REVIEW ARTICLE

Pulmonary Tuberculosis. Important role of Imaging in Diagnosis and Management

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■ INTRODUCTION

Tuberculosis (TB) is a worldwide public health problem, particularly among immunocompromised patients and other high-risk groups.(1,2)

TB is an infectious disease caused by *Mycobacterium tuberculosis* (MTB). *M. tuberculosis* commonly affects the lungs, but it may affect almost any organ system, including the lymph nodes, central nervous system, liver, bones, genitourinary tract, and gastrointestinal tract. TB is highly transmissible through respiratory droplets.(2)

The most common site for the development of TB is the lungs; 85% of patients with TB present with pulmonary complaints. Extrapulmonary TB may present with primary infection or reactivation.(2)

Extrapulmonary tuberculosis results from hematogenous or direct spread from adjacent organs. Most extrapulmonary disease is not contagious, with the exception of laryngeal tuberculosis. No evidence of tuberculosis may be seen on chest radiographs.

Immunocompromised individuals and young children are at higher risk of extrapulmonary disease. Miliary tuberculosis is a hematogenously disseminated disease characterized by numerous tiny lesions, measuring 1–3 mm, which can involve multiple organs such as the lungs, liver, spleen, and central nervous system.(1)

Common extrapulmonary sites are the following: a) mediastinal, retroperitoneal, and cervical (scrofula) lymph nodes– the most common site of tuberculous lymphadenitis (scrofula) is in the neck, along the sternocleidomastoid muscle; it is usually unilateral and causes little or no pain; advanced cases of tuberculous lymphadenitis may suppurate and form a draining sinus; b) vertebral bodies; c) adrenals; d) meninges and e) gastrointestinal tract.(2)

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Tuberculosis infects an estimated one-third of the world's population, thereby, the disease is a major public health issue.(1,2, 3) Every year 9 x 10^6 people become infected and 1.5 x 10^6 people die of tuberculosis every year. Among communicable diseases, TB is the second leading cause of death worldwide after HIV/AIDS, killing nearly 2 x 10^6 people each year; approximately 13% of TB patients have coexistent HIV infection.(4)

Tuberculosis is a disease likely as old as humanity itself. (4,5) Aristotle is credited as being the first to recognize the contagious nature of the disease, but discovery of the specific infectious agent, the tubercle bacillus *Mycobacterium tuberculosis*, did not occur for several more centuries until it was isolated by Robert Koch in 1882.(6)

In countries where the standard of living is low and health resources are scarce, the risk of infection is highest with 80% of cases involving persons in their productive years (15–59 years of age).(7)

Airborne mycobacteria are transported by droplets 1--5 µm in diameter, which can remain suspended in the air for several hours when a person with active tuberculosis coughs, sneezes, or speaks.(1, 8)Not all individuals exposed to tuberculosis are infected. The probability of transmission to another individual depends on the infectiousness of the tuberculosis source, the environment and duration of exposure, and the immune status of the exposed individual. (1,8) The airborne droplets reach the terminal airspaces by means of inhalation, where the droplets infect alveolar macrophages. In approximately 5% of infected individuals, the immune system is inadequate at controlling the initial infection, and active tuberculosis develops within the first 1–2 years; (1,7) this category is referred to as primary tuberculosis. In another 5% of infected individuals, the immune system is effective at controlling the initial infection, but viable mycobacteria remain dormant and reactivate at a later time;(1,8) this category is referred to as post primary or reactivation tuberculosis. The remaining 90% of individuals will never develop symptomatic disease and will harbor the infection only at a subclinical level,

which is referred to as latent tuberculosis infection. These individuals are asymptomatic and noncontagious. In latent infection, the host immune response prevents the multiplication and spread of mycobacteria. The immune response to mycobacteria has important implications for the clinical and imaging appearance of tuberculosis, particularly in immunocompromised patients.

■ RISK FACTORS

Clinical suspicion of tuberculosis increases in patients with various risk factors. Thus, any individual at high risk is eligible for targeted tuberculosis testing to identify and treat patients with latent infection, prevent the development of active disease, and prevent further spread of tuberculosis. (1,8)

Risk factors for tuberculosis can be grouped into two categories:
1. factors causing increased risk of exposure to tuberculosis,
2. factors increasing the risk of developing active disease.

Once a person is infected, individuals at increased risk of exposure include: 1) people from endemic regions (Asia, Africa, Russia, Eastern Europe, and Latin America); 2) people with low income and limited access to health care; 3) intravenous drug users and 4) health care workers.(1,8)

Risk factors associated with higher risk of progression to active tuberculosis include: 1) age less than 4 years; 2) intravenous drug use; 3) recent tuberculosis infection or test conversion within the past 2 years and 4) immunodeficiencies, such as those resulting from human immunodeficiency virus (HIV/AIDS) infection, organ transplantation, and treatment with immunosuppressive drugs.

HIV infection is the strongest known risk factor for developing active tuberculosis, with a risk of 7%–10% per year.(1,7) Patients treated with biological agents, such as therapy with inhibitors of tumor necrosis factor α for autoimmune disorders, have a higher risk of reactivation;(8) increasing use of these drugs means that radiologists will need to search for tuberculosis in these patient populations. Other conditions that can increase the risk of active disease include diabetes mellitus, silicosis, chronic renal failure, low body weight, prior gastrectomy or jejunoileal bypass, alcohol or tobacco abuse, and certain malignancies (leukemia, head and neck carcinoma, and lung carcinoma)

■ THE TRADITIONAL VERSUS THE NEW CONCEPT OF ETIOPATHOGENESIS AND IMAGING MANIFESTATIONS OF TUBERCULOSIS

Traditionally, TB findings have been described as primary infection that occurs in patients, who develop disease after initial exposure to TB bacilli; whereas patients who develop disease as a result of reactivation of a previous focus of TB are considered to have reactivation or post primary TB. Primary TB and secondary TB are thought to be two distinct entities on the basis of clinical, pathologic, and imaging findings. Primary tuberculosis was considered a disease of childhood, and post primary tuberculosis was thought to always represent reactivation of latent infection in adults.

More-effective therapies and the declining prevalence of tuberculosis in developed countries, result in 23%–34% of adult tuberculosis cases in developed countries being actual primary tuberculosis.(9,10) With regard to post primary tuberculosis, evidence suggests that patients in endemic areas are more likely to be infected by a second strain of tuberculosis than to experience reactivation of a previously acquired strain.(11,12) In contrast, reactivation causes the majority of cases of post primary tuberculosis in developed countries; although, a second infection is responsible for a small fraction of cases.(13) The clinical and imaging manifestations of tuberculosis may be more related to host factors, particularly immunosuppression, than to the mechanism of infection.(14) Generally, although there are several different forms of active tuberculosis, it is more important to distinguish between active and latent tuberculosis than to distinguish between primary and post primary tuberculosis. Most of the current literature still uses the traditional TB lexicon as “primary” and “post primary/reactivation” TB.

However, this concept has recently been challenged by DNA fingerprinting and genotyping of *M. tuberculosis* isolates. (15)

■ CLINICAL PRESENTATION

Active disease may initially manifest with minimal symptoms only, but later develop during the course of several months. (16) Typical symptoms of active tuberculosis include:
a) productive cough, b) hemoptysis, c) weight loss, d) fatigue, e) malaise, f) fever, and g) night sweats.(1,16)

The insidious and nonspecific nature of symptoms means that physicians caring for these patients must maintain a high suspicion level based on the risk factors. Radiologists

Clinical manifestations of extrapulmonary tuberculosis

TB lymphadenitis	Enlarged cervical or supraclavicular lymph nodes.
Tuberculous meningitis	Persistent or intermittent headache for 2--3weeks. Mental status changes, coma.
Skeletal TB	The spine is the most common site (Pott disease). Back pain, stiffness, lower extremity paralysis, 50% occurrence.
Tuberculous arthritis	Involves joints, more commonly hips and knees. Pain precedes radiographic changes.
Genitourinary TB	Flank pain, dysuria, and frequent urination. Men may present with painful scrotal mass, prostatitis, orchitis, or epididymitis. In women, the condition may mimic pelvic inflammatory disease. Accounts for 10% of sterility in women worldwide and 1% of women in industrialized countries.
Gastrointestinal TB	TB may infect any site along the gastrointestinal tract. TB can present as non-healing ulcers of the mouth or anus, difficulty swallowing, abdominal pain (peptic ulcer-like), malabsorption, pain diarrhea, or hematochezia(2).

