CHAPTER THREE

Clinical Cases

Introduction

In the first chapter, we provided a framework for approaching chest radiographs and characterizing abnormalities using standard terminology. In the second chapter, we showed examples of the many chest radiographic abnormalities that can be seen in patients with tuberculosis. In this chapter, our goal is to integrate what you have learned thus far and apply that knowledge to clinical cases.

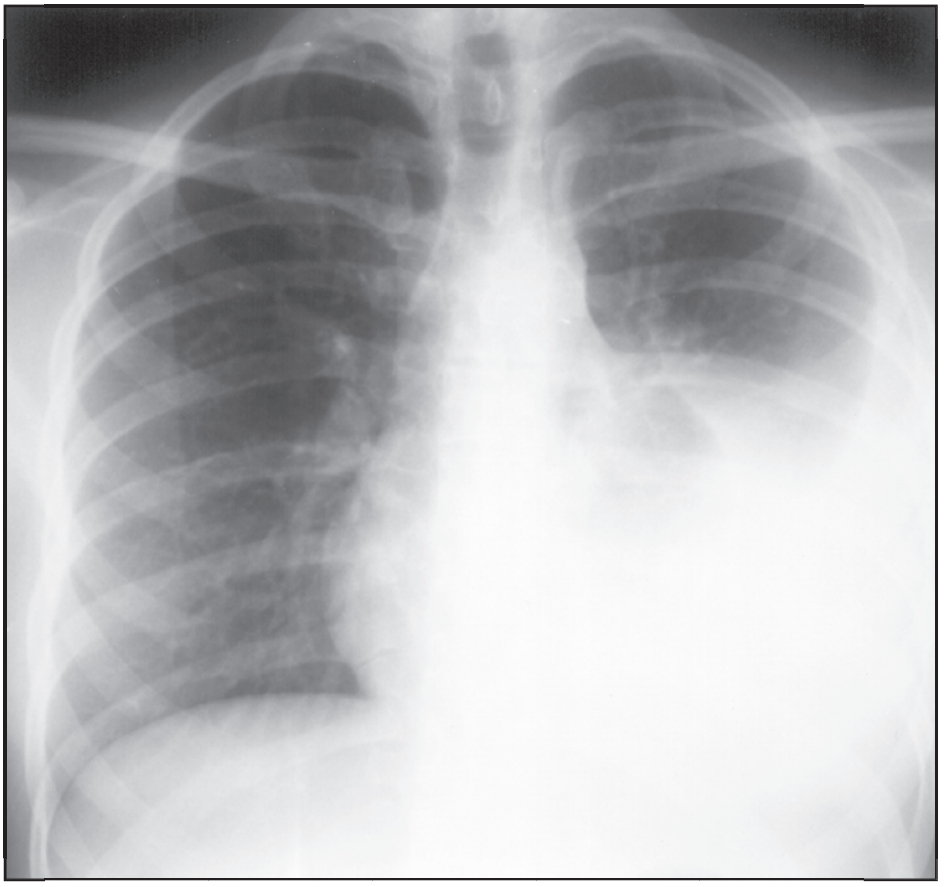
These cases are from our own practice, but include examples of clinical problems and decision-making challenges that are applicable to any clinician diagnosing and treating tuberculosis.

In each case you will be asked to describe the radiographic abnormalities and answer questions relevant to the evaluation and treatment of the case. All of the questions are brief essay or multiple choice. The answers to the questions and a summary immediately follow each case. We suggest completing each case before checking your answers.

Case One

The patient is a 27-year-old woman who was born in Pakistan and moved to the United States at age 3. She noted two weeks of pleuritic chest pain, fevers, night sweats, and a nonproductive cough for 5 days. The patient had spent the past 2 years working with the poor in India, Egypt, and Ethiopia. Her tuberculin skin test was 3 mm 2 years ago and now is 14 mm. Her chest radiograph is shown in *Figure 3.1.*

Figure 3.1



1. Describe the chest radiograph in *Figure 3.1* using standard terminology.

2. Which of the following should be done next?

   A. Bronchoscopy
   B. Thoracoscopic lung biopsy
   C. Thoracentesis
   D. Isoniazid treatment of latent tuberculosis infection

Case One Answers

1. Homogeneous opacity occupying more than one-half of the left hemithorax and extending up the lateral chest wall. The opacity is obscuring the left hemidiaphragm.

2. The correct answer is ***C.*** Because the patient's radiograph demonstrates a large left pleural effusion, the next step should be to perform a diagnostic thoracentesis. Pleural liquid should be obtained for measurement of glucose, protein, lactate dehydrogenase, cell counts, cytology, and microbiological studies. If findings suggest pleural tuberculosis, a pleural biopsy should be performed.

   Bronchoscopy (choice *A*) is not indicated because an endobronchial lesion is unlikely to be present in this case. Thoracoscopic lung biopsy (choice *B*) is not correct because the radiograph shows an effusion without obvious parenchymal involvement, and thoracoscopic lung biopsy is a more invasive procedure that should not be performed prior to thoracentesis and other non-invasive procedures. Isoniazid for treatment of latent tuberculosis infection (choice *D*) is not correct because the patient needs a diagnostic evaluation to rule out active tuberculosis prior to beginning treatment for latent tuberculosis infection. The administration of isoniazid alone to a patient with active tuberculosis can lead to the development of isoniazid-resistant tuberculosis and would be an error in management.

Case One Summary

A thoracentesis was performed and demonstrated a white blood cell count of 1,500 cells/μL (80% of which were mononuclear cells), a normal glucose, and an elevated protein concentration. No acid-fast bacilli were noted. Gram's stain and bacterial and mycobacterial cultures were negative. Three sputum specimens were negative for acid-fast bacilli. A closed left-sided pleural biopsy was performed. *M. tuberculosis* was isolated from tissue cultured from the pleural biopsy.

The patient was started on a standard four-drug antituberculosis regimen but her treatment was altered when she was discovered to have disease due to an isoniazid-resistant organism. This would not have been known had a pleural biopsy not been performed. She was treated with rifampin, pyrazinamide, and ethambutol for six months. The pleural effusion resolved with anti- tuberculosis chemotherapy.

