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RESEARCH ARTICLE

Atypical Computed Tomography Features of Pulmonary Tuberculosis: Findings and Diagnostic Challenges

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ABSTRACT

Pulmonary tuberculosis, caused by Mycobacterium tuberculosis, remains a global health concern, with diverse clinical presentations that can often pose diagnostic challenges. While conventional imaging modalities such as chest X-rays have been crucial in screening and diagnosis, limitations in sensitivity and specificity have led to an increased reliance on computed tomography imaging that plays a pivotal role in identifying features that may not be readily apparent on standard radiographs. However, computed tomography scans may show subtle and unique features that can overlap with other respiratory conditions leading to a delay in diagnosis and treatment. They mainly include uncommon lung lesions (like masses, solitary or multiple nodules, cystic lesions, ground glass opacities and reversed halo sign) and location particularly to the lower lobes as well as the association with other pulmonary conditions like emphysema, interstitial lung disease and lung cancer.

This paper aims to elucidate the atypical computed tomography features of pulmonary tuberculosis that clinicians and radiologists should be mindful of to improve diagnostic accuracy.

Keywords: Pulmonary tuberculosis, computed tomography, mass, nodule, cyst, ground glass opacity, reversed halo sign, lung lower lobe, diffuse lung disease

I. Introduction

Tuberculosis (TB), caused by Mycobacterium tuberculosis, is still an endemic infection worldwide particularly in low-and middle-income countries with 10 million new cases per year[1]. It is estimated that a quarter of the world's population has been infected with TB[1]. TB was the leading cause of death from an infection before the COVID-19 era and causes twice as many deaths as HIV/AIDS.

Screening for tuberculosis in the target population is based on symptoms, molecular tests and chest X- ray (CXR). The latter has a sensitivity varying between 85 and 94% and a specificity varying between 89% and 96%. Computer-aided detection is being recommended as an alternative to physicians' interpretation with target sensitivity and specificity higher than 90% and 70%, respectively[2].

Computed tomography (CT) is more sensitive than CXR for the detection of subtle signs of pulmonary TB. Typical features include consolidations, centrilobular micronodules with a tree-in-bud feature, nodules and consolidations. Cavitation is a hallmark of activity and is correlated with positive smear sputum. Lesions are typically located in the upper lobes and the Fowler segments[3].

However, CT scans may show subtle and unique features that can overlap with other respiratory conditions leading to a delay in diagnosis and treatment. These mainly include uncommon lung lesions and locations as well as the association with other pulmonary conditions. There is a predisposition for unusual tubercular sites and features in patients with conditions affecting cell-mediated immunity such as immunosuppression caused by HIV/AIDS, immune-mediated inflammatory diseases, steroid use, organ transplant recipients, malnutrition and low body mass index, diabetes, smoking and alcohol consumption[4].

This paper is a narrative review of atypical CT features of pulmonary TB that clinicians and radiologists should be mindful of to improve diagnostic accuracy.

II. Uncommon computed tomography features:

1. MASSES :

TB and lung cancer often present with the same clinical symptoms and physical signs such as weight loss, chest pain, hemoptysis and cough. Radiological signs of both conditions are different in most cases. However, TB may present with a phenotype that overlaps with peripheral lung cancer explained by the widespread of consumption of antibiotics and the aging population[5]. Pseudotumoral TB is rare and accounts for less than 5% of all cases of pulmonary TB, particularly in immunocompetent patients[6,7,8]. Both conditions may be associated in extremely rare cases[6]. CT is commonly used to characterize lung nodules and masses based on their size, shape, margins, density, enhancement and follow-up in order to suggest whether they are benign or malignant. Radiomics, which involves computer analysis of image features may help distinguish TB from lung cancer[9]. Some CT features that may help distinguish TB from lung cancer include the low-density center, ring-like enhancement, location to the upper lobes and Fowler segments, and association with centrilobular micronodules (figure 1). Proof of TB infection is obtained through lesion biopsy with pathological and bacteriological examinations.

