Review

Imaging in tuberculosis

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SUMMARY

Early diagnosis of tuberculosis (TB) is necessary for effective treatment. In primary pulmonary TB, chest radiography remains the mainstay for the diagnosis of parenchymal disease, while computed tomography (CT) is more sensitive in detecting lymphadenopathy. In post-primary pulmonary TB, CT is the method of choice to reveal early bronchogenic spread. Concerning characterization of the infection as active or not, CT is more sensitive than radiography, and 18F-fluorodeoxyglucose positron emission tomography/CT (18F-FDG PET/CT) has yielded promising results that need further confirmation. The diagnosis of extrapulmonary TB sometimes remains difficult. Magnetic resonance imaging (MRI) is the preferred modality in the diagnosis and assessment of tuberculous spondylitis, while 18F-FDG PET shows superior image resolution compared with single-photon-emitting tracers. MRI is considered superior to CT for the detection and assessment of central nervous system TB. Concerning abdominal TB, lymph nodes are best evaluated on CT, and there is no evidence that MRI offers added advantages in diagnosing hepatobiliary disease. As metabolic changes precede morphological ones, the application of 18F-FDG PET/CT will likely play a major role in the assessment of the response to anti-TB treatment.

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1. Introduction

Tuberculosis (TB) remains a global emergency despite substantial investment in health services over the past two decades. Patients with sputum-negative pulmonary TB (PTB) and extrapulmonary TB (EPTB) are difficult to diagnose and may be missed at all points of care. Diagnostic imaging is challenging because signs of TB may mimic those of other diseases such as neoplasms or sarcoidosis. Clinical signs and symptoms in affected adults can be non-specific and a high level of pre-test clinical suspicion based on history is fundamental in the diagnostic work-up. The global impact of TB is extremely important, considering that an estimated 9.0 million people developed TB in 2013 and 1.5 million died from the disease, according to the recent World Health Organization (WHO) global tuberculosis report 2014.

Early diagnosis promotes effective treatment and leads to a reduced onward transmission of TB. This article gives a review of imaging patterns of chest TB as may be detected on conventional radiography and computed tomography (CT). The main aim is to improve the radiologist’s familiarity with the spectrum of imaging features of this disease in order to facilitate timely diagnosis. Furthermore, we consider the emerging role of alternative methods of imaging, such as magnetic resonance imaging (MRI), which can be helpful and highly accurate for a better definition of some of the signs of TB.

Although new imaging methods are now being used, conventional radiography remains the initial modality for suspected PTB and for mass screening purposes.1 CT and MRI are the modalities of choice for the evaluation of specific body parts.1 Positron emission tomography/computed tomography with the use of 18F-fluorodeoxyglucose (18F-FDG PET/CT) is a non-invasive imaging method that has been used widely for the differentiation of malignant from benign lesions. However, 18F-FDG also accumulates in inflammatory cells such as neutrophils, activated macrophages, and lymphocytes at the site of infection or inflammation. Consequently, 18F-FDG uptake is observed in PTB, in tuberculosis, and in other TB-related lesions.3,4 Using PET/CT, pulmonary and extrapulmonary TB involvement is assessed simultaneously, with time- and cost-saving implications.

Although any organ of the body can be involved, the lung remains the most commonly involved organ in TB. The imaging appearances of TB are described below for both pulmonary and extrapulmonary involvement.

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2. Pulmonary tuberculosis

Classically, PTB can be divided into a primary and a post-primary pattern, each presenting with characteristic radiological features. In practice, however, it is very difficult to draw distinct lines between these radiographic patterns, and there is considerable overlap in the radiological manifestations.3

2.1. Primary tuberculosis

Primary TB is due to first-time exposure to Mycobacterium tuberculosis. At radiology, primary PTB manifests as four main entities – parenchymal disease, lymphadenopathy, pleural effusion, and miliary disease – or any combination thereof.1

Chest radiography continues to be the mainstay of diagnosis. Typically, parenchymal disease manifests as consolidation in any lobe, with predominance in the lower and middle lobes.2 In these cases, the bacterial infections are much more likely to be the cause of such radiological features and hence the findings are non-specific, although primary infection should be suspected in individuals at risk of exposure to TB. Multilobar consolidation can be seen in almost 25% of cases.1 In approximately two-thirds of cases, the parenchymal lesion resolves without sequelae on conventional radiography.6 In the remainder, a radiological scar persists that can be calcified in up to 15%, while persistent mass-like opacities called tuberculosis are seen in approximately 9% of cases.6 Frequently, the only radiological evidence suggestive of previous TB is the so-called Ranke complex: the combination of a parenchymal scar, calcified or not (Ghon lesion), and calcified hilar and/or paratracheal lymph nodes.5 Destruction and fibrosis of the lung parenchyma result in the formation of traction bronchiectasis within the fibrotic region.5