Pleural tuberculosis represents one of the most common forms of extrapulmonary tuberculosis. It is characterized by a lymphocytic pleural effusion that is an exudate. The diagnosis can be difficult to establish because sputum and pleural liquid cultures are often negative (culture yield <50%). Diagnosis is best accomplished by a pleural biopsy and sending the specimen for both histological examination and mycobacterial culture.

Although it is reasonable to treat empirically for tuberculosis in a patient having a positive tuberculin skin test and an exudative pleural effusion without another known cause, making a definitive diagnosis is preferable because it allows you to determine whether drug-resistant organisms are present and excludes other diagnoses that might require alternative treatment.

Case Two

The patient is a 30-year-old Asian woman who was noted to have an abnormal chest radiograph (*Figure 3.2*) when she underwent tuberculosis evaluation prior to employment in a healthcare facility. The patient had a tuberculin skin test with 12 mm induration several years earlier for which she received 6 months of isoniazid. She denies having symptoms, has no underlying medical conditions, and is a non-smoker.

Figure 3.2

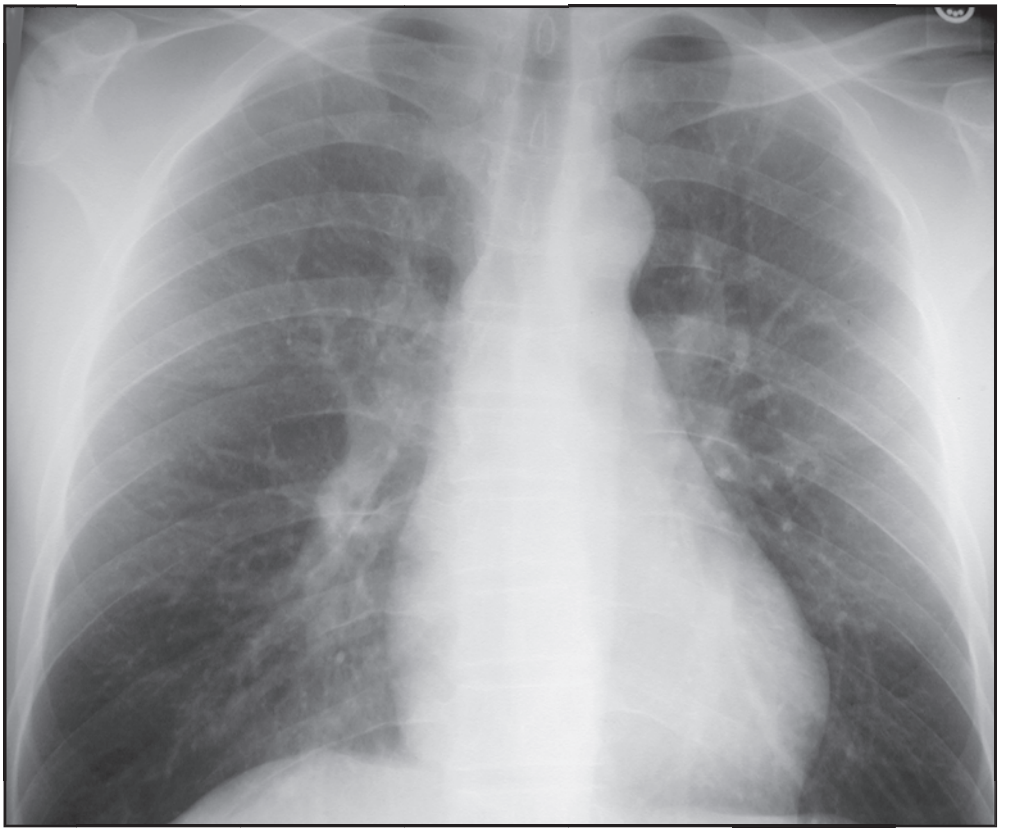
1. How would you describe the chest radiograph in *Figure 3.2?*

2. Based on your reading of the chest radiograph, which of the following is the **most** appropriate next step?

   A. Collect three sputum specimens for acid-fast smears and mycobacterial cultures
   B. Begin treatment for latent tuberculosis infection with isoniazid
   C. Repeat the tuberculin skin test
   D. Repeat the chest radiograph in 6 months

The patient was started on four antituberculosis medications pending the results of sputum cultures. After 2 months, the culture results were negative. A repeat chest radiograph was obtained *(Figure 3.3).*

Figure 3.3 - after 2 months of treatment for tuberculosis



3. How would you describe the chest radiograph in *Figure 3.3?*

4. Which of the following would be the **most** appropriate next step?

A. Continue multidrug therapy for tuberculosis
B. Obtain a chest CT scan
C. Perform a fine-needle aspiration of the nodule
D. Perform bronchoscopy to obtain a better respiratory specimen

Case Two Answers

1. There is a left upper lobe peripheral airspace opacity.

2. The correct answer is ***A***. When a patient has a positive tuberculin test and an abnormal chest radiograph consistent with tuberculosis, the first step should always consist of collecting sputum to assess the possibility of active tuberculosis.

3. Left upper lobe peripheral opacity is nearly resolved compared with the chest radiograph from 2 months ago.

4. The correct answer is ***A.*** Because the radiographic abnormality decreased in size and there was no other etiology identified, the patient is considered a clinical (culture-negative) case of tuberculosis. Therefore, the multidrug regimen should be continued and the patient treated for active disease.

Case Two Summary

In a patient at risk for tuberculosis who has an abnormal chest radiograph consistent with tuberculosis, the first step should be to obtain sputum for acid-fast smears and mycobacterial cultures to assess whether active tuberculosis is present. Sputum examination for tuberculosis is necessary because it is impossible to gauge the clinical activity of tuberculosis on the basis of a single radiograph. In addition, multidrug treatment should be given if there is a significant suspicion that active tuberculosis is present. If the diagnosis is confirmed by a positive culture, treatment can be continued to complete a standard course of therapy.