Classification of tuberculosis on the basis of clinical and radiologic findings

Class	Definition	Clinical history	Laboratory test results	Chest radiography
0	No exposure to tuberculosis, no infection	No history of exposure	Negative tuberculin skin test or interferon-γ release assay	No evidence of disease
1	Exposure to tuberculosis, no infection	History of exposure	Negative tuberculin skin test or interferon-γ release assay (at least 10 weeks after exposure)	No evidence of disease
2	Latent tuberculosis infection; no tuberculosis disease	No clinical evidence of disease	Positive tuberculin skin test or interferon- γ release assay; negative bacteriologic examination (if done)	No evidence of active disease
3	Active tuberculosis disease (current)	Meets criteria for active clinical case	Meets current laboratory criteria (e.g. positive culture)	Radiographic evidence of active disease
4	Previous tuberculosis disease (inactive)	Medical history of tuberculosis; no evidence of active disease	Positive results of tuberculin skin test or interferon- γ release assay; negative bacteriologic examination results (if done)	Abnormal but stable radiographic findings; no evidence of active tuberculosis.
5	Tuberculosis suspected; Diagnosis pending	Ongoing evaluation for active tuberculosis on the basis of clinical, laboratory and/or radiographic findings	–	–

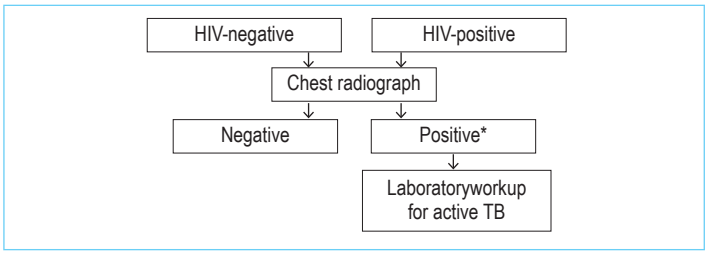
can aid in diagnosis by performing imaging examinations, sometimes even incidentally in absence of clinical suspicion.

■ ACTIVE TUBERCULOSIS

Imaging has a relevant role in the initial evaluation of patients suspected of having active tuberculosis.

If tuberculosis is not initially suspected clinically but radiographic or computed tomography (CT) findings are uncertain for active tuberculosis, then further workup for active tuberculosis is warranted. Regardless of the indication, any radiologic finding that raises the possibility of active tuberculosis should prompt immediate communication with the referring provider, so that patients may be placed in respiratory isolation until negative results of sputum staining are obtained. Infection prevention personnel should also be notified, where such a system is in place, to ensure that patients with active tuberculosis and their close contacts are managed appropriately.

Algorithm for the evaluation of active tuberculosis(1,17)



* Radiographic findings may be normal in HIV-positive patients, despite the presence of active disease.

■ PRIMARY TUBERCULOSIS

As the name indicates, primary TB is seen in patients not previously exposed to *M. tuberculosis*. It is most common in infants and children and has the highest prevalence in children less than 5 years of age. (4,7,18)

It should be noted that the prevalence of primary TB in adults is increasing now, accounting for 23% to 34% of all adult cases of TB (4,20)

Mediastinal and hilar lymphadenopathy are the most common radiologic manifestations of primary tuberculosis.(7)

Radiographic evidence of lymphadenopathy is seen in up to 96% of children and 43% of adults. Lymphadenopathy is typically unilateral and right-sided, involving the hilum and right paratracheal region; though, it is bilateral in about one-third of cases (Fig. 1). CT is better at detecting nodal disease, and oftentimes, nodes greater than 2 cm in diameter may display a low-attenuation center secondary to necrosis, sometimes with a peripheral rim of enhancement due to granulomatous inflammatory tissue (Fig. 2).(1,4) These findings are highly suggestive of active disease.(20,21,22) Although lymphadenopathy is usually associated with other manifestations of TB, it may be the sole radiographic feature, a finding more common in infants, which decreases in frequency with increasing age.(20)

The differential diagnosis of necrotic lymphadenopathy includes non tuberculous mycobacterial infection, lymphoma, and metastatic carcinoma.(20) At resolution of lymphadenopathy, calcified normal-sized lymph nodes may remain.

Besides lymphadenopathy, primary tuberculosis at imaging can also manifest as parenchymal disease, miliary disease and pleural effusion.(1,4,20)

PARENCHYMAL DISEASE

It manifests most frequently as consolidation depicted as an area of opacity in segmental or lobar distribution (Fig 3).(1,7,23) There is no strong lobar predilection in primary tuberculosis.(23) Primary infection can be anywhere in the lung in children, whereas there is predilection for the upper or lower zone in adults.(23) Predominance in the lower and middle lobes (areas of greatest ventilation) is suggestive of the disease, especially in adults.(4) Tuberculous consolidation is often indistinguishable from that of bacterial pneumonia; however, it can be differentiated from bacterial pneumonia by radiographic evidence of lymphadenopathy and lack of response to conventional antibiotics.(4) In children less than 2 years of age, lobar or segmental atelectasis is often seen, typically involving the anterior segment of an upper lobe or the medial segment of the middle lobe, usually

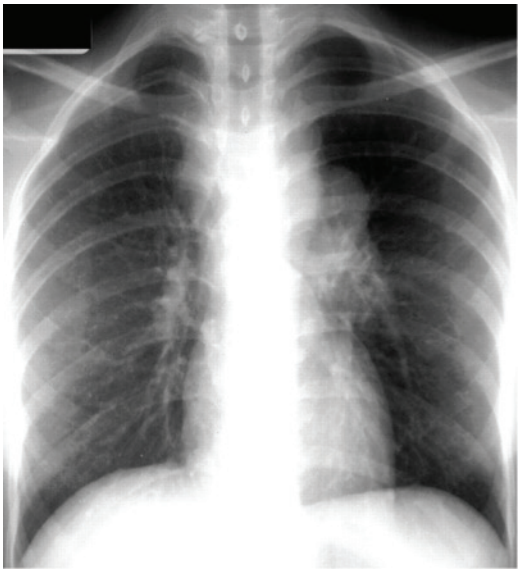


Fig. 1 There is a bulky left hilum and right paratracheal mass, findings consistent with lymphadenopathy in a patient with primary tuberculosis (typical in pediatric patients).

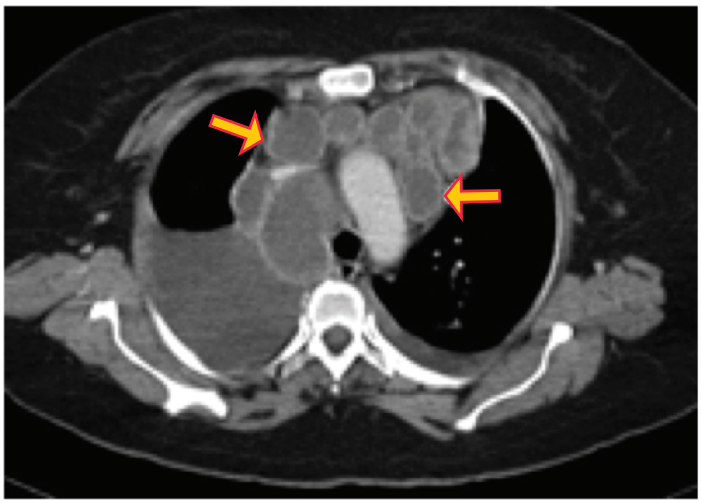


Fig. 2 A conglomerate of mediastinal lymphadenopathy with peripheral rim of enhancement and right pleural effusion can be observed.