2. SOLITARY NODULE:

Solitary pulmonary nodules are discovered in less than 1% of cases on CXR and on 30% of CT scans[10,11]. Every solitary nodule should be characterized by CT and should have the appropriate work up according to its density and size. More than 95% of identified solitary nodules are benign and correspond either to granulomas or intra-parenchymal lymph nodes[11]. Typical features of benignity include the presence of macroscopic fat, concentric, popcorn or central calcifications as well as a long doubling time. Typical features of malignancy include irregular margins, bronchogram, bubble-like lucencies as well as short doubling time and growing sub-solid nodules. Sometimes, some nodules may remain

indeterminate[12]. It is reported that TB is responsible for 57 to 92% of false positive diagnosis of primary lung cancer in endemic regions[13]. It is difficult in front of a single nodule to suggest tuberculosis particularly when it is a sub-solid nodule. TB is identified in less than 1% of surgically removed nodules. Atypical mycobacteria cause more frequently solitary nodules than Mycobacterium *tuberculosis*. Nodules may correspond to tuberculomas or less frequently to an active TB[14]. Presence of calcification and ring-like enhancement in an endemic context makes the diagnosis of tuberculomas easy (figure 2). TB solitary nodules may be cavitary or not, whether corresponding to tuberculomas or not[15]. Tree-in-bud pattern and satellite lesions favor the diagnosis of TB whereas lobulations, pleural indentations and vessel convergence favor the diagnosis of lung cancer[13].

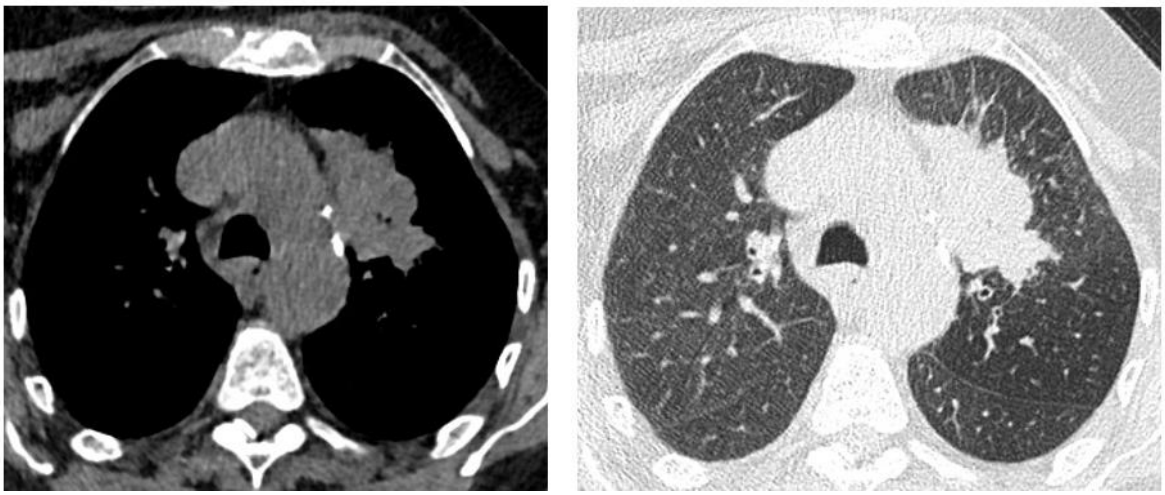

Figure 1: *Isolated mass of the culmen in a 75-year-old women. Transparietal biopsy : TB*

