EMERGING CLINICAL - RADIOLOGICAL PATTERN OF PULMONARY TUBERCULOSIS IN IMMUNOCOMPETENT PATIENTS

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ABSTRACT

Pulmonary tuberculosis (TB) is still a major health problem all over the world, not only in developing countries, but also in countries characterised by low incidence, where migration, ageing, and the increasing prevalence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) are contributing to the emergence of patterns, traditionally considered rare or unusual, before using the new imaging techniques. In this article the different clinical and radiological patterns most commonly detectable in patients with pulmonary TB are analysed in different population subgroups: paediatric and adult age, immunocompetent patients, in patients coming from high-prevalence countries, and in those with other risk factors for TB, in the MDR and XDR-TB, and in the drug sensitive (DS) forms. The increasing role of high-resolution computed tomographic (HRCT) scan in the detection of pulmonary TB will also be underlined, in cases where conventional chest X-ray was negative or inconclusive, in the mediastinal TB forms, in the differential diagnosis with tumours and interstitial lung disease, but also in the detection of active forms, and for a better assessment of therapeutic response.

Keywords: Pulmonary tuberculosis, high-resolution computed tomographic (HRCT) scan, immune status.

TUBERCULOSIS TODAY: EPIDEMIOLOGICAL OVERVIEW

Tuberculosis (TB) is still a major cause of morbidity and mortality among the diseases caused by a single infectious agent, and is considered a global emergency, albeit with a wide epidemiological variability between the different geographical areas of the planet. Among the main factors responsible for the persistence of the disease, HIV infection, multidrug resistant tuberculosis (MDR-TB), migration, and immunocompromised states are the most common.[1]

Recent estimates of the World Health Organization (WHO) report approximately 8.6 million new cases of TB a year, 13% of which are HIV positive, and 12 million are prevalent cases.[1,2] It is estimated that about one-third of the world's population (2 billion people) have come into contact with mycobacterium TB (TB infection). 85% of the total cases are recorded in the Asian and African continents (India and China together have 38% of the world's cases), while 5% of cases are in Europe, especially in Eastern European countries.[1,2] In the countries of Western Europe, TB cases among foreign people account for a large part of the notifications, with a decreasing trend among African immigrants and an increasing trend among those from Eastern European countries, and, in particular, Romania, Moldova, Russia, and Ukraine.[1,2] However, this is a stable, and not an alarming, trend despite the steady increase in the number of foreign residents in the last decade. Worldwide, and also in Western Europe, the groups at risk are elderly people, patients with co-morbidities such as diabetes, organ failures, pulmonary silicosis, cancer, or patients undergoing immunosuppressive treatments.[3]

It is estimated that about a quarter of TB patients cannot be treated with standard therapy. The cases

of MDR-TB are globally about 3.8%. Concerning forms of extensive drug resistant tuberculosis (XDR-TB) (not only resistant to isoniazid and rifampicin, but also to fluoroquinolones, and at least one of the injectable second-line drugs) there are no official data because of a lack of outcomes on second-line drug sensitivity, but estimates report about 25,000 cases in the world.[4] In 2013 there were an estimated 1.3 million TB deaths (320,000 among HIV-positive people and 170,000 among MDR-TB patients).[1]

CLASSIC CLINICAL AND RADIOLOGICAL PATTERNS OF PRIMARY AND POST-PRIMARY TB

Classically we are used to distinguishing between primary TB, typical of childhood, which may occur immediately after the first exposure to mycobacterium TB, and post-primary TB, as a reactivation of a previously dormant primary infection or exogenous superinfection. Among the radiological manifestations of primary TB, the most common is thoracic lymphadenitis: usually unilateral in the right hilum or paratracheal/subcarinal, which is found in the chest X-ray of 90-95% of children.[5,6] In adults, the most common manifestation is a pulmonary cavitated consolidation (70% of cases),[7] most often at the upper right lung, homogeneous, dense, and anatomically confined to a segment or a lobe of the upper lung. Nowadays it is much more rarely demonstrated than in the past to find the typical 'primary complex' or 'Ranke complex' consisting of parenchymal consolidation, hilar lymphadenitis, and lymphangitis, which was the most frequent manifestation of primary TB in the past.[5]