resulting from adjacent lymphadenopathy and compressive effects.(4) Cavitation occurs in a minority of patients with primary tuberculosis (29% in one series) (1,23) and when cavitation occurs, it is known as progressive primary disease. (1,7) Cavitation occurs within existing consolidation and thus, does not demonstrate upper lung zone predominance, in contrast with post primary disease.(1,7) Resolution of pulmonary consolidation is generally slow, taking as long as two years, and in many cases, residual opacities are seen. (1,18,20) After resolution, residual parenchymal scarring can be observed at sites of prior consolidation in 15%–18% of patients and is referred to as Ghon focus, or Ghon tubercle.(1,4,18,20) In addition, mass-like opacities called tuberculomas are present in approximately 9% of cases, which may cavitate and undergo calcification.(4,19, 20, 22, 24) The combination of calcified hilar nodes and a Ghon focus is called a Ranke complex and is suggestive of previous

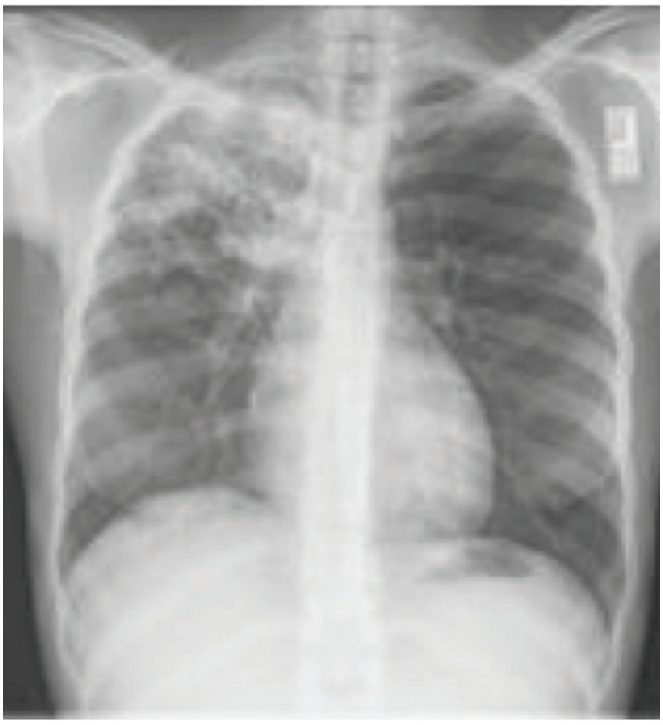


Fig. 3 Patchy areas of airspace opacity of the right upper lobe consistent with tuberculosis.

TB, although it can also result from histoplasmosis.(4)

Pleural effusion

Seen in approximately 25% of primary tuberculosis cases in adults; the vast majority of such effusions are unilateral (Fig. 4).(1,23) It is less common in children and may only appear in 6%–11% of pediatric cases; prevalence rises with increasing age.(1,7, 18) Pleural effusion is also less common in post primary disease (approximately 18% of cases). (1,20) Tuberculous pleural effusions usually result from hypersensitivity to tuberculous protein, rather than frank pleural infection; and, therefore, isolation of *M. tuberculosis* from pleural fluid is uncommon.

Cytological examination of the pleural fluid typically reveals predominantly lymphocytes. Certain fluid studies, such as determination of the adenosine deaminase level in fluid, a marker of monocytes and macrophages, are useful in the diagnosis of tuberculous effusions.(1,25) If the results of fluid analyses are not definitive, a pleural biopsy can increase the diagnostic yield in these patients.(26) Pleural specimens can be searched for granulomas at histopathology examination and can be cultured for microorganisms.

Chronic, active infections of the pleural space evolve to granulomatous empyema, characterized by the thick rind of pleura with thick and irregular calcification of both parietal and visceral pleura, usually surrounding a loculated pleural fluid which contains a large number of tubercle bacilli (Fig. 5). It is different from the more common tuberculous pleural effusions, which are an inflammatory response to a localized paucibacillary pleural infection with tuberculosis.(27)

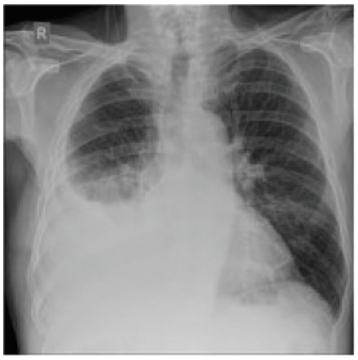


Fig. 4 Homogeneous opacity in the right lower hemithorax consistent with pleural effusion

Airway disease

Bronchial wall involvement may be observed in primary and post primary tuberculosis, although it is more common in primary TB.(1,19,28) Bronchial stenosis occurs in 10%–40% of patients with active tuberculosis and is due to direct spread from tuberculous lymphadenitis by means of endobronchial or lymphatic dissemination.(19) The main radiographic features of proximal airway involvement are indirect, including segmental or lobar atelectasis, lobar hyperinflation, mucoid impaction, and post obstructive pneumonia.(19) In CT scans, airway involvement can appear as a long narrowing segment with irregular wall thickening, luminal obstruction, and extrinsic compression (Fig. 6).(20)

Miliary tuberculosis

Hematogenous dissemination results in miliary tuberculosis, especially in immunocompromised and pediatric patients. Miliary disease may occur in primary or post primary tuberculosis. In primary tuberculosis, it often manifests as an acute, severe illness with high mortality.(29) Miliary tuberculosis may also manifest insidiously, such as with a fever of unknown origin or failure to thrive, also with relatively high mortality.(30) On chest radiograph or CT image, miliary disease manifests as diffuse, randomly distributed 1–3-mm nodules (Fig. 7, 8).

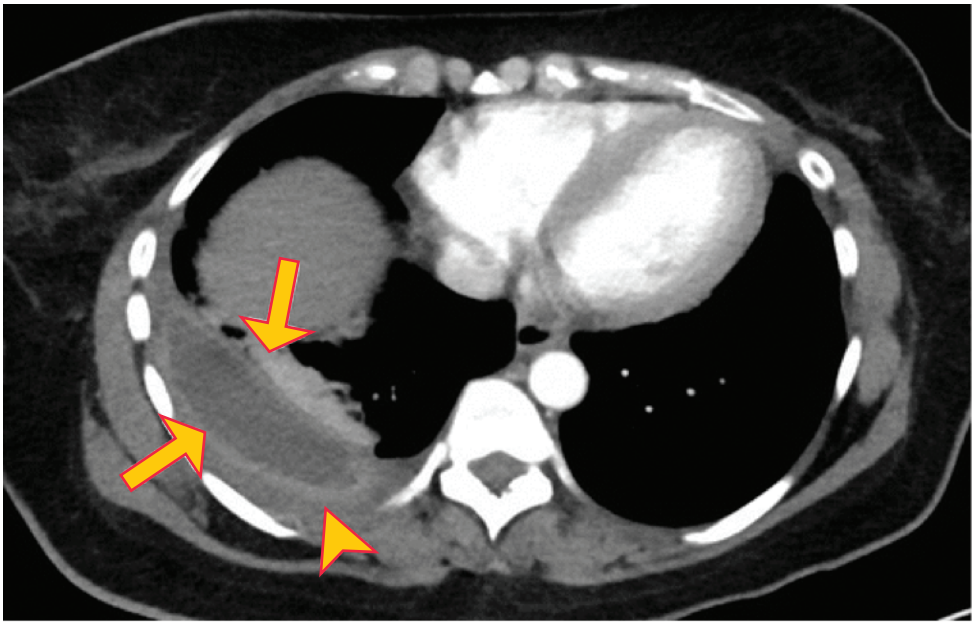


Fig. 5 Axial contrast enhanced chest CT, tuberculous empyema, loculated right-sided pleural effusion with thickened enhanced pleura and infiltration of extrapleural fat.