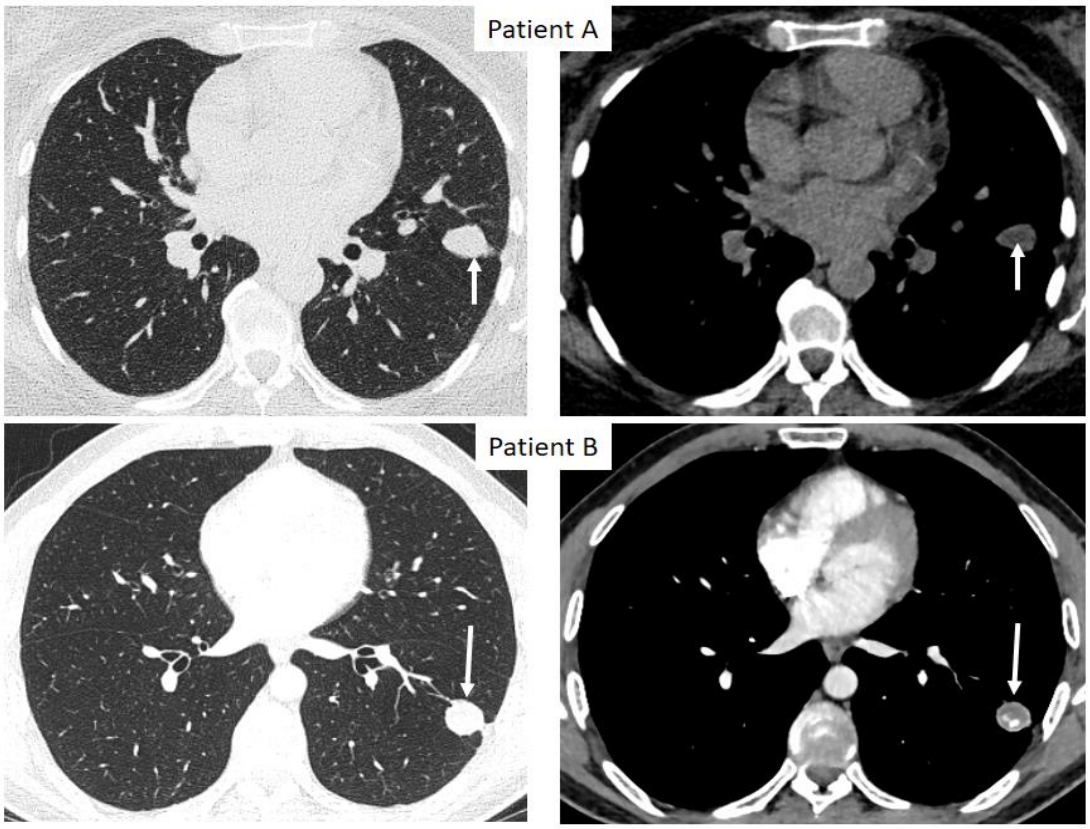

Figure 2: *Solitary nodules in two different patients (arrows). Patient A: nodule of the lingula with central necrosis. Patient B: Nodule of the left lower lobe with central necrosis, calcifications and ring-like enhancement. Lung biopsy in patient A and surgery in patient B confirmed the diagnosis of pulmonary TB.*

3. MULTIPLE NODULES:

Hematogeneous dissemination of TB typically results in a miliary feature, which corresponds to dense, tiny and randomly distributed micronodules. Nodules with more than three millimeters size is a rare feature of hematogeneous spread. They may be associated to a pleural effusion or to other organs involvement[16]. Presence of multiple nodules, first suggest metastasis, especially when there is no sign of bronchial dissemination. Cavitation may suggest granulomatosis with polyangeitis[17] (figure 3).

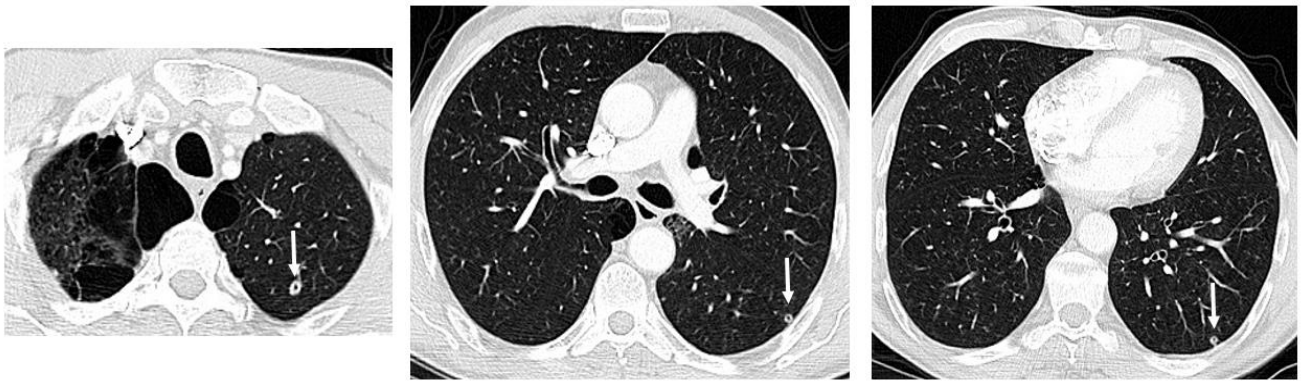

Figure 3: three cavitary nodules of the left lung with no other sign suggestive of TB in 54-year-old men. Surgical biopsy confirmed the diagnosis of TB