The most common abnormality in children is lymph node enlargement, which is seen in 90–95% of cases; by comparison, in adults the percentage reaches up to 43%.7 Right paratracheal and hilar lymph nodes are the most common sites of nodal involvement, although involvement is bilateral in about a third of cases. CT is more sensitive than plain radiography in detecting tuberculous lymphadenopathy. It reveals nodes often measuring more than 2 cm, with a very characteristic, but not pathognomonic, ‘rim sign’ that consists of a low-density centre, representing caseous necrosis, surrounded by a peripheral enhancing rim due to granulomatous inflammatory tissue.6,9

In contrast to lymphadenopathy, the prevalence of radiographically detectable parenchymal involvement is significantly lower in children up to 3 years old (51%) than in older children, among whom the prevalence is similar to the reported percentage in adults (80%).7,8 Also, evolution to cavitary disease is rare in children.5

Concerning the role of 18F-FDG PET/CT, two distinct patterns of PTB have been described: (1) the lung pattern, related to a restricted and slight hypermetabolic infection, with 18F-FDG uptake in areas of lung consolidation ± caviation surrounded by micronodules and mild uptake within lymph nodes, and (2) the lymphatic pattern, related to a systemic and intense infection, with more enlarged and 18F-FDG-avid hilar and mediastinal lymph nodes.10

A limitation to the use of 18F-FDG PET/CT for the assessment of a single pulmonary nodule, especially in endemic areas, is the inability to distinguish tuberculous from malignant lesions (Figure 1).11 Studies investigating the diagnostic value of dual time-point 18F-FDG PET/CT imaging have shown limited promise, but further investigations in larger series of patients are warranted.12,13

2.2. Post-primary tuberculosis

Post-primary PTB is one of the many terms (including reactivation, secondary, or adulthood) applied to the form of TB that develops and progresses under the influence of acquired immunity.9 The most common radiographic manifestation of post-primary TB is focal or patchy heterogeneous, poorly defined consolidation involving the apical and posterior segments of the upper lobes and the superior segments of the lower lobes (Figure 2).14,15 In the majority of cases, more than one pulmonary segment is involved.6 Caviation, the radiological hallmark of PTB, is radiographically evident in 20–45% of patients (Figure 3), while air-fluid levels in the cavity occur in 10% of cases.14,15 Caviation may progress to endobronchial spread and results in a typical ‘tree-in-bud’ distribution of nodules in addition to caviation; this is considered a reliable marker of active TB.16 High-resolution CT is the method of choice to reveal early bronchogenic spread, with 2- to 4-mm centrilobular nodules and sharply margined linear branching opacities around terminal and respiratory bronchioles (tree-in-bud sign).16 The tree-in-bud sign is the constellation of small centrilobular nodules and concomitant branching opacities, which mimics the branching pattern of a budding tree.17 The centrilobular nodules are peripheral, spare the subpleural lung, and denote the inflammatory lesions in the bronchioles and peribronchial alveoli.16,17 Hilar or mediastinal lymphadenopathy is uncommon in post-primary PTB, seen in only 5–10% of patients (Figure 4).18,19

Although pulmonary tuberculosis are most often the result of healed primary PTB, a pulmonary tuberculosis is the main or only abnormality on chest radiographs in approximately 5% of patients with reactivation.20 The CT scan shows a round or oval granuloma, measuring from 0.4 to 5 cm in diameter, with a well lined by

Figure 1. Arrows indicate a mildly 18F-FDG avid right lower lobe nodule measuring 1.5 cm (SUVmax 2). The differential diagnosis for this nodule would include cancer or tuberculosis.
inflammatory granulomatous tissue or encapsulated by connective tissue.\textsuperscript{21} Tuberculomas can cavitate, while calcification is found in 20–30% of them.\textsuperscript{21} In 80% of cases, satellite lesions are observed in the immediate vicinity of the main lesion.\textsuperscript{2} Because of increased glucose metabolism caused by active granulomatous inflammation, tuberculomas may accumulate \textsuperscript{18}F-FDG.\textsuperscript{22} Maximum standardized uptake values (SUV\textsubscript{max}) tend not to be significantly different for tuberculous and malignant lesions.\textsuperscript{23,24} One study has suggested that unlike \textsuperscript{18}F-FDG PET, the \textsuperscript{11}C-choline PET scan can help to differentiate between lung cancer and tuberculoma, because tuberculoma shows low tracer uptake on \textsuperscript{11}C-choline PET scan.\textsuperscript{25}