Post primary tuberculosis

Post primary TB (PTB) is one of the many terms (including reactivation, secondary, or adulthood TB) applied to the TB form that develops and progresses under the influence of acquired immunity. (4,23) PTB is typically thought to result from reactivation of dormant M. tuberculosis infection but may also result from a second infection with a different strain, especially in endemic areas.(11,12)

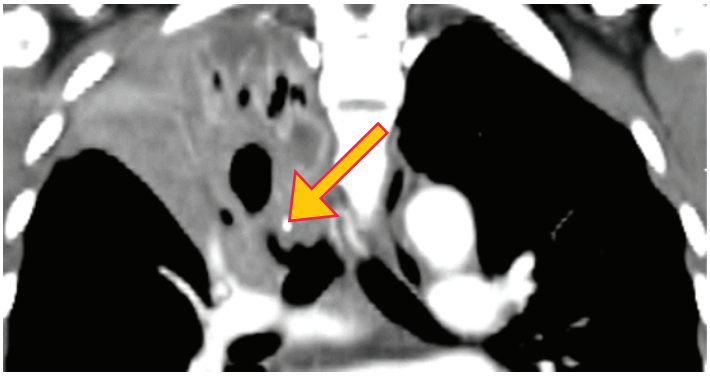


Fig. 6 Coronal contrast-enhanced reformatted chest CT image at the level of the central bronchi shows irregular thickening of the right upper lobe bronchus (arrow), as well as right upper atelectasis.

The most commonly involved parts of the lung in post primary TB are the apical and posterior segments of the upper lobe and superior segments of the lower lobes. (4,31) The predominance of the apical and upper lung zones may be related to the relatively reduced lymphatic drainage and increased oxygen tension in these regions, factors that facilitate bacillary replication.(19,32)

Patients typically present with insidious fever, cough, weight loss, and night sweats. A chest radiograph is obtained to evaluate for active disease. Chest CT may be useful in identifying active tuberculosis even if the chest radiograph is negative; although chest CT is not the standard of practice.(33)

Parenchymal consolidations in these areas of the lungs are often associated with cavitation and are the characteristic radiographic manifestations of PTB.(4,7,23) Parenchymal involvement occurs in more than one segment in most cases.(1,4,7) Commonly, in addition to the aforementioned typical locations, consolidation and fibronodular opacities may occur in

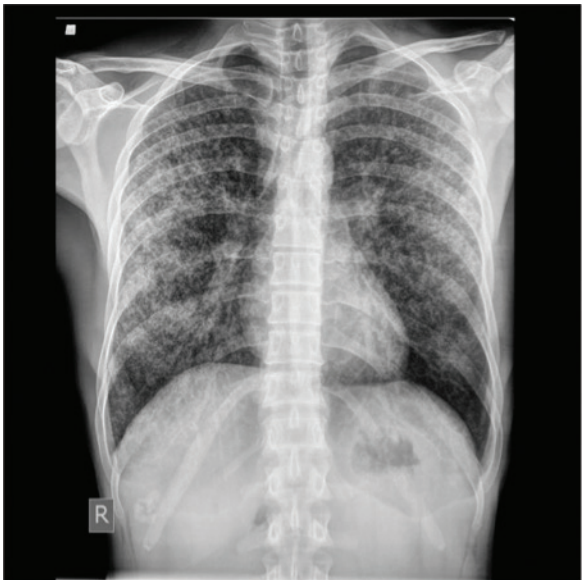


Fig. 7 Multiple tiny nodules distributed along both pulmonary fields consistent with miliary tuberculosis.

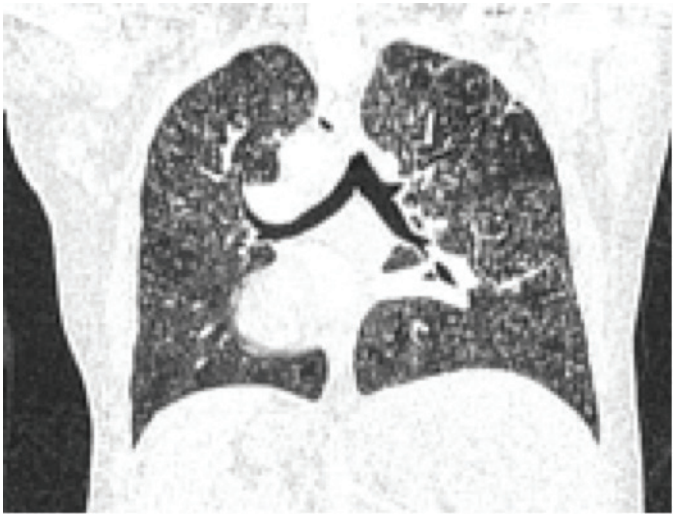


Fig. 8 Coronal reformatted plain chest CT showing multiple tiny nodules spread throughout both lungs in a patient with miliary tuberculosis.

other lobes and segments of the lungs. From 20% to 45% of patients present cavitation, which is the hallmark of post primary TB (Figs. 9, 10).(23) Walls of cavities may range from thin and smooth to thick and nodular.(23,34) Air-fluid levels have been reported to occur in 9% to 21% of tuberculous cavities.(23,34)

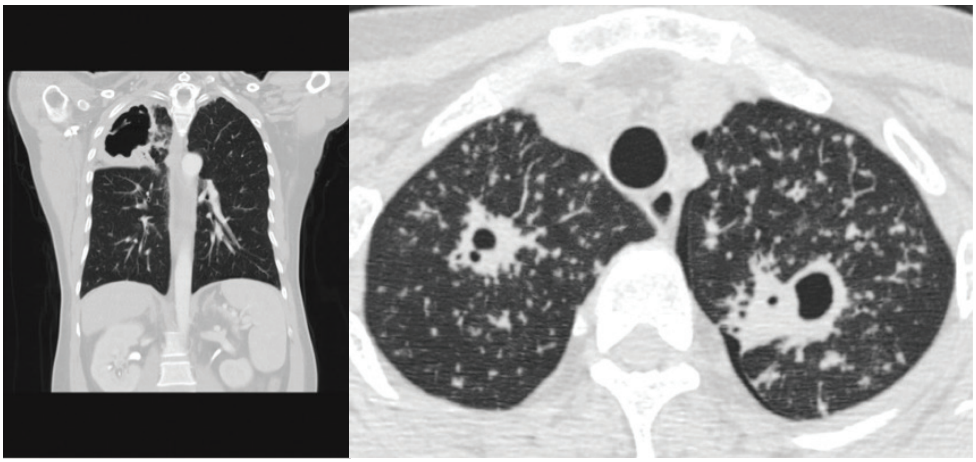
Centrilobular nodules

Active tuberculosis often communicates with the bronchial tree, which results in endobronchial spread. (1,7) Histological, caseous necrosis and granulomatous inflammation fill respiratory bronchioles and alveolar ducts. This histological finding manifests radiologically as centrilobular nodules and the tree-in-bud sign (Fig. 10). In the CT, centrilobular nodules are seen in approximately 95% of active tuberculosis cases.(1,7) Unlike cavitary lesions and consolidation, centrilobular nodules may be seen in the lower lobes, distant from the cavitary lesions.(19) Involvement of the airways and pleura is less common in post primary than in primary tuberculosis, but shows similar imaging features.

Tuberculosis in immunocompromised patients

Immunocompromised patients are at higher risk of developing primary and post primary tuberculosis. For example, HIV-positive patients with latent tuberculosis infection are 20--30 times more likely to develop active tuberculosis, when compared to HIV-negative patients. (1, 35) Although most TB cases in immunocompromised individuals are related to reactivation of latent tuberculosis, the radiologic and clinical manifestations more closely resemble those of primary tuberculosis (with consolidation and lymphadenopathy). In severely immunosuppressed patients with pulmonary tuberculosis, chest radiographs may be normal 10%–40% of the time.(1, 4, 36)

CT evaluation for pulmonary TB in HIV-seropositive persons with normal radiographs usually shows subtle abnormalities.(37) Leung and colleagues(37) identified 3 patterns of disease on CT scans in patients with normal chest radiograph. The dominant patterns (in order of decreasing frequency) consisted of multiple nodules, tuberculoma, and lymphadenopathy (right paratracheal, hilar, and subcarinal stations). Persons with relatively intact cellular immune function show radiographic findings similar to those of non-HIV-infected individuals. In CT, HIV-seropositive patients with a CD4 T-lymphocyte count below 200/mm3, characteristically show an atypical radiographic pattern, for example, middle and lower lung involvement, absence of cavity formation, presence of lymphadenopathy and pleural effusions, or a miliary pattern.(38, 39) A study performed to determine the CT spectrum of PTB in HIV-patients showed nodular opacities (78.5%), consolidation (46.4%),



Figs. 9 and 10 Coronal reformatted and axial views of plain chest CTs in different patients showing the typical apical cavitations of PTB and multiple centrilobular nodules connected to linear branching opacities (tree-in-bud appearance)

lymphadenopathy (35.7%), pleural effusion (35.7%), ground glass opacity (21.4%), and cavitation (21.4%).(38,39) Patients with severe immunosuppression have an increased incidence of miliary pulmonary disease, with diffuse, randomly distributed nodules in CT.(1)

TB diagnosis in HIV-infected patients can be challenging. Up to 50% of AIDS patients with culture-proven TB have false-negative sputum and bronchoalveolar lavage for *M. tuberculosis* bacilli.(40) Clinical and imaging features depend on the level of immunosuppression and CD4 counts.