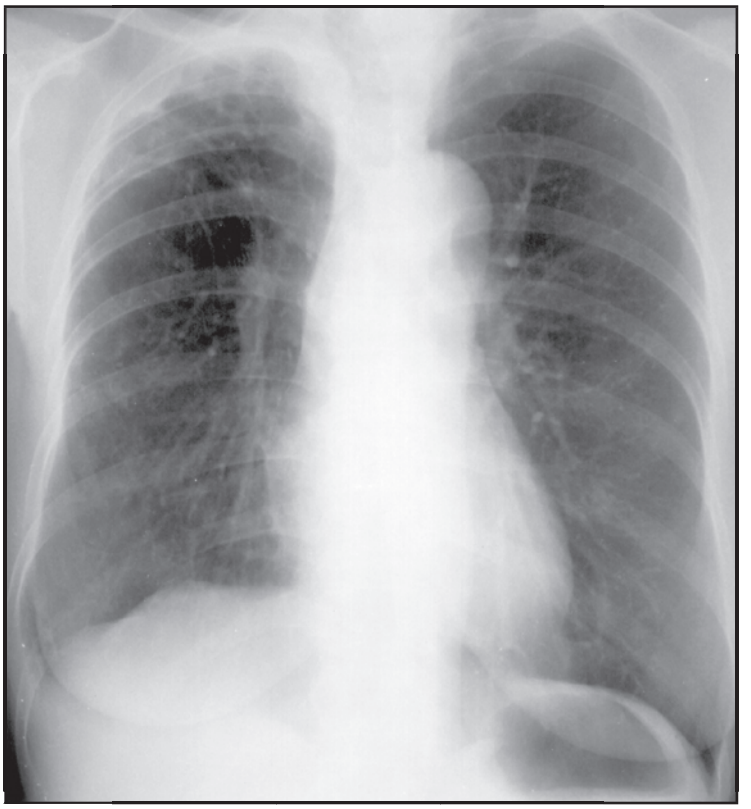
Negative cultures do not necessarily exclude a diagnosis of active tuberculosis; up to 15% of cases in the United States may be culture-negative. The low bacillary load in nodules compared with cavities is one explanation for negative cultures. These cases are best identified and managed by follow-up clinical and radiographic evaluation after 2–3 months of therapy to determine if there has been a response to antituberculosis treatment.

If patients exhibit either a clinical response or significant improvement in their chest radiograph after 2–3 months of treatment and no other etiology is identified, treatment should be continued for a total of 4–6 months for active tuberculosis.

Case Three

A 60-year-old woman, who immigrated from China 1 month ago, is evaluated for tuberculosis. She denies symptoms of tuberculosis and has no history of previous tuberculosis or other significant past medical history. Her tuberculin skin test has 13 mm of induration. Her chest radiograph is shown in *Figure 3.4*.

Figure 3.4



1. How would you describe the chest radiograph in *Figure 3.4?*

Treatment was begun with isoniazid, rifampin, ethambutol, and pyrazinamide. Acid-fast smears and mycobacterial cultures of sputum were negative. After 8 weeks, she continued to be asymptomatic and her chest radiograph was without change.

2. What would be the **most** appropriate next step?

   A. Continue isoniazid, rifampin, and ethambutol to complete a 6-month course
   B. Stop ethambutol and pyrazinamide and continue isoniazid and rifampin for an additional 2 months
   C. Stop rifampin and isoniazid and continue ethambutol and pyrazinamide for an additional 4 months
   D. Add levofloxacin and ethionamide to his current antituberculosis medications

Case Three Answers

1. Right upper lobe fibronodular opacities with volume loss and hilar retraction. Right apical pleural thickening.

2. The correct answer is ***B,*** stop ethambutol and pyrazinamide and continue isoniazid and rifampin for an additional 2 months (to complete a total of 4 months of treatment.) This would constitute an adequate course of treatment of latent tuberculosis infection in someone with radiographic evidence of prior tuberculosis. Treatment options in this circumstance include isoniazid for 9 months or rifampin (preferably with isoniazid) for 4 months. An alternative approach would have been to withhold treatment until the results of sputum cultures were known at 8 weeks. At that point, treatment could be initiated with isoniazid alone for 9 months or 4 months of rifampin (preferably with isoniazid) for treatment of latent tuberculosis infection in someone with radiographic evidence of prior tuberculosis.

Case Three Summary

Patients with a positive tuberculin skin test who have radiographic evidence of prior tuberculosis and who have not received prior treatment are at increased risk for the subsequent development of tuberculosis.

The radiographic findings that constitute evidence of prior tuberculosis are upper lobe opacities, often with volume loss. Patients with radiographic findings of healed primary tuberculosis (e.g., calcified solitary pulmonary nodules, calcified hilar lymph nodes, and pleural thickening) are not at increased risk for tuberculosis compared with persons with normal chest radiographs.

