Computed Tomography Features of Multi-drug-Resistant Pulmonary Tuberculosis in Non-HIV-Infected Patients

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ABSTRACT

OBJECTIVE: Pulmonary tuberculosis is one of the most common infectious diseases worldwide and is a problem with not only medical but also social implications. This disease causes high mortality and morbidity, especially in developing countries. Currently, the study findings by Computed Tomography (CT) in Multidrug-Resistant Tuberculosis (MDR-TB) are an issue that is arousing much interest in the scientific community, appearing new investigations that shed light on this important problem. The objective of this review is to describe the CT findings in the MDR-TB. The information will be presented in accordance with what is reflected in the most recent scientific literature.

CONCLUSION: There are a number of findings on CT as the presence of multiple cavitations or sign “tree in bud”, among others, that have proven to be more prevalent in the MDR-TB. CT features allow a suspected diagnosis, with the potential benefit that this has for the good management of the infected patient.

Keywords: Computed tomography; Tuberculosis; Multidrug-resistant; Pulmonary tuberculosis
INTRODUCTION

Tuberculosis is currently the second among all infectious diseases that contribute to mortality of adults; about 1.7 million people worldwide die from it every year. The WHO estimates that one third of the world’s population is infected with *Mycobacterium tuberculosis* [1].

Multidrug-Resistant Tuberculosis (MDR-TB) is defined as a strain resistant to at least isoniazid and rifampicin. It is considered that the extensively Drug-Resistant Tuberculosis (XDR-TB) is caused by a strain of *Mycobacterium tuberculosis* that is resistant to any type of fluoroquinolone and at least one of the three following injectable drugs: amikacin, capreomycin and kanamycin, in addition to isoniazid and rifampicin [2]. MDR-TB and XDR-TB are problems of confirmed importance to public health worldwide. With a didactic purpose, in this chapter we will address the differences between MDR-TB and DS-TB, in their radiological presentation. Although findings have also been suggested to differentiate MDR-TB from XDR-TB, is not the purpose of this chapter to address them [3].

A fundamental cause in the genesis of resistance to anti-tuberculosis drugs is the misuse of antibiotics to treat patients suffering from drug-susceptible tuberculosis, causing the mutation that occurs in the genome of Mycobacterium. Such misuse is the result of a series of actions, especially the administration of inadequate therapeutic regimens by health workers and the fact that they do not ensure that the patient follows the treatment until the end. Drug resistance arises mainly in areas where anti-tuberculosis programs are deficient. Moreover, immunodeficient patients of any background (both solid organ and bone marrow transplant, such as leukemia or lymphoma patients and those treated with corticosteroids) are more susceptible to infection with *Mycobacterium tuberculosis*. The association of MDR-TB with HIV has contributed to a slowdown in the fight for the reduction of tuberculosis cases in the last two decades, which represents one of the most difficult barriers towards reaching WHO objectives in this respect [4].

The WHO Global Project on Anti-Tuberculosis Drug Resistance Surveillance and the International Union against Tuberculosis and Lung Disease have found MDR-TB (prevalence > 4% of new TB cases) in Eastern Europe, Latin America, Africa and Asia [1].

In some countries, the treatment of MDR-TB is becoming increasingly difficult. Treatment options are limited and expensive, recommended medications are not always available, and patients suffer many side effects. Given the increasing level of globalization and the intensification of transnational migration and tourism around the world, no country is safe from suffering an outbreak of MDR-TB.

As for the diagnosis of MDR-TB, it begins with a bacillus smear (AFB), but to be confirmed a sputum culture is required, which often takes 2-3 weeks (especially in the case of non-tuberculous mycobacteria) [5,6]. Other clinical characteristics that can be associated with MDR-TB are the patient’s age (most common in youths) and the presence of a previous episode of tuberculosis.
treated with anti-tuberculosis therapy. It is not the purpose of this chapter to establish the different diagnostic and therapeutic algorithms related to pulmonary tuberculosis. However, we propose a flow chart similar to that developed by Bhalla et al., but with minor modifications that make it closer to our experience [7]. This graphical representation helps us to understand when and why to perform the different imaging tests in a patient with suspected multidrug-resistant tuberculosis (Figure 1).