4. GROUND GLASS OPACITIES:

Ground glass opacities (GGO) are defined by high-density parenchymal areas with vessels and bronchial walls remaining visible inside. They may result from an interstitial modification or from an incomplete alveolar filling. GGO are rare in TB, they are present in less than 1% of cases of active TB. They are particularly observed in HIV seropositive patients[18]. Patients present generally with respiratory failure or acute respiratory distress syndrome. GGO generally coexist with a miliary feature and with interlobular septal thickening[19,20,21] (figure 4). It may also be observed in paradoxical reaction or in patients with lung transplant[22,23].

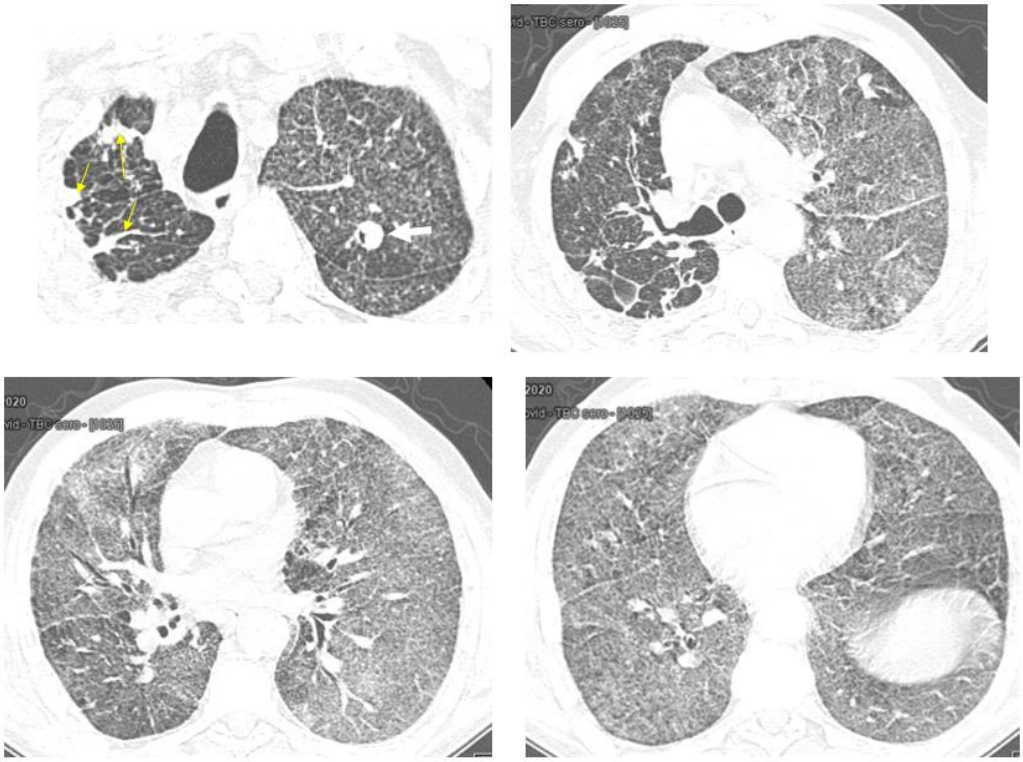

Figure 4: Respiratory failure in a 54 year-old men. CT showed TB sequels of the right lung (yellow arrows), with a cavitary nodule of the culmen (white arrow) and diffuse GGO. Sputum culture: TB positive