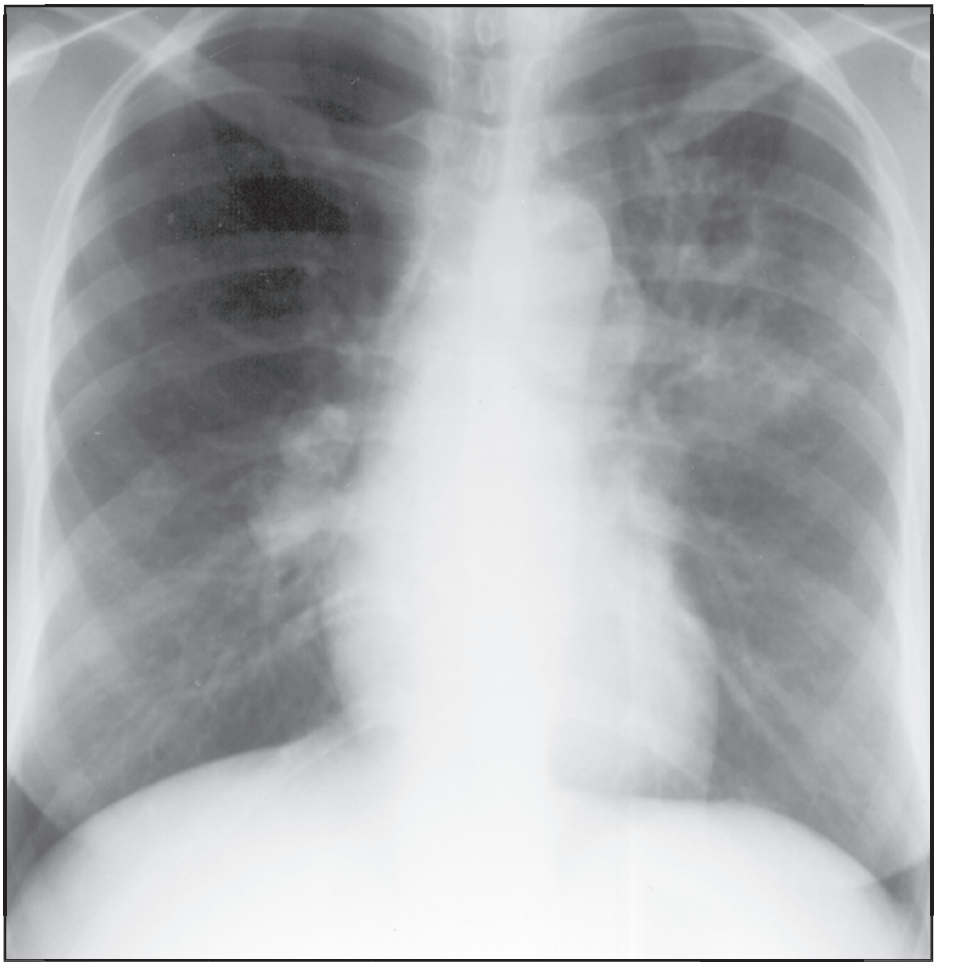
Disease activity cannot be determined from a single chest radiograph. Unless previous radiographs show that the abnormality has not changed, sputum examination should be performed to assess the possibility of active tuberculosis. Once active tuberculosis has been excluded, current recommendations for treatment of latent tuberculosis infection in persons with radiographic evidence of prior tuberculosis include isoniazid alone for 9 months or 4 months of rifampin (preferably with isoniazid).

The decision to initiate multidrug antituberculosis treatment at the initial evaluation should be based on the degree of clinical suspicion for active tuberculosis. If suspicion for active tuberculosis is high, multidrug therapy should be initiated before smear/culture results are known. If suspicion is low, treatment can be deferred until later when additional data have been obtained to clarify the diagnosis.

Case Four

A 32-year-old male patient with AIDS presents with a history of fever, cough, dyspnea, and night sweats for the past 3 weeks. His last CD4 lymphocyte count was 200 cells/μL. His radiograph is shown in *Figure 3.5*.

Figure 3.5



1. How would you describe the chest radiograph in *Figure 3.5?*

2. Based on the clinical presentation and your reading of the chest radiograph, what would be the **least** likely diagnosis?

   A. Tuberculosis
   B. Fungal infection
   C. *Pneumocystis carinii* pneumonia
   D. *Mycobacterium kansasii* disease

Case Four Answers

1. Left upper lobe consolidation with areas of cavitation and mediastinal and hilar lymphadenopathy. Note the lymphadenopathy in the aortopulmonary window.

2. The correct answer is **C.** Infection with *P. carinii* does not usually cause lymphadenopathy, although cavitation can occur. Tuberculosis is a classic cause of cavitation and lymphadenopathy, but nontuberculous mycobacteria such as *M. kansasii* can present with identical radiographic findings. Finally, fungal infections can cause cavitation and lymphadenopathy and thus need to be included in the differential diagnosis as well.

Case Four Summary

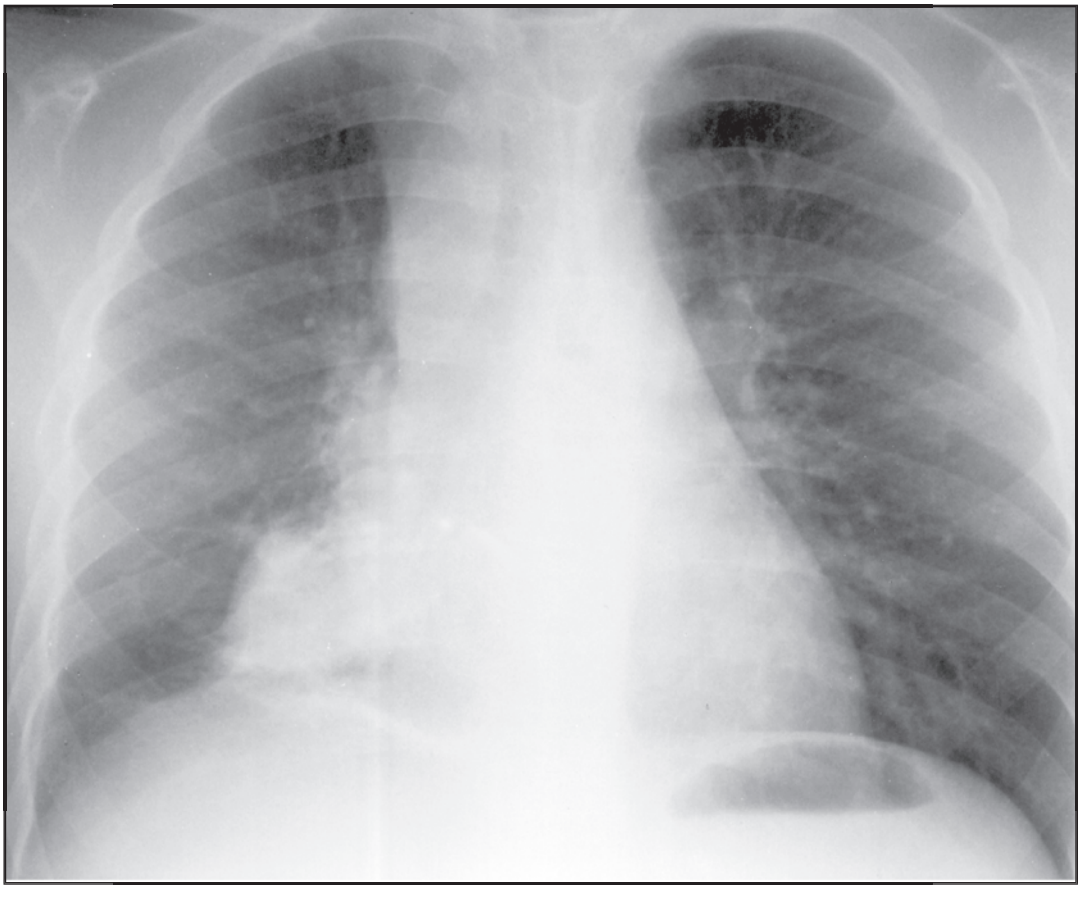
The patient had three acid-fast smears which were positive and the cultures grew *M. tuberculosis*. He was started on directly observed therapy with four antituberculosis medications.