### 2.3. Radiological patterns in primary and/or post-primary PTB

Miliary pulmonary disease affects between 1% and 7% of patients with all forms of TB.\textsuperscript{6} It is usually seen in the elderly, infants, and immunocompromised persons.\textsuperscript{6} Initially, standard radiographs are normal in 25–40% of cases.\textsuperscript{26} CT can demonstrate miliary disease before it becomes radiographically apparent, and its characteristic findings consist of innumerable 1- to 3-mm-diameter nodules randomly distributed throughout both lungs, often associated with intra- and interlobular septal thickening.\textsuperscript{14,27} The nodules usually resolve within 2–6 months with treatment, without scarring or calcification; however, they may coalesce to form focal or diffuse consolidation.\textsuperscript{6}

A pleural effusion is seen in approximately one-fourth of patients with primary PTB and in 18% of post-primary PTB.\textsuperscript{26} Although, usually observed in association with parenchymal and/or nodal disease, pleural effusion has been reported to be the only radiographic finding indicative of primary PTB in approximately 5% of adult cases.\textsuperscript{25} Pleural effusion is usually unilateral and on the same side as the primary focus of PTB, while complications such as effusion, empyema, and bronchopleural fistula are rare.\textsuperscript{6} The CT scan of patients with post-primary pleural effusion typically shows smooth thickening of visceral and parietal pleura.\textsuperscript{28} Ultrasonography often demonstrates a complex septated effusion.\textsuperscript{6} Fibrothorax with diffuse pleural thickening, but without pleural effusion on CT, suggests inactivity.\textsuperscript{29} The \textsuperscript{18}F-FDG PET/CT scan may demonstrate diffusely intense \textsuperscript{18}F-FDG uptake in thickened pleura that can be confused with pleural mesothelioma.\textsuperscript{30}

### 2.4. Differentiation between active and inactive TB

TB makes its presence felt on imaging long after the resolution of disease. Sometimes a question that needs to be answered is whether the infection is active or not. Active disease is in general characterized by the presence of centrilobular nodules, tree-in-bud pattern, thick-walled cavities, consolidation, miliary nodules, pleural effusions, or necrotic lymphadenopathy.\textsuperscript{1} Resolution to thin-walled smooth cavities, fibrosis, and parenchymal, nodal, or pleural calcifications often denotes inactive disease.\textsuperscript{1}

Chest radiographs may be normal or show only mild or nonspecific findings in patients with active disease.\textsuperscript{26} The diagnosis of PTB with radiography is initially correct in only 49% of all cases: 34% for primary and 59% for post-primary PTB.\textsuperscript{26} On the other hand, CT can correctly diagnose 91% of cases of PTB and correctly
characterize 80% of patients with active disease and 89% with inactive disease.31

CT is more sensitive than radiography in the detection and characterization of both parenchymal disease and mediastinal lymphadenopathy.9,32 In a study that compared the two methods, high-resolution CT showed cavities in 58% of patients with active PTB, whereas chest radiographs in only 22%.32 The diagnosis of active PTB was based on positive acid-fast bacilli in sputum and changes on serial radiographs obtained during treatment.32 CT may also show pleural disease that is not evident on chest radiography and be helpful in the evaluation of pleural complications.33

CT features predictive of highly infectious/active PTB include the following:34 (1) consolidation involving the apex or the posterior segment of the right upper lobe or the apico-posterior segment of the left upper lobe, (2) consolidation involving the superior segment of the right or left lower lobe, (3) a cavity lesion, (4) clusters of nodules, and (5) absence of centrilobular nodules. High-resolution CT is better than chest radiography in predicting active PTB, with a sensitivity of 96% versus 48%.35

It has been reported that 18F-FDG PET is able to differentiate active PTB from old or inactive disease, as active tuberculoma has significantly higher SUVmax values compared with inactive tuberculoma.3 When a SUVmax of 1.05 (at 60 min) was used as the cut-off, the sensitivity and specificity were 100% and 100%, respectively.3 A recent study concluded that 18F-FDG PET/CT has the potential to become a tool for monitoring the treatment response in selected cases of EPTB or multidrug resistance.36 An interesting study of patients with radiographic lesions suggestive of old healed TB aimed to gather information on the metabolic status of TB lesions using 18F-FDG PET/CT imaging.37 The authors showed that patients with old healed TB lesions with a higher SUVmax may be at higher risk of active TB.37 Further investigation is needed to confirm these results.