The post-primary TB, in its nodular form, tends to be initially localised to the apical and posterior segment of the upper lobes, and is most often the result of reactivation of a primary disease, which starts simultaneously with an immunosuppression state.[3] It has been hypothesised that these localisations are linked to a relatively higher partial pressure of oxygen in these areas of the lung as a result of a higher pulmonary ventilation/perfusion ratio, or a lower lymphatic drainage, resulting from a decreased pulmonary arterial flow.[6] In 50-70% of patients, focal areas of consolidation with no defined margins can be observed, and, in most cases, the consolidation is confined to a segment or portions of different segments of a lobe. Frequently, bronchovascular structure thickening is evident in the direction of the ipsilateral hilum, and cavitations are more frequently observed than in the primary disease.[7] These may be single or multiple, and are most often localised in the apical and posterior segment of the upper lobes or the superior segments of the lower lobes.[6] The miliary TB, another classic form of post-primary TB, is now more frequently seen, but not exclusively, in immunocompromised patients (Figure 1).[6]

Currently, however, at least from a radiological point of view, the distinction in primary and post-primary TB has been challenged: the radiological features of TB are described in relation to the host immune status. Jeong YJ et al.,[3] in a recent study based on genotyping of mycobacterium TB isolated by restriction analysis technique of restriction fragment length polymorphism, shows that the radiological manifestations of primary and post-primary TB are often similar, and that the time between infection and TB disease is not a reliable predictor of radiographic appearance. The only proved independent risk factor seems to be the integrity of the host immune response. More specifically, patients with severe immunodepression would most often develop forms of 'primary TB' or atypical forms, while immunocompetent patients tend to develop classical post-primary forms by a mechanism of 'reactivation or reinfection'.[3] In light of these new concepts and recent developments in imaging techniques, we would like to describe the emerging clinical and radiological patterns of pulmonary TB, emphasising the increasingly central role that high-resolution CT scan has achieved in the diagnosis of this disease.

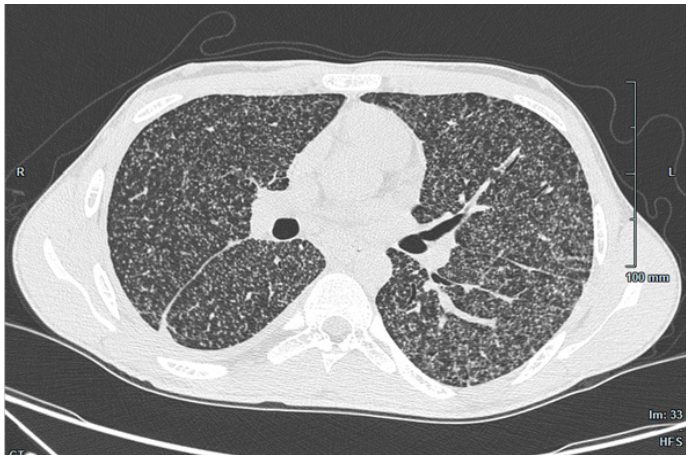

Figure 1: Miliary tuberculosis in a young immunocompetent Italian patient.

High-resolution Computed Tomographic (HRCT) Patterns

Patients with pulmonary TB, even in its active form, may be asymptomatic or paucisymptomatic and, even when present, symptoms are nonspecific. Furthermore, microscopic examination of sputum is negative in a significant percentage of patients (approximately 50%),[1,2] particularly in those who are immunocompromised, and then it is an important role that radiology, especially in these cases, can play, in order to start an early treatment, even before a definitive diagnosis has been obtained with a culture test.

Chest X-ray, which is the radiological investigation of first choice, and still has an important role as a screening test, and in the assessment of therapeutic response, may be normal (especially in HIV-positive patients with low CD4+ cell count <50 cells mm^3) or shows nonspecific features. On the other hand, chest CT scan, and, in particular, high-resolution CT, shows a higher sensitivity in detecting small localised lesions, not detectable by standard X-ray, scattered lesions, hilar and mediastinal lymphadenopathy, cavitations, endobronchial spreads, sequelae, and complications.[7,8] It has also been found to be most useful in distinguishing the active forms of TB and in the management of more complex forms, such as MDR-TB. Balkan et al.[9] concluded that the sensitivity, specificity, and positive and negative predictive value of high-resolution CT in defining the forms of active TB were respectively 97%, 86.7%, 94.2%, and 92.9%.