Laboratory evaluation of active tuberculosis

Laboratory evaluation starts by obtaining sputum for smear and culture. Three successive sputum samples should be collected at 8–24-hour intervals, preferably in the early morning.(41) The number of bacilli identified in the smear correlates with the patient's degree of infectiousness.(8) When the patient cannot produce sputum, expectoration may be induced with administration of nebulized hypertonic saline.

In children, who commonly swallow sputum, gastric washings obtained by nasogastric aspiration in the early morning have a diagnostic yield of approximately 40% in cases with radiographic signs of pulmonary disease.(42) If sputum cannot be obtained, bronchoscopy is the next step in evaluation. In cases of sputum smear-negative pulmonary tuberculosis, bronchial washing has a sensitivity of 73% and a negative predictive value of 93%.(43) In addition, if there is mediastinal lymphadenopathy, endobronchial ultrasound (US)-guided transbronchial needle aspiration may be useful for diagnosis.(44)

Staining

Once a sputum sample is obtained, it is processed by using an acid-fast staining method. Mycobacteria have a lipid-rich cell wall (rich in mycolic acids) that binds basic fuchsin dyes, and the staining is resistant to acid and alcohol. Therefore, these mycobacteria are termed acid-fast bacilli (AFB).The sensitivity of the AFB smear using three successive sputum specimens is 68%–72% in patients with culture-positive tuberculosis(45,46) and 62% in HIV-positive patients.(45) Thus, the clinical context and imaging results are important to determine the need for empirical antituberculous therapy, as compared to waiting for culture confirmation. Respiratory isolation can be concluded after three successive negative AFB tests, even if culture results are pending.(47)

Culture

Culture can detect as few as 10 mycobacteria per milliliter of sample, whereas at least 5000 mycobacteria per milliliter are required for a positive smear.(48) Once growth is detected, the mycobacterial species can be identified, allowing the distinction of *M. tuberculosis* from other non-tuberculous mycobacteria.

Mycobacterial culture remains the standard for diagnosing active tuberculosis, with 80%–85% sensitivity and 98% specificity. In 10% of adult cases, confirmation is never established by culture.(49) The rate of culture confirmation is even lower in children, approximately 28%.(49) Thus, clinical judgment must be used in treating culture-negative patients empirically. Cultures should be obtained monthly from culture-positive patients until two consecutive negative results are obtained, known as culture conversion.(8) Culture conversion is an important event in monitoring treatment response and affects the duration and type of treatment.

Culture studies are also important in determining drug susceptibility of the organism. In developing countries, multidrug-resistant strains, which are resistant to isoniazid and rifampin therapy and extensively drug-resistant strains, which are resistant to therapy with isoniazid, rifampin, any fluoroquinolone drug, and one of the injectable antituberculous drugs, are emerging.(8) Although, imaging cannot be used to distinguish multidrug-resistant strains, extensively drug-resistant strains, and susceptible strains of tuberculosis, at least one group of investigators has suggested that extensively drug-resistant tuberculosis has more-extensive parenchymal findings than multidrug-resistant tuberculosis.(50)

Nucleic acid amplification test

TB diagnosis relies on the AFB smear and culture results. Two rapid tests that use nucleic acid amplification (NAA) have been approved by the US Food and Drug Administration (FDA) for TB diagnosis based on detection of *Mycobacterium tuberculosis* from specimens obtained in the respiratory tract.(51) NAA is a molecular test that can rapidly detect genetic material of tuberculous mycobacteria in sputum samples within 48 hours.(52) According to current guidelines, at least one respiratory specimen from a patient suspected of having active tuberculosis should be tested with the nucleic acid amplification test, concurrently with an AFB smear.(53) If both the NAA test and sputum smear yield positive findings, this combination is sufficient for confirmation of tuberculosis, and treatment should be started.(49) The nucleic acid amplification test cannot be used to follow clinical response to treatment, because the test can also detect non-viable tuberculous mycobacteria.(49)

The GeneXpert test

This is a molecular test of great potential for the diagnosis of tuberculosis with high sensitivity and specificity. It requires a sputum sample and can give a result in less than 2 hours. The GeneXpert test diagnoses TB by detecting the presence of TB bacteria, and tests for resistance to the drug rifampin as well, by detecting resistance-associated genetic mutations.

The test was endorsed by the World Health Organization in December 2010. WHO recommends that it be used as the initial diagnostic test for individuals suspected of having multidrug resistant tuberculosis (MDR-TB), or HIV-associated TB.(54)

Multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis

Multidrug-resistant tuberculosis (MDR-TB) is defined as a strain of *M. tuberculosis* resistant to at least isoniazid and rifampin. Extensively drug-resistant (XDR-TB) is a dreaded infection caused by a strain of *M. tuberculosis* that is also resistant to any type of fluoroquinolone and at least 1 of the 3 following injectable drugs: amikacin, capreomycin, or kanamycin, in addition to isoniazid and rifampin. Up to 10% of MDR-TB isolates are in fact found to be XDR strains. Soman and colleagues have coined the terms MDR+ and pre-XDR-TB for patients who have intermediate spectrum of drug-resistance between MDR-and XDR-TB. Successful treatment of fully susceptible TB depends on the combination of drugs and duration of therapy, cost, and drug's side effects. Conversion of culture-positive to culture-negative sputum within 2 months and subsequent clearing of infiltrates on chest radiograph are positive signs, whereas positive sputum cultures after 4 months of multidrug therapy indicate treatment failure. Incomplete and inappropriate therapy results in acquired resistance. Primary resistance occurs when the resulting *M. tuberculosis* strain is transmitted to a new host, as it causes TB that is already resistant to the indicated drug(s). The major concerns of drug resistance are fear regarding the spread of drug-resistant organisms and the ineffectiveness of chemotherapy in patients infected with them. In addition, MDR-TB is a fatal disease because of the high mortality, depending on the underlying diseases, particularly in HIV-infected patients (40%–80% mortality). (4,50,55,56,57,58,59)

■ LATENT TUBERCULOSIS INFECTION

Latent tuberculosis infection (LTBI) is a condition in which a person is infected with *Mycobacterium tuberculosis*, but does not have active tuberculosis. An estimated 10 to 15 million persons in the United States have LTBI. Because 5% to 10% of persons with LTBI are at risk of progressing to active disease, identification and treatment of LTBI are essential for the elimination of tuberculosis.(60)

More narrowly defined, latent infection refers to positive findings in laboratory screening tests in absence of radiographic or clinical evidence of active disease. By definition, previous (inactive) disease demonstrates radiographic or clinical evidence of previous, but no evidence of currently active tuberculosis.(1,49)

Inactive tuberculosis is characterized by stable fibronodular changes, including scarring (peribronchial fibrosis, bronchiectasis, and architectural distortion) and nodular opacities in the apical and upper lung zones(Figs. 11, 12). Fibronodular change is associated with considerably higher risk of developing tuberculosis reactivation.(61) In contrast, calcified granulomas and calcified lymph nodes are associated with an extremely low risk of reactivation and are commonly seen in other granulomatous diseases, such as endemic fungal infections and sarcoidosis.(61) Healed tuberculous cavities may persist after active disease resolves and can be complicated by hemoptysis, bacterial infection, or mycetoma.

