results showed an exudative pleural fluid with a lactate dehydrogenase level of 449 U/L and a total protein level of 5.4 g/dL. Her pleural fluid showed 4950 total nucleated cells/μL with 88% lymphocytes.

4. Which one of the following tests would be the most useful to diagnose pleural TB in this patient?

a. *Induced sputum cultures*
b. *AFB test on pleural fluid*
c. *Pleural fluid culture*
d. *Adenosine deaminase levels in pleural fluid*
e. *Closed pleural biopsy for microbiology and histology*

Induced sputum cultures have been shown to have a moderate diagnostic yield of 52% in diagnosing cases of pleural TB.[9] The yield of pleural fluid cultures or AFB stains have been demonstrated to be low (12% and 2%, respectively).[9] Adenosine deaminase of pleural fluid has a diagnostic yield that ranges from 56% to 100%.[10] The diagnostic yield of a culture and AFB stain on a closed pleural biopsy is 62%, whereas biopsy histopathology has a diagnostic yield of 78%.[9] The combination of microbiology and histopathology of a pleural biopsy has a diagnostic yield of up to 93%.[9] This patient underwent closed pleural biopsy with an Abrams needle. Results from pleural tissue AFB tests were negative. Pleural biopsy specimens showed granulomatous inflammation (Figure 2) consistent with pleural TB infection. Cultures of all specimens remained negative.

5. Which one of the following would be most appropriate regarding initial treatment of this patient?

a. *Drainage of the pleural fluid by chest tube or pigtail catheter and immediate antimicrobial therapy*
b. *Delay treatment until after the delivery of the baby*
c. *No drainage of pleural fluid but immediate antimicrobial therapy*
d. *Corticosteroid therapy and immediate antimicrobial therapy*
e. *Corticosteroid therapy alone*

In a study of 61 patients with TB pleural effusion randomized to either pigtail catheter drainage and antimicrobial therapy or antimicrobial therapy alone, no differences in symptoms or residual pleural thickening were seen after 1 week.[11] Therefore, drainage of pleural fluid is not recommended as initial treatment. Treatment of pregnant women with active TB should not be delayed; immediate antimicrobial therapy consisting of isoniazid (INH), rifampin, and ethambutol should be initiated.[12] Corticosteroid therapy is not recommended for pleural TB because it has not been shown to provide significant difference in respiratory function, symptoms at 14 days, residual pleural thickening, or the presence of adhesions.[13] Corticosteroid therapy alone would be inappropriate in the presence of active TB disease.

In this patient, INH, rifampin, and ethambutol were initiated. Culture results remained negative, but the patient responded radiologically and symptomatically to antimicrobial therapy. She was diagnosed as having culture-negative TB. Treatment for 9 months was recommended with a 3-drug regimen of INH, rifampin, and ethambutol.

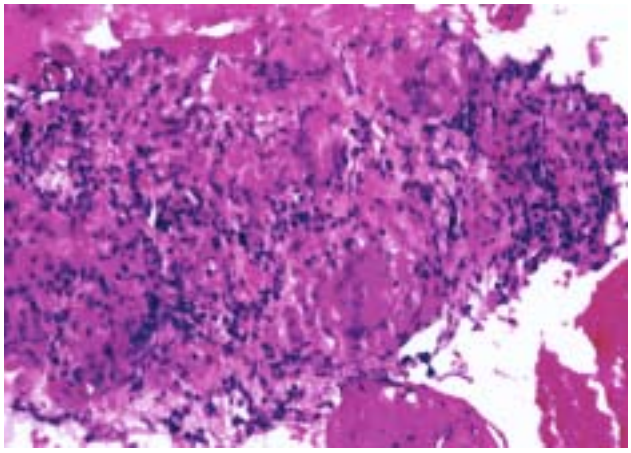

FIGURE 2. Pleural biopsy specimen demonstrating granulomatous inflammation (hematoxylin-eosin, original magnification ×200).

DISCUSSION

M tuberculosis is an AFB that is spread by respiratory droplets. Infection with *M tuberculosis* may lead to active disease (pulmonary or extrapulmonary infection in 10% of immunocompetent individuals). The Centers for Disease Control and Prevention has emphasized the use of targeted testing and pretest probability in managing this disease. Certain conditions increase the risk of progression to active TB such as diabetes mellitus, silicosis, an iatrogenic or acquired immunosuppressed state, certain cancers and hematologic diseases, end-stage renal disease, and malnutrition. Others are at increased risk secondary to exposures either from close personal contact with people known to have TB pulmonary disease or from substantial exposures to jails, health care settings, or the medically underserved.

Patients with positive PPD-TST results should be evaluated for TB infection and disease, and a medical history should be obtained; physical examination, chest radiography, and sputum studies should be performed. Patients who are asymptomatic with normal findings on physical examination and chest radiography are considered to have LTBI. These patients are treated with INH for 9 months. When associated with new skin test conversion, recent exposure to pulmonary TB, or immunocompromised state, LTBI in pregnancy is treated with daily INH (self-administered) or directly observed twice weekly INH with pyridoxine supplementation. Patients with active pulmonary TB com-

monly are treated with 2 months of 4 antimicrobial therapies (INH, pyrazinamide, rifampin, and ethambutol) followed by 2 months of INH and rifampin. Culture-negative TB responding to therapy is treated similarly. Pregnant patients are not prescribed streptomycin because it is associated with fetal hearing loss. Although pyrazinamide is recommended by the World Health Organization for pregnant patients, it is not prescribed commonly in the United States unless it is required because of drug resistance since its safety is less well established than other agents. If pyrazinamide is not used in the initial treatment regimen for active TB infection, then a minimum treatment regimen of 3 drugs for 9 months is suggested. Common extrapulmonary TB sites include the lymph nodes, the bones and joints, the genitourinary tract, or the central nervous system; also, disease can be disseminated systemically (miliary TB). Extrapulmonary TB is treated similarly to pulmonary TB except that prolonged therapy is recommended for meningeal infection.[12]

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Correct answers: 1. *d*, 2. *c*, 3. *c*, 4. *e*, 5. *c*