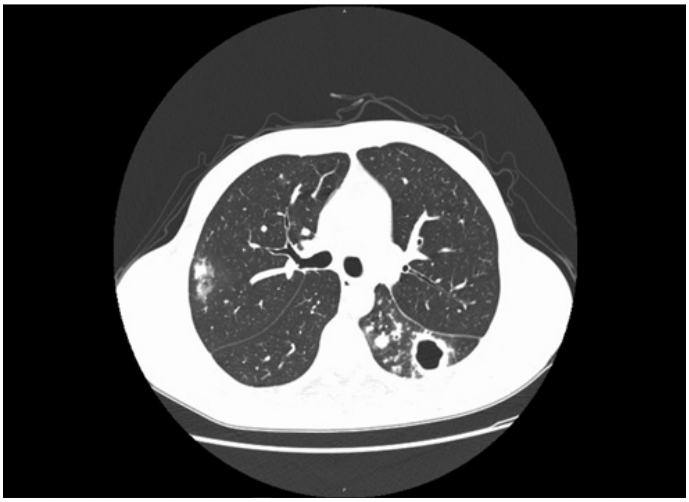

Figure 2: Nodular pattern with cavitation in a young immunocompetent patient from Senegal.

Furthermore, chest HRCT scan can be used as a non-invasive diagnostic method; especially in patients suffering from smear and culture negative active TB.

The most common HRCT patterns of the chest can be summarised as follows:

1. Parenchymal consolidation, understood as a uniform increase in the density of the lung parenchyma, associated or not with air bronchogram sign;
2. Solitary nodule or multiple nodules with a diameter >1 cm, rounded, margins defined, in random distribution, homogeneous, or with cavitation in their context (Figure 2);
3. Ground-glass pattern, with uniform increase in the density of the lung parenchyma and preservation of vessels and bronchi;
4. Reticular, or reticular/nodular pattern with smooth or nodular thickening of interlobular septa and of peribronchovascular connective;
5. Bronchiectasis, defined as irreversible dilatation of the bronchi throughout their course and thickening of their walls;
6. Centrilobular nodules of <1 cm in diameter, localised in the centre of the lobule on the respect of the secondary pulmonary lobule, related to linear thickening (tree in bud) (Figure 3);
7. Mediastinal lymphadenopathies with a diameter >1 cm, and presence of calcifications in their contest (Figure 4).

The ability to differentiate old fibrotic lesions, bronchiectasis, bronchovascular distortion, paracicatricial emphysema (all signs of not active TB), from active tuberculous lesions, mainly centrilobular nodules, three in bud pattern, acinar nodules, consolidations, cavitations, is of crucial importance for starting an early treatment, especially in forms sputum and culture negative, but with a strong clinical and radiological suspicion of TB.[10] Chest CT scan has now reached such an accurate definition of the pulmonary lesions that, in contrast to what happened in the era of the conventional radiography, today for the radiologist and clinician, it is like looking at a slide under the microscope: the observed alterations at CT scan correspond perfectly to the histopathologic pattern.[11,12]

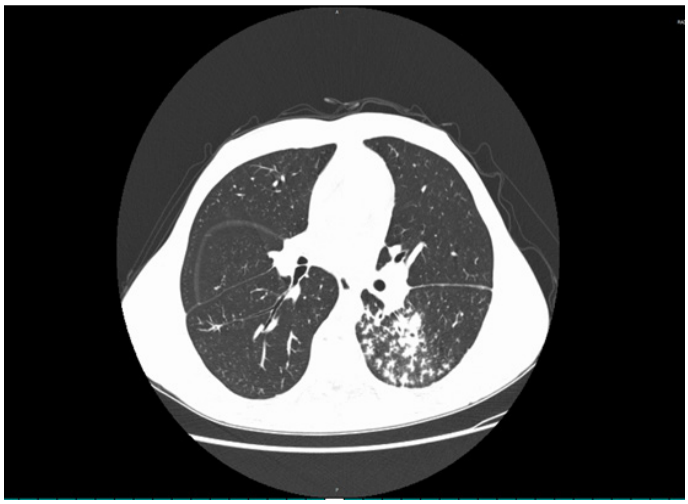

Figure 3: 'Tree in bud' pattern in a young immunocompetent patient from Morocco.