5. REVERSED HALO SIGN:

Reversed halo sign refers to a parenchymal consolidation surrounding an area of a central lucency or GGO. It was first described in cryptogenic organizing pneumonia. However, it was later on described in secondary organizing pneumonia to many other conditions such as infections or radiotherapy and in many other conditions[24,25]. It is significantly highly observed in granulomatous diseases, particularly in TB, rather than in non-granulomatous diseases[25]. This sign is observed in 17% to 29% of patients with active TB[25,26]. It is characterized by the presence of nodules or micronodules within and inside the wall. The peripheral rim may be complete or incomplete[26,27]. Lesions may be solitary or multiple[28] (figure 5). Pathology studies confirm the presence of granulomas in the wall, with or without acid-fast stain positivity as well as caseous necrosis[25,28]. The nodular reversed halo sign is not exclusively observed in TB. It may also be found in cryptogenic organizing pneumonia, lung cancer, sarcoidosis, cryptococcosis, and granulomatosis with polyangiitis[26]. Its association with more typical features is suggestive of the diagnosis.

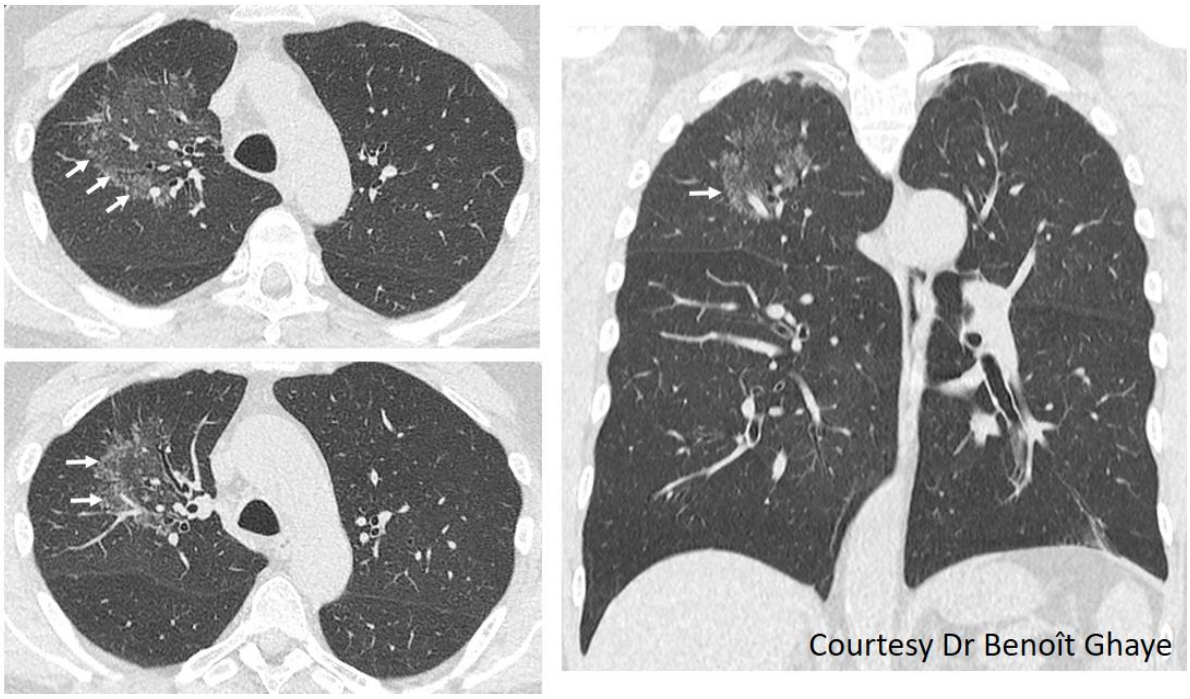

Figure 5: Subtle reversed halo sign of the right upper lobe with peripheral micronodules (arrows). The diagnosis of TB was confirmed by surgery

6. CYSTIC AND BULLOUS LESIONS

Cysts, defined as airspaces with a thin wall, are an extremely rare feature of pulmonary TB. There are only few published papers about this condition. This pattern occurs accordingly often in young people and children as well as in women[29,30,31,32,33]. Patients present generally with severe respiratory impairment[29]. Cysts may appear before or during anti-tuberculous treatment and they may be complicated by pneumothorax or pneumomediastinum[24,29]. Cysts predominate to the upper lobes and the mid lungs and curiously to the anterior regions[29,34]. They are frequently of a small size[29]. They generally coalesce and have an irregular shape[30] (figure 6). Proposed mechanisms for the development of such lesion include the check-valve effect caused by granulomatous inflammation development in distal bronchi, cystic bronchiectasis following caseous necrosis of bronchial walls, interstitial air leakage following rupture of tubercle lesions and bronchioles dilatation[29,30,31,32]. They may increase in size especially in the first weeks of treatment and they may resolve or be stable later on[29]. Cystic TB is lethal in 14% of cases[32,34,35].