HIV-infected patients who develop pulmonary disease often present challenging diagnostic dilemmas to clinicians. One reason is the myriad radiographic appearances the same infection can take in an HIV-infected individual. For example, tuberculosis in an HIV-infected person can appear as lower lung zone involvement, lymphadenopathy, and pleural effusion instead of the more typical post-primary reactivation pattern of upper lobe cavitary disease. As a general rule, the more immunosuppressed the patient, the more atypical the chest radiograph findings with respect to tuberculosis. Proper interpretation of the chest radiograph is critical in such patients to help guide the diagnostic evaluation. The presence of cavitation and lymphadenopathy in this patient made tuberculosis and other mycobacterial and fungal infections much more likely than *P. carinii* pneumonia.

Case Five

The patient is a 4-year-old child who presents to a local hospital with a cough and wheezing. The child has no underlying medical conditions. He has recently been exposed to several cases of tuberculosis in his family. His chest radiograph is shown in *Figure 3.6*.

Figure 3.6



1. How would you describe the chest radiograph in *Figure 3.6?*

2. What would be the **most** appropriate next step?

   A. Perform bronchoscopy to obtain a good respiratory specimen
   B. Collect three sputum specimens for acid-fast smears and cultures
   C. Begin a broad-spectrum antibiotic for community-acquired pneumonia
   D. Begin multidrug antituberculosis therapy

Case Five Answers

1. Right paratracheal and hilar adenopathy and right lower lung zone consolidation with probable volume loss.

2. The correct answer is ***D.*** Any child with lymphadenopathy on the chest radiograph and recent exposure to adults with tuberculosis should be started on antituberculosis therapy. The yield from bronchoscopy is low, and the procedure is not always readily available. It can be very difficult to obtain sputum specimens from a young child. The presence of lymphadenopathy is unlikely to be due to community-acquired pneumonia. Definitive microbiological diagnosis is best made in children by obtaining aspirates of gastric secretions.

Case Five Summary

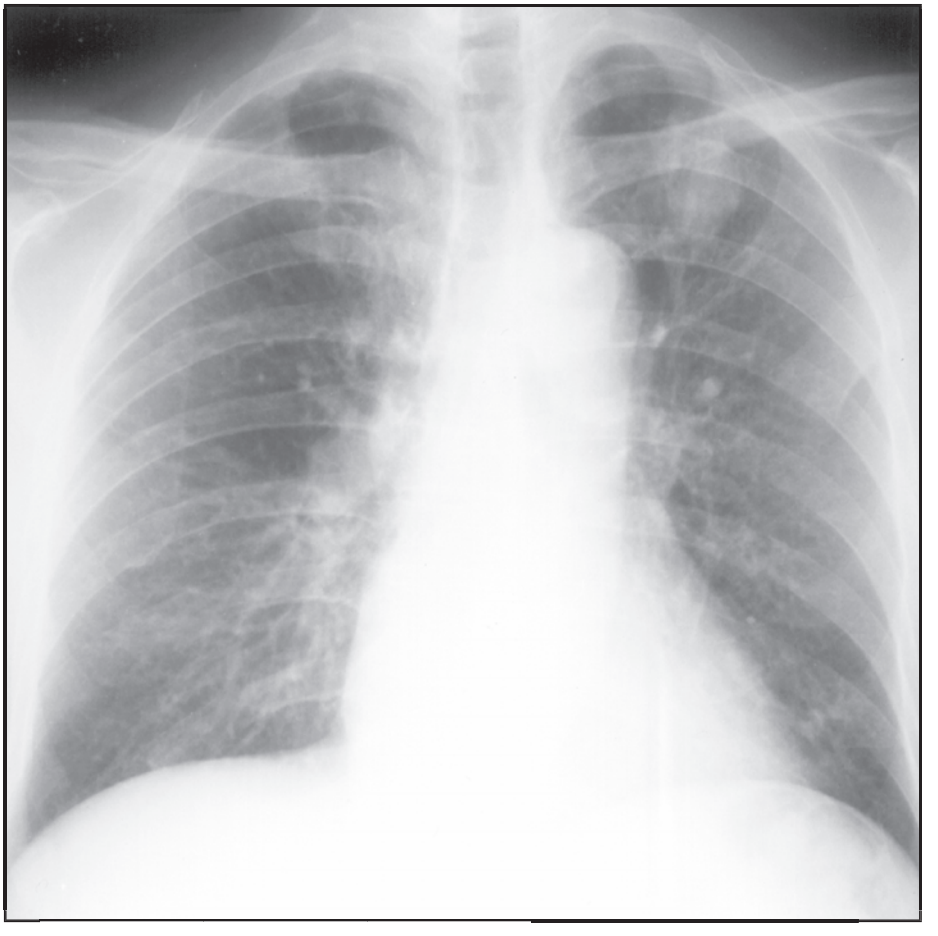
It is often challenging to establish a diagnosis of tuberculosis in children because of difficulties in obtaining sputum or other diagnostic specimens. Symptom review and chest radiographs of children who have recently been in contact with adults with active tuberculosis should be carefully evaluated to detect evidence of active disease.