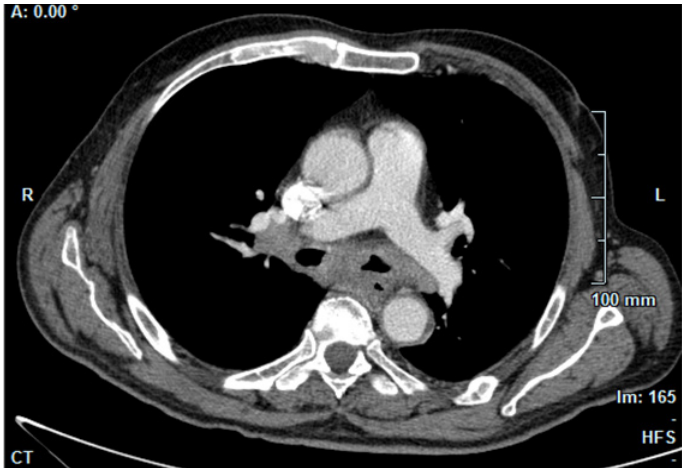

Figure 4: Endobronchial tuberculosis and subcarinal lymphadenitis in an elderly Italian patient.

CT images correlate with the histopathologic lesions suggestive of TB: the defined nodules normally underlie an area of central necrosis with peripheral nonspecific inflammation, while well-defined nodules and random distribution, suggestive of miliary TB, histologically correspond to nodules of 4-5 mm in diameter, each consisting of 3-4 granulomas consisting of central caseous necrosis, epithelioid cells, and Langhans giant cells, surrounded by lymphocytes and fibrous tissue in the periphery. These correspondences also help us in evaluating the effectiveness of treatment for TB: the resolution of the lesions begins from the most peripheral portions, and is confirmed by the presence of nodular calcifications, parenchymal fibrotic area, bronchovascular distortion, emphysema, and bronchiectasis.[7,8]

Atypical Pulmonary Patterns of TB

The combination of several abnormalities such as cavitations, nodules, and segmental or lobular consolidations, associated with mediastinal or hilar lymphadenopathy, makes it probable for the diagnosis of active TB.[13] This set of features, however, is rarely seen in clinical practice, where the differential diagnosis is a complex exercise that makes it necessary, and recommends a constant comparison between clinicians, radiologists, clinical microbiologists, and pathologists. With the reduction of the circulation of mycobacteria in the environment, the classic primary disease has become more common in adults, but the thoracic lymphadenopathy is observed only in 10-30% of cases. The mediastinal or hilar lymphadenopathy may also be present in the form of post-primary TB, often associated with parenchymal consolidations, but also as the only manifestation of the disease.[14] This presentation is rare and has been observed especially in immunocompromised patients, such as those with AIDS, but also in young immigrants from countries with high TB endemicity.[15,16]

Unusual and most typical of immunocompromised patients, and the elderly, are the consolidations localised in the basal segments of the lower lobes.[14] In these cases, while a chest X-ray is not able to distinguish the tubercular lesions from a nonspecific bacterial pneumonia, chest CT scan is able to highlight typical features such as the presence of necrosis or cavitations (especially after infusion of contrast medium) or bronchial and bronchiolar lesions, including the typical pattern of 'tree in bud'.[16] Pulmonary TB can radiographically manifest as interstitial disease with patterns different from the 'tree in bud', such as 'ground glass', patchy bilateral opacities, and centrolobular lesions, making it difficult to establish a differential diagnosis from interstitial lung diseases.[8] Expression of haematogenous dissemination of the bacteria, the miliary disease makes major problems of differential diagnosis, especially with metastatic carcinoma, and radiologically occurs as a spread of innumerable nodules of a diameter of 1-5 mm, in random distribution, and in relation to structures of the secondary pulmonary lobule. It is more common among the elderly and in the young immunocompromised patients, and is easily identifiable by chest high-resolution CT scan.[6]