Chest radiographs are important in the evaluation and risk stratification of patients suspected of having latent or inactive tuberculosis. Radiology reports should describe whether the radiograph shows entirely normal findings, calcified granulomas, fibronodular scarring (note the duration of stability), or findings that raise concern for active tuberculosis It is important to remember that any finding that raises the possibility of active tuberculosis should prompt communication with the referring provider and placement of the patient in respiratory isolation.(1)

Chest CT may be helpful for better characterization of radiographic findings, particularly when no prior imaging results are available.

Tests for latent infection

Testing for latent tuberculosis is advised for:

(a) Individuals without symptoms, but who are at high risk of exposure or reactivation, and

(b) Individuals with incidental imaging findings suggestive of inactive tuberculosis.

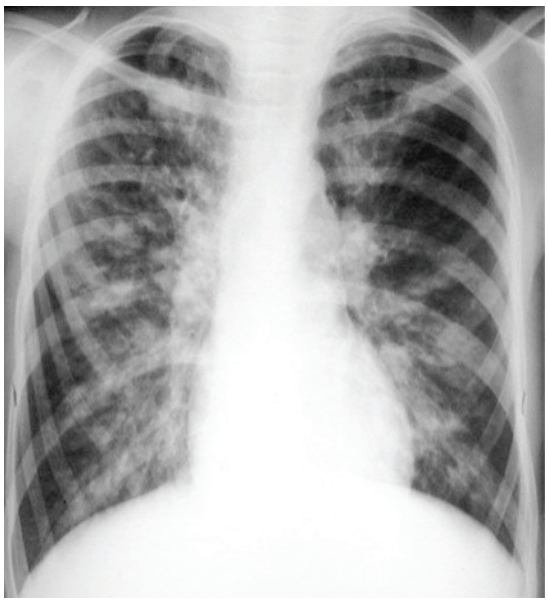


Fig 11. Bilateral peribronchial fibrosis and bronchiectasis

Asymptomatic individuals without any risk factors should generally not be tested. Testing is important because patients with latent tuberculosis are at risk for developing active tuberculosis later: a risk of approximately 0.1% per year for healthy patients with normal chest radiographs, and up to 10% per year in patients with HIV infection.(62) A number of different tests are available.

Tuberculin skin test

The most commonly used test for latent tuberculosis is the tuberculin skin test, also known as the purified protein derivative (PPD) or Mantoux test. A dose of protein extracted

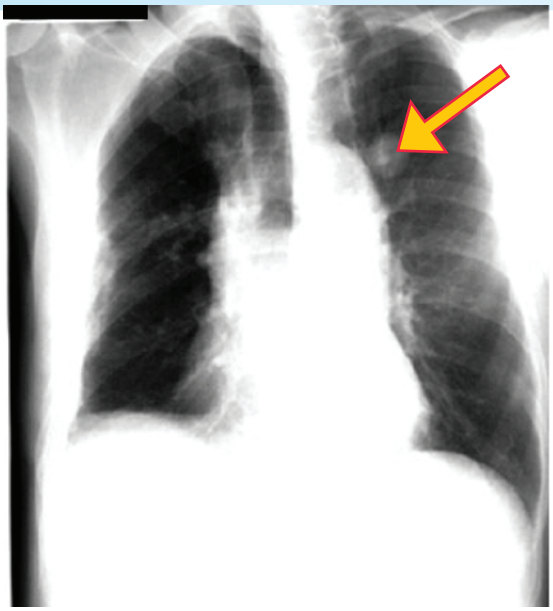


Fig 12. Oblique view of the thorax with tuberculoma in the left upper lobe

from *M. tuberculosis* is injected intradermally, and a delayed cell-mediated hypersensitivity immune response is mounted against the bacterial proteins. The size of any resulting induration is measured after 48–72 hours. Depending on patient risk factors, different size thresholds of induration are used, with a trade-off between sensitivity and specificity. (49)

A threshold of more than 5 mm of induration is used for extremely high-risk patients, as:
(a) patients with radiographic findings of previous tuberculosis,
(b) individuals, who had recent contacts with persons having infectious tuberculosis, and
(c) immunocompromised patients with HIV infection, organ transplants, or therapy with immunosuppressive drugs, such as prolonged corticosteroid therapy or therapy with tumor necrosis factor α inhibitor.

In patients at high risk, such as immigrants from endemic regions, drug abusers, individuals with exposure in high-risk congregate settings, persons with certain medical conditions, and certain pediatric patients, a threshold of more than 10 mm of induration is used. In the absence of any risk factors, a threshold of more than 15 mm of induration is used.

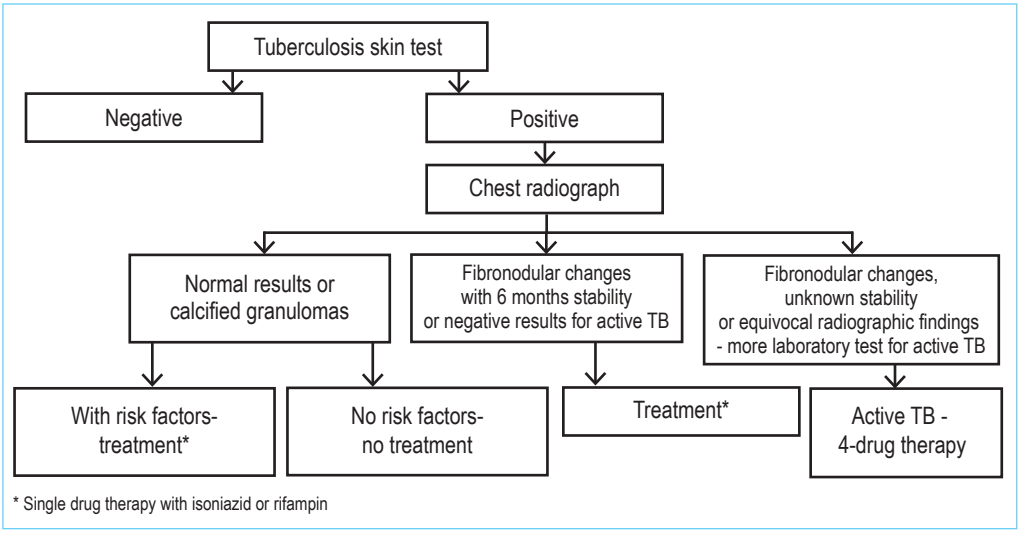
False-positive reactions to the tuberculin skin test may occur because of exposure to non-tuberculous mycobacteria.(63) In addition, BCG vaccination in childhood can cause lasting tuberculin skin test positivity in some individuals, particularly if they were vaccinated after 1 year of age.(63) False-negative reactions may occur in patients with recent tuberculosis infection (8–10 weeks), recent live-virus vaccination, infants younger than 6 months, and immunocompromised patients. (8) A patient's tuberculin skin test positivity can revert to negative with time, at a rate of about 5% per year after initial exposure. As a result, a substantial proportion of the elderly population will have a negative reaction despite previous exposure to tuberculosis.(64) In these patients, a repeat test performed 1–3 weeks later will generally be positive owing to the "booster phenomenon."

INTERFERON-GAMMA RELEASE ASSAYS

An alternative to the tuberculin skin test for the evaluation of patients suspected of having latent tuberculosis is the interferon-γ release assay. A patient's blood is exposed to *M. tuberculosis* antigen, and the resulting interferon-γ immune response is measured. In comparison with the tuberculin skin test, interferon-γ release assays require only one visit to conduct the test, with the results available within 24 hours. As with the tuberculin skin test, a negative reaction cannot absolutely exclude tuberculosis infection.(1)

The tuberculin skin test is limited by its inability to distinguish between infection with *M. tuberculosis* and non-tuberculous mycobacteria (NTM). Newer interferon-γ release assays using ESAT-6 and CFP-10 antigens should have higher specificity for tuberculosis.(65)

Algorithm for the evaluation of latent tuberculosis(1,8,19,49)



It is important to note that the tuberculin skin test and interferon-γ release assays are not designed to evaluate subjects for active tuberculosis.