**Figure 1:** Flowchart depicting the role of CT in diagnosis of CTB. TB: Tuberculosis; MDR-TB: Multidrug-Resistant Tuberculosis; IGRA: Interferon Gamma Release Assay; CT: Computed Tomography.

With regard to non-tuberculous mycobacteria, it is sometimes difficult to detect anatomopathological findings that allow us to differentiate them from MDR-TB. Regarding imaging techniques, neither simple radiography nor computed tomography has allowed us to distinguish both entities infallibly [8]. The presence of similar laboratory, radiological, and clinical findings in MDR-TB infections and non-tuberculous mycobacteria, and also the failure of the first line of treatment leads not only to a misdiagnosis but also to delayed treatment and likely spreading of pathogens [8,9].
IMAGING TESTS

X-Ray

The simple thoracic radiograph, in its posteroanterior and lateral projections, is the first imaging test performed in patients with suspected pulmonary tuberculosis. Able to establish alternative diagnoses, it is also useful for tracking the disease and may be the only imaging method selected when the sputum is positive. The usefulness of X-ray lies in its ability to detect signs of disease activity and other findings that may be associated with multidrug-resistance.

Ultrasonography

Is more sensitive than plain radiography for the diagnosis and monitoring of pleural effusion and allows us to guide interventional procedures [10,11]. It also exceeds CT sensitivity in identifying septa within the effusion [11].

Chest CT

CT is more sensitive than radiography in the detection and characterization of parenchymal disease and lymphadenopathy and other mediastinal disorders [12]. It is, therefore, an important tool in detecting radiographically hidden diseases, for differential diagnosis, to assess disease activity and associated complications. The greatest value of CT resides in the fact that it allows us to suggest the diagnosis of tuberculosis in patients with negative sputum test and in those from whom sputum cannot be obtained noninvasively. Moreover, the CT can indicate the beginning of empirical antibiotherapy until culture results are obtained [7].

PET-CT

(FDG-PET) may be useful in the assessment of disease activity and response to treatment [13]. Although it is not specific to tuberculosis, FDG-PET CT can evaluate the full extent of the disease, detecting distant lesions. The problem with this technique is the high radiation to which the patient is subjected.

MRI

It has advantages over CT because it does not use ionizing radiation and enables a better assessment of soft tissue structures (adenopathy, pleura, caseating lesions) (Figure 2). Technical advances and refinement of pulse sequences have improved the quality and time to obtain MRI images. A study on the subject showed that, in terms of the identification of pulmonary lesions in patients with non-miliary pulmonary tuberculosis, MRI has a comparable diagnostic ability to HRCT, but with better and faster identification of pulmonary parenchymal abnormalities due to the excellent contrast resolution [14]. The objective of this technique is the evaluation of mediastinal adenopathies, evaluating signs of disease activity and signs of fibrosis. The presence of restricted diffusion and peripheral enhancement suggest active disease [14].
Figure 2: Axial T2-weighted turbo spin-echo MR image shows right pleural effusions (white arrow).

**FINDINGS OF MDR-TB IN CT**

MDR-TB is divided into primary (PMDR-TB) and acquired MDR-TB (AMDR-TB). The PMDR-TB is characterized by the condition in which patients have no prior TB treatment or treatment has been less than one month [15]. There is a correlation between patients with AMDR-TB and the lower educational level and economic status of the patients. This may be due to the lower performance of TB treatment in this population group [15]. Therefore, it is expected that patients with PMDR-TB show a better response to treatment than patients with AMDR-TB.

So far no statistically significant differences between CT findings observed in drug-sensitive TB and MDR-TB have been shown [3]. However, certain findings are detected more frequently in patients with MDR-TB.

Radiological manifestations of pulmonary tuberculosis depend on several host factors, including prior exposure to TB, age and underlying immune status. In people with normal immune function, radiological manifestations can be logically divided into two different forms of primary and post-primary disease that develop in individuals with and without prior exposure and specific acquired immunity.