Differential diagnoses include Langerhans histyocytosis, lymphangioleiomyomatosis, pneumocystois and lymphocytic interstitial pneumonia[29,30].

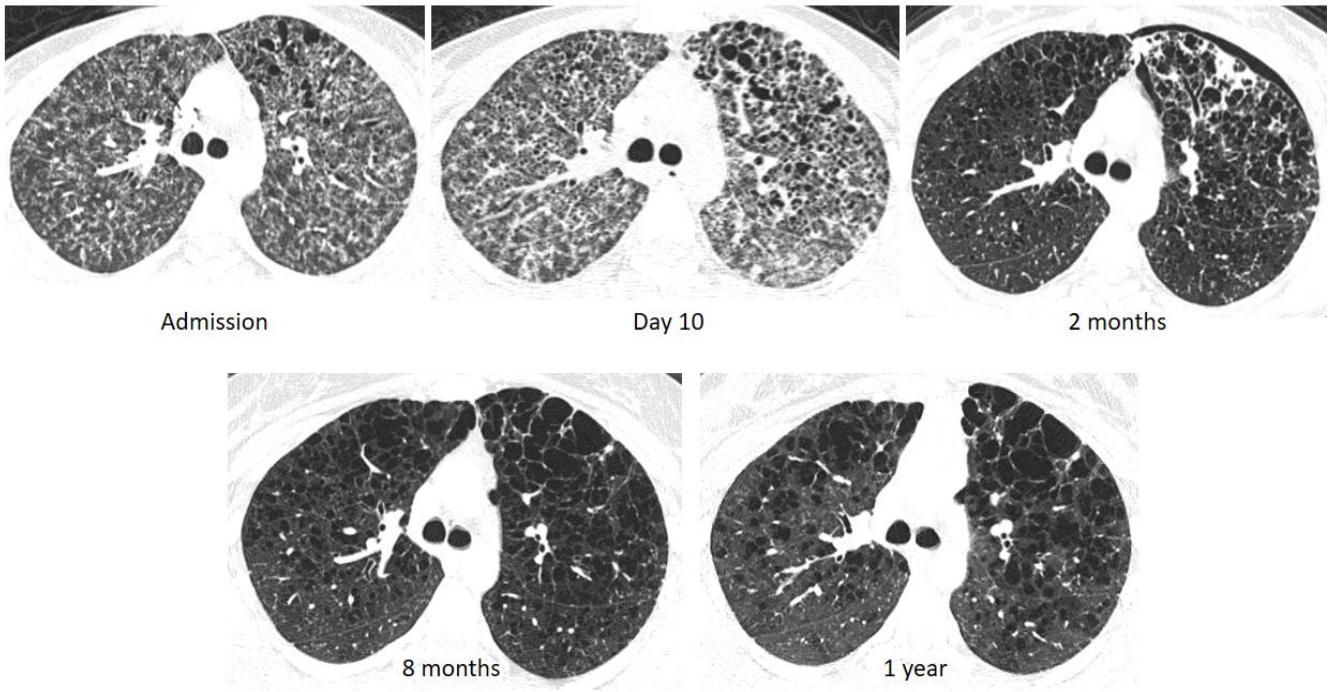

Figure 6: a 21 year-old women presented with fever and respiratory failure. CT at admission showed a pulmonary miliary and few cysts of the culmen. PCR fo TB was positive. Cysts enlarged at day 10 control. They were complicated by a pneumothorax at 2 months. They became bigger and remained stable thereafter

III. Uncommon location of pulmonary tuberculosis:

Classically, post primary TB lesions are located in the upper lobes and in the Fowler segments. However, in immunocompromised patients, consolidations can be observed in the basal segments of the lower lobes. TB of the lower lobes is defined by the presence of lesions exclusively under the carina[36] (figures 7 and 8).