3. Extrapulmonary tuberculosis

Despite recent advances in imaging, the diagnosis of extrapulmonary involvement sometimes remains difficult.38 The imaging of some frequent extrapulmonary sites of TB is reviewed below.

3.1. Musculoskeletal tuberculosis

Approximately 50% of cases of skeletal TB involve the spine.6 Spondylodiscitis, also known as Pott’s disease, is the most common form.39 The infection begins in subchondral bone and spreads slowly to the intervertebral disk space and the adjacent vertebral bodies, commonly in the lower dorsal and upper lumbar spine.40 Failure to identify and treat these areas of involvement at an early stage may lead to serious complications such as vertebral collapse, spinal compression, and spinal deformity.38 Plain radiography is normal early in the disease.1 The first sign may be demineralization of the endplates with resorption and loss of dense margins. As the disease progresses, radiography will show progressive vertebral collapse with anterior wedging and gibbus formation.1 MRI is the preferred imaging modality in the diagnosis and assessment of tuberculous spondylodiscitis.41,42 Because of the often multifocal nature of spinal TB, the MRI imaging of the entire spinal column could be more effective in the early diagnosis of the disease.43 In cases of spinal TB, the spinal cord is susceptible to myelopathy secondary to compression from an epidural abscess.6 The collapsed vertebra along with the epidural collection/abscess is also best evaluated on MRI.6 After antibiotic administration is initiated, repeat imaging is advised at approximately 4-week intervals or at any time if neurological deterioration occurs.44

As tubercular lesions demonstrate high 18F-FDG uptake, 18F-FDG PET/CT is a promising technique for the diagnosis of spinal infection (Figures 5 and 6).45–48 An interesting finding was that 63.6% of patients with spinal TB had clinically occult non-contiguous multifocal skeletal involvement at the time of whole-body 18F-FDG PET/CT scan.49

Besides the spine, any part of the musculoskeletal system can become involved, but the large joints of the lower limbs are most commonly affected. Imaging findings in musculoskeletal TB are often non-specific. MRI is the most sensitive modality for early diagnosis and complete delineation of the disease.1

Figure 4. Left panel: Multiple intensity projection image showing 18F-FDG uptake in the mediastinal and bilateral hilar lymph nodes (arrows). Right panel: Multiple fused trans-axial section 18F-FDG PET/CT images showing hilar and mediastinal lymph nodes (arrows).
3.2. Central nervous system (CNS) tuberculosis

TB of the CNS is a highly devastating form of the disease. Various forms of involvement of the CNS are observed: parenchymal, meningeal, calvarial, spinal, or any combination thereof. MRI is generally considered superior to CT in detecting and assessing CNS TB. Parenchymal involvement is most frequently seen in the form of a tuberculoma, which may be single or multiple. In the paediatric age group it is seen more frequently in the cerebellum, whereas in adults it has a predilection for the cerebral hemispheres and basal ganglia. The appearance of a tuberculoma varies on MRI depending on its stage of maturation. A non-caseating granuloma is hyperintense on T2 and hypointense on T1 and shows solid enhancement, while a solid caseating granuloma is usually hypointense on both T1 and T2 images. On CT, tuberculomas appear as round or lobulated soft tissue masses with varying attenuation and homogeneous or ring enhancement. Miliary TB is often associated with TB meningitis and presents as small (<2 mm) foci of hyperintensity on T2 acquisitions, while after gadolinium administration, T1 images show numerous, round, small, homogeneous, enhancing lesions. Contrast-enhanced MRI is also superior to CT for the evaluation of meningitis and its complications, including hydrocephalus.

3.3. Abdominal tuberculosis

Abdominal lymphadenopathy is the most common manifestation of abdominal TB, seen in 55–66% of patients, and may or may not be associated with other abdominal organ involvement. Abdominal lymph nodes are best evaluated on CT, which reveals enlarged nodes with hypoattenuating centres and hyperattenuating enhancing rims. On MRI, the appearance is typically hypointense on T1 images, whereas on T2 images the signal is generally hyperintense or with peripheral low-intensity signal.