Findings suggestive of active tuberculosis include lymphadenopathy. Children in whom active tuberculosis is suspected on the basis of either symptoms or radiographs should have treatment with antituberculosis therapy started. The best way to establish a diagnosis of pulmonary tuberculosis in children is from clinical and radiographic evidence and identification of a source case. Microbiological confirmation is frequently not available but is most likely to come from cultures of gastric aspirates. Cultures of gastric secretions are positive for *M. tuberculosis* in up to 40% of cases of pulmonary tuberculosis in children. When susceptibility results from the source case are imminent, gastric aspirates do not always need to be collected from the child.

Case Six

A 71-year-old man is evaluated because of a 1-month history of a cough with occasional blood-streaked sputum. He denies fever or weight loss. He used to smoke cigarettes but stopped 23 years previously. He thought he was treated for tuberculosis in the past, but he is unable to provide any details of the therapy. The man arrived in the United States from the Philippines 8 months ago. The physical exam is unremarkable. A tuberculin skin test shows 11 mm in induration. No prior radiographs are available. Three sputum smears are negative for acid-fast bacilli. His chest radiograph is shown in *Figure 3.7.*

Figure 3.7



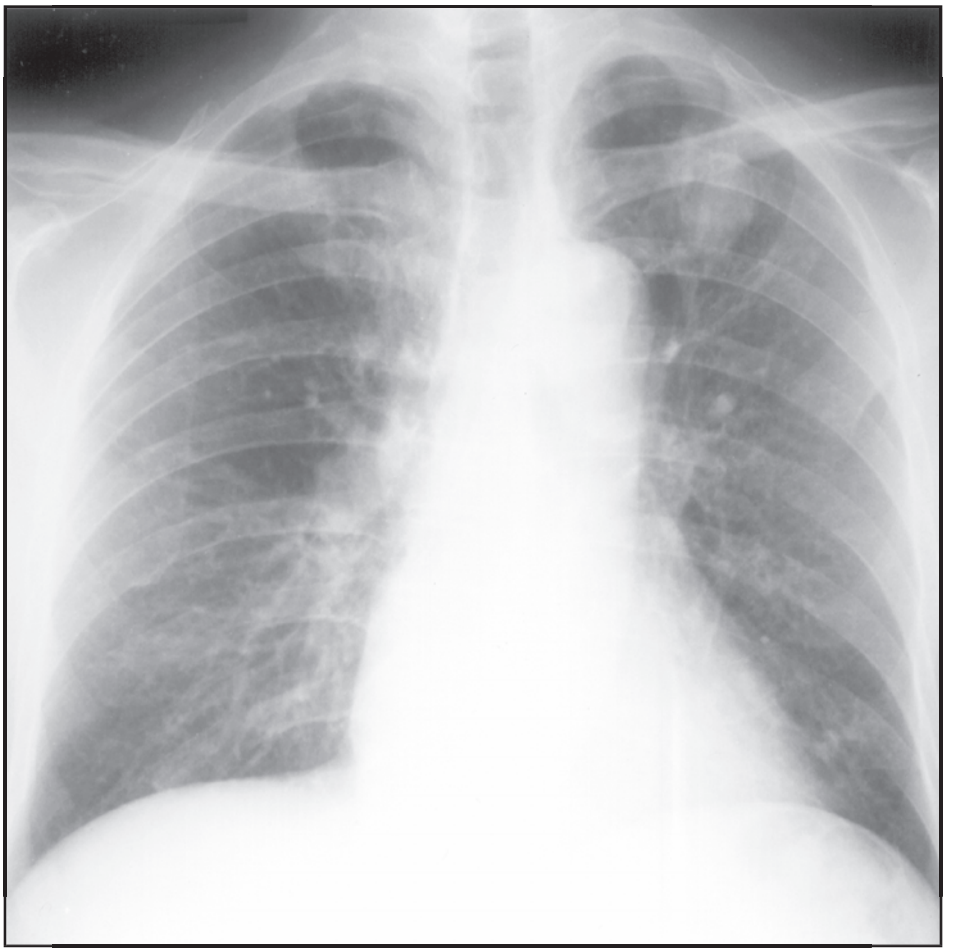
1. How would you describe this chest radiograph?

2. Which of the following would you do next?

   A. Begin isoniazid for treatment of latent tuberculosis infection
   B. Perform direct amplification test of sputum for *M. tuberculosis* complex
   C. Repeat chest radiograph in six months
   D. Begin multidrug therapy for tuberculosis

The patient was begun on multidrug therapy for tuberculosis. All sputum cultures were negative for mycobacteria and the patient still had intermittent hemoptysis. A repeat chest radiograph was taken 3 months after therapy started and is shown in *Figure 3.8.*

Figure 3.8 - After 3 Months



3. How would you describe the second chest radiograph in *Figure 3.8?*

4. What is the **most** appropriate next action?

A. Continue isoniazid, rifampin, ethambutol, and pyrazinamide for an additional 3 months
B. Continue isoniazid and rifampin for an additional 3 months
C. Obtain a CT of the chest
D. Stop all medications and schedule for repeat chest radiograph in 3 months

Case Six Answers

1. Left upper lobe focal rounded mass with crescent-shaped air collection in its superior aspect.

2. The correct answer is ***D,*** begin multidrug therapy for tuberculosis. Clinical suspicion for active tuberculosis is high in this case, so multidrug therapy should be started. Isoniazid alone should not be started in someone suspected of having active tuberculosis. The direct amplification tests perform best in smear-positive specimens and may not be available in all areas. A repeat chest radiograph in 6 months would be too long an interval for follow-up.