The sensitivity of both tests for active tuberculosis is limited, particularly because of the time that it takes for the cell-mediated immune response to develop after initial infection.(66) Although, a positive result of these tests supports the diagnosis of active tuberculosis, it should not be used alone for diagnosis. A negative result of these tests, as mentioned,

does not exclude tuberculosis. Thus, although many experts may consider the use of screening tests in cases of suspected active tuberculosis as a diagnostic aid, such tests should not be regarded as providing a definitive answer.(17,67)

■ ROLE OF IMAGING IN DIAGNOSIS AND MANAGEMENT

Imaging plays a critical role in the diagnosis and treatment of active tuberculosis. A chest radiograph is generally obtained at the time of diagnosis; typically, a single PA (posteroanterior) view is adequate. Adjunctive views, such as a lordotic view or dual-energy radiography with bone subtraction, can improve the depiction of the lung apices.(68) Imaging findings suggestive of active tuberculosis, whether it is clinically suspected or not, should prompt immediate communication with the referring provider and placement of the patient in respiratory isolation until negative sputum samples are obtained.

Treatment of patients with active tuberculosis has two phases:

(a) an initiation phase, also known as the bactericidal or intensive phase, and
(b) a continuation phase, also known as the sterilizing phase(69)

The bactericidal phase typically lasts for 2 months and requires administration of a four-drug regimen of isoniazid, rifampin, ethambutol, and pyrazinamide. The length of the continuation phase can vary, depending on the risk of relapse of the patient. Isoniazid and rifampin are typically administered together in the continuation phase.

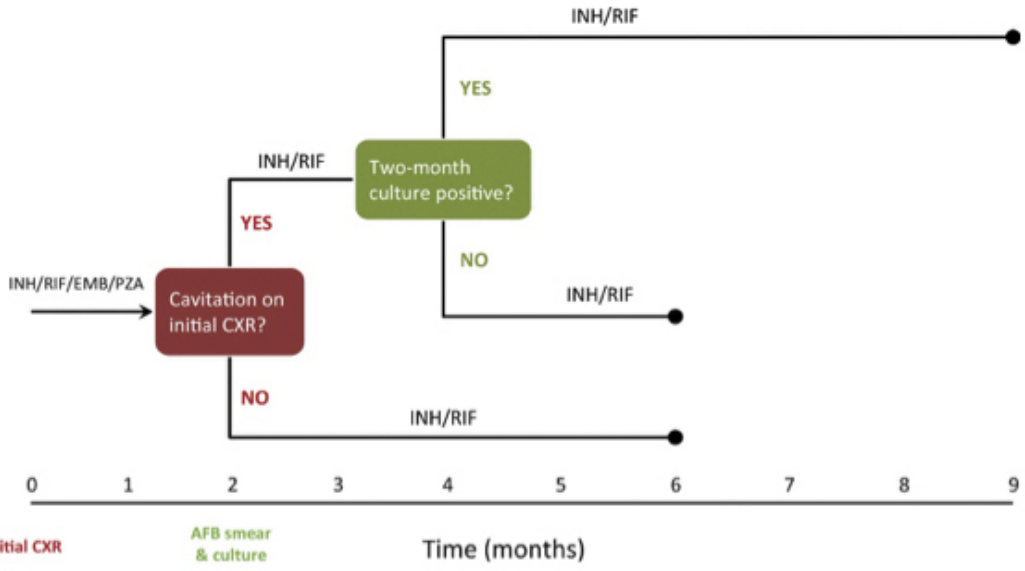
A treatment algorithm for active tuberculosis, highlighting the role of imaging in management, is shown below:(67)

Treatment algorithm for active tuberculosis

Patients with active tuberculosis, who show cavitation in the initial chest radiograph and who, at the completion of the initiation phase of treatment, still demonstrate positive two-month tuberculosis cultures, are at a high risk of relapse and should continue therapy for a total of nine months.

Thus, careful examination of the initial chest radiograph should be made for cavitary disease. Although CT is twice as sensitive as chest radiography in the detection of cavities (70) and may be useful in raising suspicion of active tuberculosis, the decision about the length of treatment in the algorithm is based on the presence of cavities in the chest radiograph, rather than on CT images. Patients without cavitation in the initial chest radiograph and patients with a negative 2-month culture may need therapy for only 6 months. A chest radiograph should be obtained for all patients at completion of treatment to establish a new baseline.

The main treatment regimen indicated for latent tuberculosis is nine months of therapy with isoniazid. If the patient is HIV-negative and if the chest radiograph shows normal findings, then 6 months of therapy with isoniazid may be enough. For patients, intolerant to isoniazid therapy or exposed to isoniazid-resistant *M. tuberculosis*, four months of rifampin therapy is recommended. The results of new studies have shown that weekly therapy with isoniazid and rifapentine for three months is an acceptable alternative in selected patients.(71)



CXR = chest x-ray, *INH* = isoniazid, *RIF* = rifampin, *EMB* = ethambutol, *PZA* = pyrazinamide.

■ COMPLICATIONS AND SPECIAL FORMS OF TUBERCULOSIS

Tracheobronchial tuberculosis

Even though the incidence of tracheobronchial TB has declined, when compared to the pre-antibiotic era, this complication still affects patients with advanced disease, particularly in endemic areas. The most significant complication resulting from bronchial TB is bronchial stenosis with a prevalence between 10% and 40%.(72) (See figure 6.)

Bronchopleural fistula

A bronchopleural fistula, consisting in an abnormal communication between the pleural space and the bronchial tree, most often results as a postoperative complication after pulmonary surgery and resection, but may also result from a necrotizing lung infection such as TB.

Rasmussen aneurysm

Rasmussen aneurysm is the name given to pulmonary artery

pseudoaneurysm associated with pulmonary TB, caused by erosion of the artery by the adjacent tuberculous cavity. Fritz Valdemar Rasmussen, a Danish physician, was the first to describe the intimate relation between a pulmonary artery and the wall of a pulmonary cavity in patients with TB and hemoptysis.(73)

Mycetoma

Pulmonary mycetomas develop from saprophytic infection of a pre-existing pulmonary cavity, cyst, or space, from previous pulmonary TB, sarcoidosis, bronchiectasis, or bullous emphysema, with the formation of an intracavitary fungus ball formed by a mass of tangled fungal hyphae, fibrin, epithelial cells, mucus, and cellular debris with blood cells.(74) In immunocompetent patients, TB is by far the most common cause of the pre-existing cavity (60%–80%), but in HIV-infected patients, pneumocystis pneumonia infection is a common predisposing condition (40%). (75,76,77) *Aspergillus fumigatus* is the most common fungal organism found in these cavitary lesions (70%), followed by *Aspergillus niger* (20%) and *Aspergillus flavus* (<10%).(77)

Empyema necessitatis

A rare complication of pleural infection in which purulent fluid extends from the pleural space through the parietal pleura into the soft tissues of the chest wall resulting in abscess formation known as empyema necessitatis or necessitans. Increased pressure within a loculated pleural collection facilitates chest wall extension with necrosis and migration of inflammatory exudates into the chest wall. (78,79)

Chest wall tuberculosis

TB of the chest wall is an uncommon manifestation of the disease, which constitutes less than 5% of all musculoskeletal TB, far less common than other skeletal sites more commonly affected, such as the spine, pelvis, hip, and knee joints. Excluding the spine, the most commonly affected site is the ribs, but chest wall TB may affect the sternum, sternoclavicular joints, as well as soft tissue including myositis, cellulitis, and breast infection. (4,80,81)