**Primary Disease**

Lymphadenopathy is the radiological signature of primary tuberculosis (Figure 3). Adenopathies are observed in 83%-96% of pediatric cases [16], while the prevalence of
lymphadenopathy decreases as age increases [17]. The right paratracheal and hilar ganglion stations are most commonly affected in primary tuberculosis [16]. On CT, enlarged lymphatic nodes, especially when they are larger than 2 cm, typically show a low central attenuation which becomes necrosis caseosa, and an enhancement in its periphery which represents the edge of granulomatous inflammatory vascular tissue [18]. Although some classic author like Im et al. [19] has suggested that this pattern of ganglionic enhancement is characteristic enough to support the diagnosis of TB in younger patients, there are also other entities that produce it, such as atypical mycobacterial infection, lymphoma, metastases, especially testicular carcinoma and benign conditions such as Whipple and Crohn’s disease [16]. As shown by the study of Cha et al., noncavitated consolidations, mediastinal adenopathies and pleural effusion are the most common manifestations in PMDR-TB [20]. Moreover, as Lee et al. reported, the presence of adenopathies is more frequent in the multiresistant forms than in those sensitive to antibiotics [15].

![Chest CT. Axial images. CT reveals enlarged lymph nodes in right paratracheal (white arrow) and paraaortic (white arrowhead) chains.](image)

**Figure 3:** Chest CT. Axial images. CT reveals enlarged lymph nodes in right paratracheal (white arrow) and paraaortic (white arrowhead) chains.

Parenchymal consolidation is another typical manifestation of PMDR-TB and can affect any lobe, although it is more common in the lower and medial lobes, especially in adults (Figure 4). In children younger than 2 years old, consolidation is more often detected in the anterior segment of the upper lobe or the medial segment of the middle lobe [21]. These consolidations are indistinguishable by X-ray and CT scan from those produced by bacterial pneumonia. However, some clues such as radiological evidence of lymphadenopathy and lack of response to conventional antibiotics allow us to suggest the diagnosis of primary tuberculosis. Consolidation is one of the most common findings in the primary form of MDR-TB, differing from the primary form by the absence of cavitation [5].
These consolidations typically resolve without sequelae, although in some cases a persistent radiation scar that can calcify in up to 15% of patients is formed, forming the so-called Ghon focus. Other calcified foci can also be seen, in up to 9% of cases, other small persistent parenchymal opacities, called Tuberculomas, which may also cavitate and calcify [21]. Obstructive atelectasis can also be seen due to extrinsic compression of the bronchi by adenopathies, predominantly affecting the right lung and lobar or intermediate bronchus [16].

Pleural effusion is a rare manifestation of primary tuberculosis in infants and young children (<2 years old). Unlike the adenopathies, the prevalence of effusion increases with age [17]. A pleural effusion usually develops on the same side as the site of the initial TB infection and is typically unilateral, with rare complications (empyema, fistula, bone erosion) [21]. Pleural effusion is one of the typical findings of primary tuberculosis (Figure 4). However, if there is no consensus whether it appears more often in the forms of MDR-TB or its drug-sensitive form [15,20].

**Acquired Disease**

The most common CT findings of pulmonary tuberculosis reactivity are small nodules of centrilobular distribution, the “tree in bud” sign and lobe consolidation with cavitation [22].

CT has a sensitivity of 98% for detecting endobronchial spread of tuberculosis, which manifests as 2-4 mm centrilobular nodules with well-defined edges. These can be connected to multiple branched linear formations representing bronchiolar branches and give an appearance of a tree in bud (“tree-in-bud” sign) [23,24] (Figure 5). This pattern reflects a spectrum of endo
and peribronchiolar disorders including mucosal impaction, inflammation or fibrosis. The centrilobular micronodules and pattern of tree in bud are the most common CT findings of active pulmonary tuberculosis [23]. Although these findings are observed both in the AMDR-TB and the S-TB, some authors describe a broader pulmonary involvement in the multiresistant forms [15].

**Figure 5:** Chest CT. Axial images. CT reveals a left lingula consolidation (white arrow). In right lower lobe is detected centrilobular nodules and a tree-in-bud pattern (white arrowhead).

The parenchymal consolidations are one of the most common manifestations of AMDR-TB, observed in 60-93% of cases [20,25], the presence of consolidations and cavitation being more common in MDR-TB than in S-TB [5]. Its most typical location is in the apical and posterior segments of the upper lobes and in the upper segment of the lower lobes [19]. Said parenchymal affection tends to affect more than one segment and is accompanied by other concomitant disorders [26]. One study suggested that the appearance of cavitation consolidation in patients with MDR-TB that have had at least a month of anti-TB treatment strongly suggests the existence of a reactivation of tuberculosis [22].