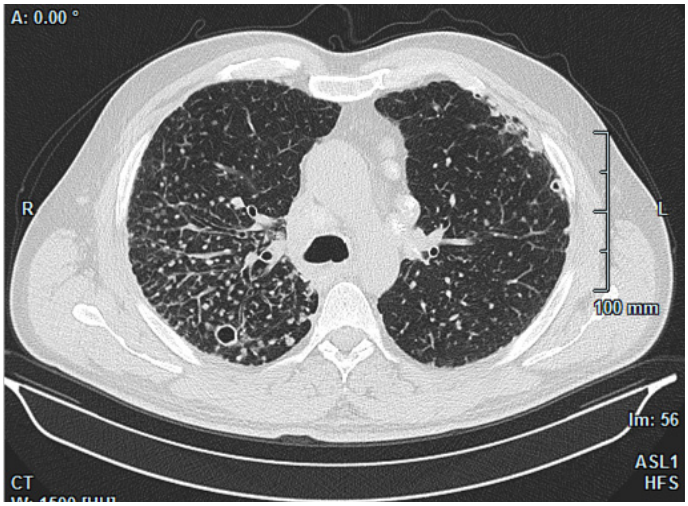

Figure 5: Pulmonary tuberculosis and silicosis in a patient aged 55 years.

Other rare radiological manifestations are tuberculoma (nodule larger than 1 cm in diameter, with calcifications inside and surrounded by satellite nodules), nodular thickening of the interlobular and interlobar septa, nodular irregularities of vessels, ground glass areas, and bronchiectasis, the latter most often as a fibrotic recovery of the disease.[6] According to current beliefs on imaging in pulmonary TB, which correlate the radiographic changes with the immune status of the patient, many authors agree that, especially in immunosuppressed individuals, such as HIV-seropositive patients, the chest X-ray features are similar to that of nonspecific pneumonia and in a small percentage of cases (10%), it is negative. This non-specificity of the lesions, associated with the frequent negativity of the sputum microbiological examinations, makes pulmonary TB even more difficult to diagnose. In these patients, in contrast to what has been shown in HIV-seronegatives or in a population not severely immuno-compromised, atypical patterns are most frequently found, most often diffuse nodules or reticular-nodular opacities (Figure 5). Consolidations and cavitations are less common in patients with low CD4+ cell count (≤50 cells mm^{-3}), with frequent hilar mediastinal lymphadenopathy as the only thoracic finding in the absence of parenchymal lesions.[17,18]

In addition, several authors have evaluated in studies of adults who were seronegative for HIV, the different CT patterns in sensitive pulmonary TB and MDR-TB and XDR-TB, concluding that in the latter group patients are often observed with bilateral diffuse localisations of the illness and alterations not commonly found in drug sensitive (DS) patients, such as multiple cavitations, spreading of small nodules, 'tree in bud', and bronchial dilatations.[19,20] Obviously TB is a slowly progressive disease and presentation may be very different, depending on whether the examination is performed at an early or late stage. The 'ground glass pattern' and larger nodules are observed quite frequently in the DS forms.[19]

CONCLUSIONS

Since early diagnosis of pulmonary TB plays a crucial role in the spread of the disease and in the prognosis of the patients, it is crucial to recognise the specific or unspecific radiographic patterns of pulmonary TB, which is now possible thanks to the chest CT scan, both with the infusion of contrast medium or using the high-resolution technique. A useful exercise is to review the CT images as a pathologist, looking for matches between radiologic features and pathologic lesions. Numerous studies have shown that the chest X-ray features of TB do not correlate with the time of infection, but with the immune status of the host, so that the primary and post-primary TB may occur in a similar manner. Among the less frequent patterns, the hilar or mediastinal lymph node enlargement, especially when not associated with pulmonary consolidations, displays features indistinguishable from those of non-specific pneumonia, not classified lesions, diffuse nodules, reticulonodular opacities, and are more typical of TB in HIV-positive patients. Bilateral localisations, multiple cavitations, pleural effusion, disseminated micronodules, 'tree in bud', and bronchial dilatation are more frequently found in the MDR and XDR-TB forms.

The progress of imaging techniques helps us in the diagnosis of the most cryptic forms, not only from a radiological point of view, but also in the clinical management of severe disease, as well as in the differentiation between active and inactive forms, and in the differential diagnosis with other diseases (cancer, ILD, pneumonia). This has important clinical implications and allows doctors to not only start an appropriate early treatment, but also evaluate the effectiveness of therapy with greater accuracy.

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