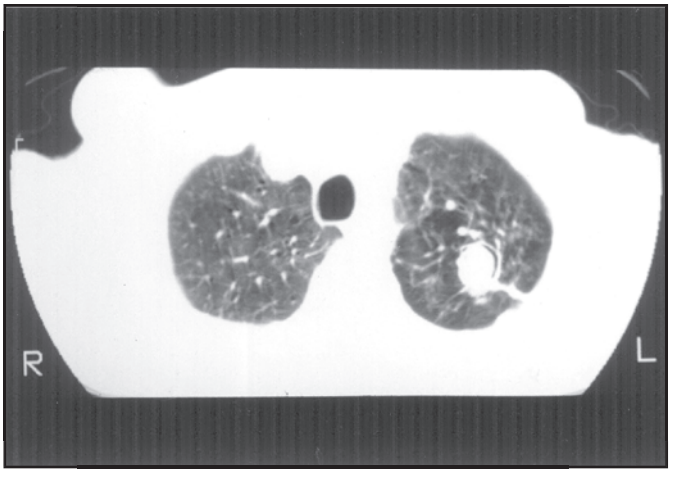
3. Left upper lobe focal rounded mass with crescent-shaped air collection in its superior aspect. There has been no significant change from the prior radiographs.

4. The correct answer is ***C,*** obtain chest CT. This patient's radiographic abnormality has not changed despite 3 months of empirical antituberculosis therapy. Therefore, the patient *does not* have active tuberculosis. However, he could have another disease process so the work-up should continue. A chest CT scan would be the most appropriate test.

Case Six Summary

The first step in approaching a patient with a positive tuberculin skin test and an abnormal chest radiograph is to obtain sputum for acid-fast smears and cultures. Treatment should be given if clinical suspicion for active tuberculosis is high. If cultures do not yield tuberculosis and the patient does not exhibit a clinical or radiographic response to treatment, then the chest radiographic abnormality does not represent active tuberculosis, and another diagnosis should be pursued.

The CT scan (shown below) indicates that the radiographic abnormality is a mycetoma, which is a fungus ball that develops in a preexisting cavity (in this case, as a result of prior tuberculosis). When a patient with a mycetoma develops massive hemoptysis, lung resection is the procedure of choice for definitive treatment.



Case Seven

The patient is a 62-year-old man from India with a 3-month history of fevers, night sweats, intermittent cough, and a 10-kilogram weight loss. His chest radiograph is shown in *Figure 3.9*.

Figure 3.9

1. Describe the radiograph in *Figure 3.9* using standard terminology.

2. Which of the following diagnostic tests has the highest sensitivity for identifying *M. tuberculosis* in this patient?

   A. Mycobacterial cultures of blood
   B. Mycobacterial cultures of sputum
   C. Mycobacterial cultures of transbronchial biopsies
   D. Mycobacterial cultures of bronchoalveolar lavage fluid

Case Seven Answers

1. The radiograph in *Figure 3.9* shows multiple well-defined, small nodules, mostly 2–3 mm in diameter, that are widespread in distribution.

2. The correct answer is ***C.*** The diagnostic yield of tuberculosis from transbronchial biopsy (combining both histology and culture) is 50–70% in patients with miliary disease. This patient has a miliary pattern on his chest radiograph. This pattern is found in patients with disseminated tuberculosis and can also be seen in disseminated fungal infections and some malignancies. Miliary nodules result from hematogenous dissemination rather than endobronchial spread. As a result, the diagnosis of patients with miliary tuberculosis can be difficult to establish on the basis of sputum studies alone. The culture yield from sputum for miliary tuberculosis is <30%. Cultures of bronchoalveolar lavage fluid improve upon this slightly and are positive in up to 40% of patients with miliary tuberculosis. Blood cultures are uncommonly positive (<10%) in patients with miliary tuberculosis.

Case Seven Summary

Miliary tuberculosis is a classic radiographic manifestation of disseminated tuberculosis and consists of the presence of small nodules on the chest radiograph. Miliary nodules are defined by multiple, small discrete opacities, mostly 2 mm in diameter, that are widespread in distribution. The miliary pattern results from hematogenous dissemination of tubercle bacilli, which explains its widespread distribution. It is not specific for tuberculosis and can also be seen in disseminated fungal infections and some malignancies (e.g., renal cell carcinoma). Because the miliary pattern is an example of an interstitial pattern, transbronchial tissue provides the highest diagnostic yield. Transbronchial tissue should be examined for the presence of granulomas and cultured for mycobacteria (yield: 50–70%). Because miliary tuberculosis almost always involves other organs, diagnostic alternatives include biopsies of bone marrow (especially in patients with cytopenias) and liver (especially in patients with elevated serum alkaline phosphatase), and cultures of urine. Given the high mortality of disseminated tuberculosis, evaluation should occur without delay.

Case Eight

The patient is a 54-year-old woman with a 5-week history of a cough productive of foul-smelling sputum, fever and night sweats. Medical problems include a history of chronic obstructive pulmonary disease and heavy alcohol use. Her last tuberculin skin test 3 years ago had 13 mm of induration. Her chest radiographs are shown in *Figures 3.10a* and *3.10b*.