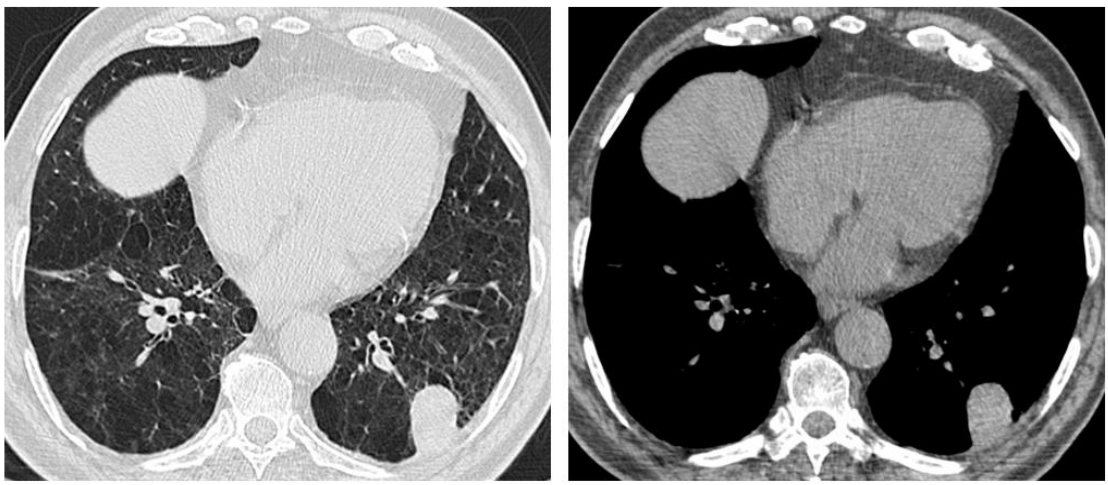

Figure7: a well-limited and isolated mass of the lower left lobe that was removed by surgery. Pathology examination confirmed the diagnosis of TB