Spinal tuberculosis

Spinal TB (Pott spine or Pott disease) remains one of the most common forms of extrapulmonary TB and roughly accounts for 50% of all cases of skeletal TB infection. In 1779, Sir Percival Pott, a British physician, was the first to describe the destruction of disk space and adjacent vertebral bodies primarily in children who developed progressive kyphosis; hence, the condition subsequently became known as Pott disease. Spinal TB is uncommon in the western world, where *Staphylococcus* spp are the most common cause of vertebral osteomyelitis, but still remains the most common cause in countries with high burden of pulmonary TB.(82) Spinal involvement typically results from hematogenous spread from a pulmonary, genitourinary, or gastrointestinal infection, via either arterial or venous route into the rich vasculature of the vertebral bodies. The destruction typically affects the intervertebral disc space and the adjacent vertebral bodies with usually slow and insidious collapse of the anterior elements, resulting in wedge deformity and gibbus formation. Neurologic manifestations are common and often signal the devastating complication of spinal cord involvement (pain, numbness, weakness, paraplegia, quadriplegia, weak, or absent reflexes). Kyphosis is the most common deformity resulting from vertebral body collapse, which can involve any spinal segment, but more commonly affects the lower thoracic spine or upper lumbar region.(83,84) Concomitant pulmonary TB is common (67%) in patients with spinal TB. Imaging results include

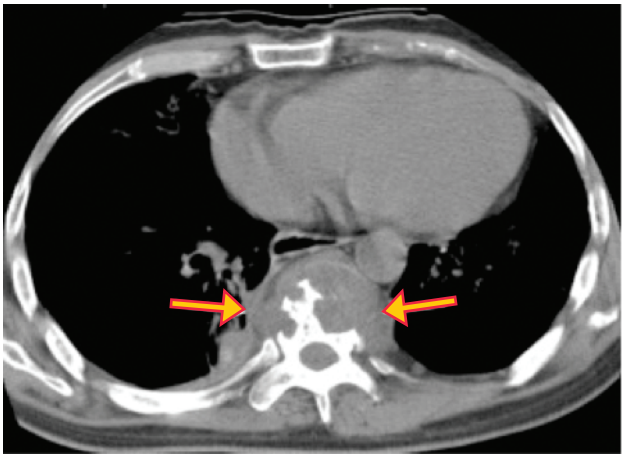


Fig 13.Pott disease. Non-contrast CT shows vertebral body osteolytic lesions surrounded by a paraspinal abscess (arrows) and small right-side pleural effusion.

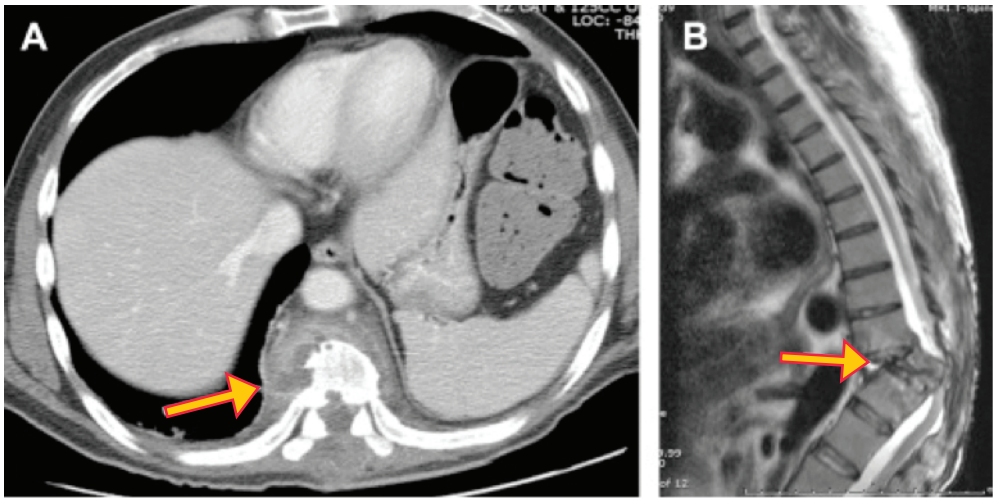


Fig 14.Pott disease. Contrast-enhanced CT (A) shows vertebral body lytic lesions with paraspinal abscess (arrow). (B) Sagittal MR imaging shows the vertebral body collapse, kyphotic deformity, and spinal cord compression (yellow arrow) better.

bone destruction with osteolytic changes, occasionally in association with bone sclerosis, soft tissue involvement with paraspinal abscess that may present as mediastinal mass (Fig. 13). The presence of calcification within a paraspinal abscess is fairly characteristic of TB infection. Although contrast-enhanced CT is an excellent imaging modality for the evaluation of the bone and mediastinal disease, MR imaging is the imaging technology of choice for examination of the spine and spinal cord and should always be performed in patients with suspected neurologic involvement (Fig. 14).

Cardiovascular tuberculosis

Tuberculous pericarditis, the most common cardiovascular complication of TB, is found in 1% to 2% of patients with pulmonary infection and remains the most common manifestation in countries with high TB prevalence.(85) Pericardial involvement may result from mediastinal lymph node retrograde lymphatic spread or by hematogenous spread. Tuberculous pericarditis may present clinically as pericardial effusion, constrictive pericarditis, or as a combination with effusive-constrictive pericarditis.(85)

■ CONCLUSIONS

Although clinical scenarios in which pulmonary TB can present are numerous, imaging examination is often performed both for initial diagnosis and for follow-up. In addition, it is not infrequent that TB is initially suspected from the imaging studies. Although chest radiograph still has an essential role in the initial evaluation, advanced cross-sectional imaging, in particular multiple detector computed tomography (MDCT), is critical for improved lesion detection, characterization, and disease extension assessment, both in limited and advanced disease and also in detecting the presence of complications. The role of the radiologist is pivotal, and appropriate understanding of the pathophysiology associated with imaging manifestations allows the radiologist to narrow the differential diagnosis and, when appropriate, suggest management options, significantly impacting patient outcome.

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WHO publishes first ever list of bacteria for which new antibiotics are urgently needed

• 27 February 2017 | Geneva

WHO today published its "Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics." It is a catalogue of 12 families of bacteria that pose the greatest threat to human health.

The list, drawn up in a bid to guide and promote research and development (R&D) of new antibiotics as part of WHO's efforts to address growing global resistance to antimicrobial medicines, highlights in particular the threat of gram-negative bacteria that are resistant to multiple antibiotics. These bacteria have built-in abilities to find new ways to resist treatment and can pass along genetic material that allows other bacteria to become drug-resistant as well.

The WHO list is divided into three categories according to the urgency for new antibiotics: critical, high and medium priority.

The most critical group of all includes multidrug resistant bacteria that pose a particular threat in hospitals, nursing homes, and among patients, whose care requires devices such as ventilators and blood catheters. They include *Acinetobacter*, *Pseudomonas* and various *Enterobacteriaceae* (including *Klebsiella, E. coli, Serratia*, and *Proteus*). They can cause severe and often deadly infections in the bloodstream and pneumonia. They have become resistant to a large number of antibiotics, including carbapenems and third generation cephalosporins -- the best available for treating multi-drug resistant bacteria.

The second and third tiers in the list contain other increasingly drug-resistant bacteria that cause more common diseases such as gonorrhea and food poisoning by *Salmonella*.

Tuberculosis, whose resistance to traditional treatment has been growing in recent years, was not included in the list because it is targeted by other, dedicated programs. Other bacteria that were not included, such as *Streptococcus A* and *B* and *Chlamydia*, have low levels of resistance to existing treatments and do not currently pose a significant public health threat.

The list, intended to spur governments to put in place policies that incentivize basic science and advanced R&D by both publicly funded agencies and the private sector, can be found at: http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1.

It was developed in collaboration with the Division of Infectious Diseases at the University of Tübingen, Germany, using a multi-criteria decision analysis technique vetted by a group of international experts. The criteria for selecting pathogens on the list were: how deadly the infections they cause are; whether their treatment requires long hospital stays; how frequently they are resistant to existing antibiotics; how easily they spread between animals, from animals to humans, and from person to person; whether they can be prevented (e.g. through good hygiene and vaccination); how many treatment options remain; and whether new antibiotics to treat them are already in the R&D pipeline.

While more R&D is vital, alone, it cannot solve the problem. To address resistance, there must also be better prevention of infections and appropriate use of existing antibiotics in humans and animals, as well as rational use of any new antibiotics developed in future.