Figure 3.10a, Frontal

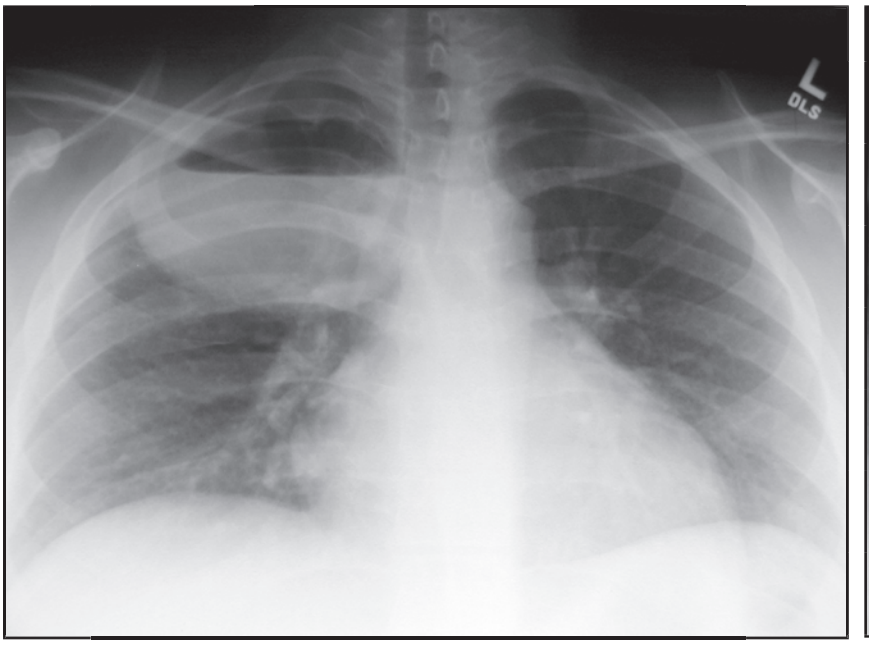
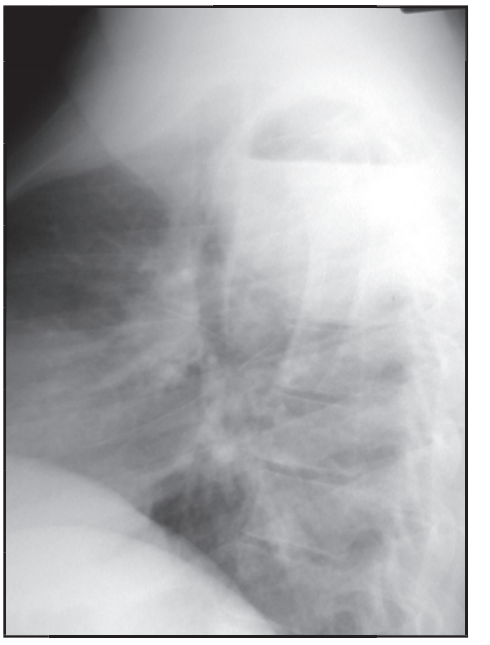


Figure 3.10b, Lateral



1. Describe the radiographs *Figures 3.10a* and *3.10b* using standard terminology.

2. Which of the following would be the **most** appropriate treatment for this patient?

   A. Doxycycline
   B. Clindamycin
   C. Isoniazid, rifampin, pyrazinamide, and ethambutol
   D. Fluconazole

Case Eight Answers

1. The radiographs in *Figures 3.10a* and *3.10b* show a large air-filled spherical density in the right upper lobe that has an air-fluid level.

2. The correct answer is ***B.*** The differential diagnosis of an air-fluid level in the chest includes lung abscess and other pyogenic infections, tuberculosis, hemorrhage into a bulla or cyst, bronchogenic cancer, and noninfectious cavitary lung disease (e.g., Wegener's granulomatosis). In this case, lung abscess is more likely than the other diagnostic possibilities given the symptoms of foul-smelling sputum, and radiographic findings of a thick-walled cavity with an air-fluid level and absence of surrounding infiltrate. Antibiotics like doxycycline do not provide sufficient anaerobic bacterial coverage to be useful for treating a lung abscess. Fluconazole (choice *D*) should not be used unless a fungal infection is found to be the cause.

Case Eight Summary

It is important to identify and properly characterize focal lucent areas on the chest radiograph. There are many causes of focal lucent lesions on chest radiographs, but diseases that result in cavitation are among the most important. Causes of pulmonary cavitation include tuberculosis, lung abscess, pulmonary infarction, bronchogenic cancer, and non-infectious inflammatory diseases (e.g., Wegener's granulomatosis). These diseases have different clinical presentations, so obtaining a good history is an important first step. The next step in the diagnostic evaluation is usually collecting sputum for microbiologic studies and cytologic examination. Patients should also be placed in respiratory isolation if tuberculosis is suspected on the basis of either the radiographic findings or clinical examination.

Conclusion

These cases demonstrate important principles regarding the interpretation of chest radiographs and the diagnosis and treatment of tuberculosis. One such principle is that it is essentially impossible to distinguish active from inactive tuberculosis from a single chest radiograph. Therefore, sputum should be obtained in any patient with an abnormal chest radiograph in whom a diagnosis of tuberculosis is being considered.

The radiographic findings that constitute evidence of prior tuberculosis are upper lobe opacities, often with volume loss. Persons with radiographic findings of healed primary tuberculosis (e.g., calcified solitary pulmonary nodules, calcified hilar lymph nodes, and pleural thickening) are not at increased risk for tuberculosis compared with persons having normal chest radiographs.

Another basic principle is that if clinical suspicion is high that a patient has active tuberculosis, treatment should be administered immediately rather than waiting for culture confirmation, which can take up to 8 weeks. If cultures cannot be obtained or are negative for tuberculosis, a follow-up clinical and radiographic evaluation can be extremely helpful in determining whether active disease is present. If there is either a clinical response to antituberculosis treatment or significant improvement in the chest radiograph after 2–3 months of treatment, and no other etiology is identified, treatment should be continued for active tuberculosis.

Once active tuberculosis has been excluded (i.e., no clinical or radiographic response to treatment and negative cultures), current recommendations for treatment of latent tuberculosis infection in patients with radiographic evidence of prior tuberculosis include isoniazid alone for 9 months or 4 months of rifampin (preferably with isoniazid).

Proper interpretation of the chest radiograph is an essential component of the diagnostic evaluation. For example, the radiographic finding of miliary nodules signifies disseminated tuberculosis because it results from hematogenous spread of tubercle bacilli. Because the miliary pattern is an example of an interstitial pattern, bronchial tissue (best obtained by transbronchial biopsies) provides the highest diagnostic yield and should be both examined for the presence of caseating granulomas and cultured for acid-fast organisms.

Children and HIV-infected persons with tuberculosis often present challenging diagnostic and treatment dilemmas for clinicians. It is often quite difficult to establish a definitive microbiological diagnosis in children, so clinical suspicion is usually the reason treatment is started. Clinical suspicion for tuberculosis in children is often based on a positive tuberculin skin test and an abnormal chest radiograph showing lymphadenopathy.

The treatment of HIV-infected patients with tuberculosis can be complicated by 1) drug interactions between rifamycins, such as rifampin or rifabutin, and antiretroviral therapy such as protease inhibitors and nonnucleoside reverse transcriptase inhibitors; and 2) paradoxical reactions as a result of immune reconstitution, particularly if they are taking antiretroviral therapy. Clinicians should seek the advice of experts in the care of HIV-infected persons with tuberculosis if these issues arise.

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