Hepatic TB can be classified into local, miliary TB, or tuberculomas. Miliary TB is the most common form of liver TB and is a part of generalized disease; innumerable small nodules are found on the liver which may or may not be seen on CT, but on ultrasound usually present as bright liver or spleen patterns in the form of a diffuse increase in echogenicity.

Calcification in the hepatic region on plain radiography may occasionally be seen in local hepatic TB. On CT, liver tuberculoma appears as a non-enhancing, central, low-density lesion with a slightly enhancing peripheral rim, while liver calcifications can also be demonstrated. MRI offers no added advantage in diagnosing hepatobiliary TB.

Figure 5. CT (left panel) and 18F-FDG PET/CT fused images (right panel): trans-axial and sagittal sections. Moderate to intense 18F-FDG uptake is seen in a paravertebral soft tissue mass lesion extending from the level of T7–T10 vertebral with associated lytic sclerotic changes in T7–T9 vertebral and collapse of the T8 vertebral (arrows). The lesion infiltrates into the spinal canal at the level of the T8 vertebral and involves the spinal cord (small arrow). The lesion is seen to extend along the left costal margin, with faint 18F-FDG uptake and foci of calcification, likely representing a cold abscess (courtesy of Prof. B.R. Mittal).
Few reports are available on 18F-FDG PET/CT imaging in abdominal TB, showing that the appearance of abdominal TB is non-specific and varied (Figure 6).56–58

4. Assessment of treatment response

This is potentially the most important clinical application of 18F-FDG PET/CT in TB. During anti-TB treatment, some bacillus-negative tuberculomas do not decrease in size and may even increase, making it difficult for the physician to decide whether or not to modify treatment. In these cases, 18F-FDG PET/CT imaging may help, as the changes in glycolytic activity within the inflammatory lesion, measured by 18F-FDG uptake, correlate well with the clinical markers of response.49 Several studies have confirmed the value of 18F-FDG PET/CT in the follow-up and evaluation of the treatment response, especially in patients with extrapolumonary involvement and when drug resistance is prevalent.37–59 In pulmonary and extrapolumonary TB, a decrease of approximately one-third in SUVmax has been reported after 1 month of anti-TB treatment when there is a good response.49 Initial data has shown that SUVmax (both early and delayed) of involved lymph nodes and the number of involved lymph node basins are significantly higher in non-responders than in responders.64 These findings warrant further confirmation in larger cohorts of patients.

After 4 months of anti-TB treatment 18F-FDG PET/CT can also evaluate the treatment response in patients with high sensitivity and specificity, using the value of 4.5 as the SUVmax cut-off.52 Other authors have aimed to monitor the metabolic changes in spinal TB during the course of therapy.49 The mean changes in SUVmax at various time points – from baseline to 6, 12, and 18 months, from 6 to 12 months, from 6 to 18 months, and from 12 to 18 months – were calculated and found to be highly significant (p-value < 0.001).49 18F-FDG PET/CT also shows encouraging results for the prognosis and detection of residual disease in patients with spinal infection, particularly when MRI is unconvincing in distinguishing between degenerative changes and infection.65

5. Tuberculosis in HIV patients

The diagnosis of active PTB is a major challenge, especially in individuals with severe immunosuppression, such as those co-infected with HIV. Such patients characteristically demonstrate 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

The radiographic appearance of HIV-associated PTB has been found to be dependent on the level of immunosuppression at the time of overt disease.60 Radiological manifestations in patients with a CD4 T-lymphocyte count of <200/mm3 show a higher incidence of mediastinal or hilar lymph node enlargement, a lower prevalence of cavitation, and often extrapolumonary involvement compared with HIV patients with a CD4 T-lymphocyte count of ≥200/mm3.56 A study performed to determine the CT spectrum of PTB in HIV patients showed nodular opacities (in 78.5% of cases), consolidation (46.4%), lymphadenopathy (35.7%), pleural effusion (35.7%), ground glass opacity (21.4%), and cavitation (21.4%).57 Other authors have reported that features of post-primary PTB are patchy consolidation with involvement at unusual sites.61 Cavitation is less common at lower CD4 counts. Patients with severe immunosuppression have an increased incidence of mediastinal pulmonary disease, with diffuse, randomly distributed nodules on CT.63 Mediastinal and hilar lymphadenopathy occurs in 75–77% of cases and is more commonly seen in HIV-positive than in HIV-negative patients.65 Extrapolumonary localizations are frequent in HIV-infected patients and may involve brain, pericardium, gastrointestinal tract, peritoneum, and genitourinary tract.70 Currently there are no data to support the use of 18F-FDG PET/CT in this patient group.

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