Cavitation is the hallmark of post-primary tuberculosis, cavities typically being thick and irregular walls at the beginning of the disease (Figure 6). If treatment is successful, these walls will become thin and regular over time, and then disappear, leaving sequela fibrotic tracts and emphysema scars [16].
Figure 6: The chest CT-images demonstrate a cavitary lesion in left upper lobe.

One of the most common findings in post-primary tuberculosis are nodules, which can be called micronodules when they are less than 10 mm and macronodules when they have a size between 10 and 30 mm [27]. According to some studies, nodes can be seen in 90% of patients with MDR-TB, micronodules and macronodules being most frequently observed in MDR-TB compared to DS-TB [20]. We also detected an increased presence of cavitation in these nodules, in patients who have developed resistance to anti-TB drugs [20]. Calcification of nodules is also observable [21].

Miliary tuberculosis is the presence of multiple nodules of 1-3 mm, randomly distributed in the pulmonary parenchyma, diffusely but with slight predominance in the lower lobes. They are produced by hematogenous spread of tuberculosis and usually do not calcify or scar, although they may coalesce to form consolidations. This pattern of disease is usually seen more often in young children and immunosuppressed elderly, observed in the first 6 months from the initial exposure and resolved in 2-6 months after starting TB treatment [21].

Miliary disease is a rare form of extrapulmonary tuberculosis that has been reported rarely in the forms of MDR-TB in immunocompetent patients, being more common in immunocompromised patients [28]. However, its rarity makes its incidence unknown today in patients with MDR-TB, there being no study that has managed to establish it reliably [28,29].

Some common manifestations in primary pulmonary tuberculosis are less so in the post-primary. An example of this is the mediastinal and hilar adenopathies, which are usually seen only in 5% of cases [30]. Something similar happens with pleural effusion, considered a genuine manifestation of the primary form of DS-TB and typically unilateral in post-primary DS-TB. In the case of MDR-TB, pleural effusion may appear less frequently as a study suggests. However, this has not been demonstrated with statistically significant evidence [20,27].
Active Pulmonary Tuberculosis

The utility of CT to detect findings suggesting disease activity has been the subject of many studies [31,32]. The presence of nodules of centrilobular distribution and the sign of the “tree in bud” are findings suggestive of active TB, being more frequently seen in patients with MDR-TB, as suggested by Lee et al. in a study [15].

The development of scar emphysema, bronchiectasis, peribronchovascular distortion and dystrophic calcification are commonly observable sequelae after tuberculosis is cured. Some of these manifestations in CT, such as bronchiectasis and calcified granulomas are more frequently observed in patients with MDR-TB than in those with DS-TB [33]. This can be explained by the evolution towards chronicity in patients with multidrug-resistant forms of the disease. It is believed that these sequelae characteristics associated with the healing of pulmonary tuberculosis are less frequent in the form than in the acquired form of MDR-TB.

MDR-TB in HIV Patients

The radiological findings in acquired immunodeficiency syndrome vary depending on the level of immunosuppression of the subject at the time of observation. In patients with sustained or not too low cell immunity, the manifestations are super imposable to those of immunocompetent patients. However, in severe levels of immunosuppression, depending on the state of exposure to the disease, patients may show normal X-ray or typical findings of primary tuberculosis. In a classic study, in HIV-positive patients with severe immunity (less than 200/mm3) there is a higher prevalence of manifestations such as hilar and mediastinal adenopathies, as well as the form of miliary spread, with the existence of cavitation being less common compared to other HIV-positive patients with better immune status.

At present there are few studies that have reviewed the expected CT findings in HIV patients with multiresistant forms of pulmonary tuberculosis, the door being open for further work to shed some light on this subject.

CONCLUSION

In short, when a patient presents with multiple cavitary lesions associated with the sign of “tree in bud”, centrilobular nodules, consolidations and bronchiectasis, of bilateral distribution, the possibility that it is a case of MDR-TB should be considered. Knowledge of the typical CT findings of MDR-TB allows a diagnosis of suspicion, which is useful for selecting proper anti-TB treatment in infected patients before reaching a definitive diagnosis based on bacteriology. This, together with good therapeutic compliance, is the best strategy for controlling this important public health problem that is MDR-TB.
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