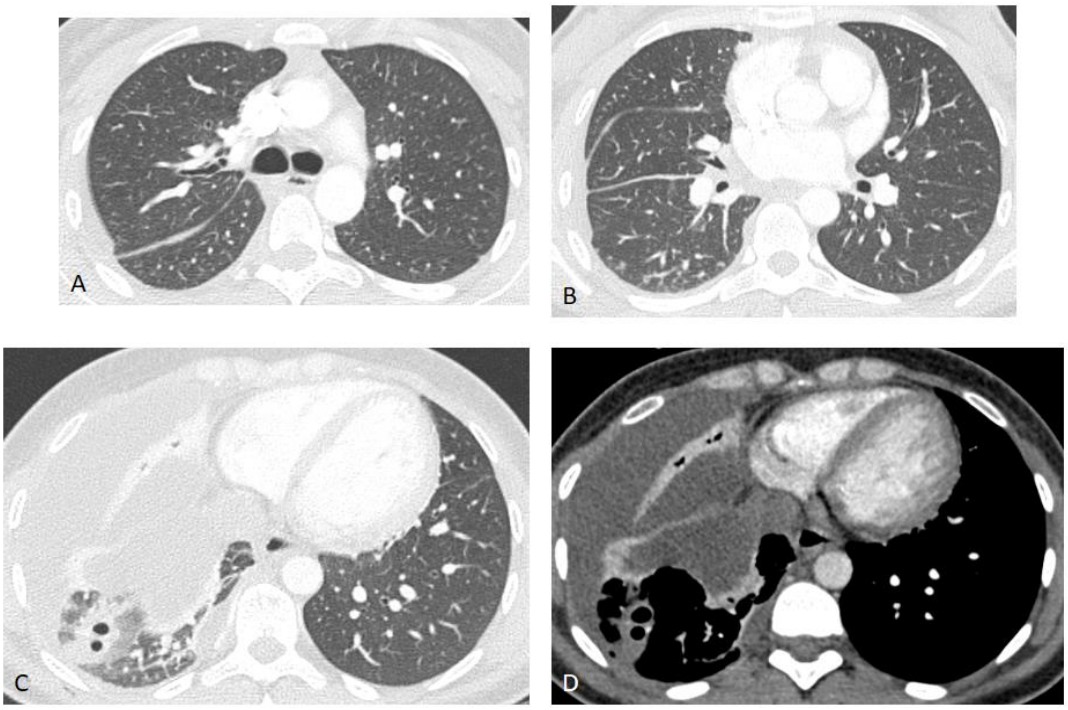

Figure 8: A 28 year-old women presented initially with isolated right pleural effusion. Two weeks later, she developed acinar nodules and cavitary consolidation of the right lower lobe with no lesions of the upper lobes. TB positive in the pleural fluid.

IV. Association with other pulmonary conditions:

1. EMPHYSEMA

Patients with chronic obstructive lung disease have a higher risk than normal population to develop tuberculosis[37]. In fact, in case of emphysema, there is a local lack of phagocytocis cells and general immune suppression explained by constant systemic inflammation. Lesions location does not differ between patients with or without emphysema. However, consolidations are more frequent than tree-in-bud feature. In fact, they are present in 82% of TB cases whereas tree-in-bud is present in only 36% of cases[37,38].

Development of consolidations on a background of emphysema may result in a honeycomb-like feature or may look like tuberculosis cavity[16] (figure 9).

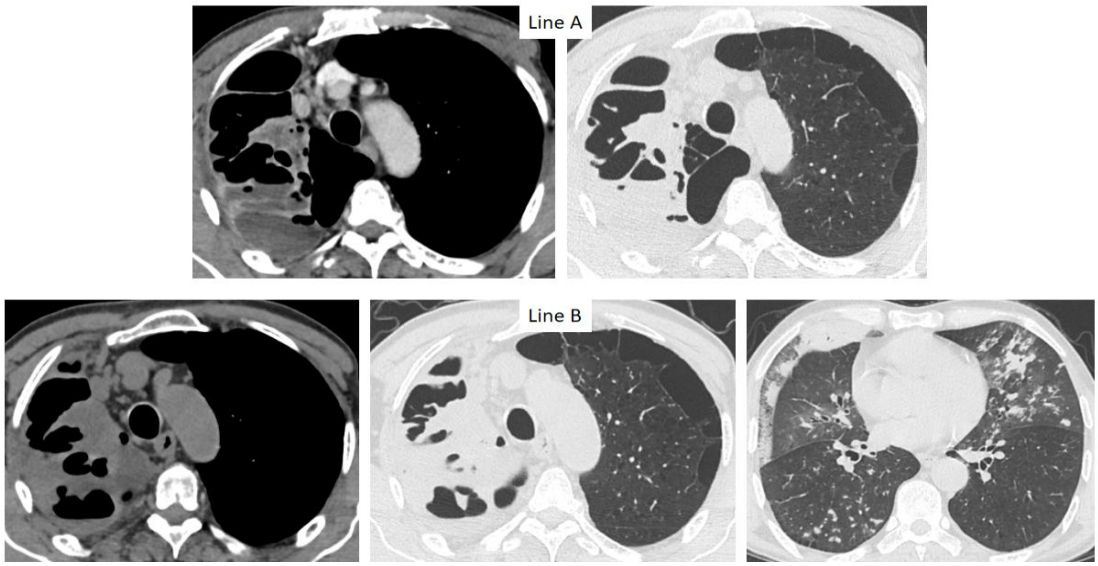

Figure9: A 59 year-old men presented with fever and increased blood inflammatory markers. First CT (line A) showed complicated bullous emphysema of the right upper lobe. The patients didn't improve under antibiotics. Second CT showed persistence of complicated emphysema and new signs of active TB. Sputum culture positive for TB.

2. INTERSTITIAL LUNG DISEASE:

Coexistence of TB with an interstitial lung disease (ILD) is a rare situation. ILDs are observed in 6% of TB positive patients. UIP is the most frequently reported ILD to be reported[39]. Previous studies confirmed that TB is 4 to 5 times more frequent in patients with ILDs, than in other patients. Presence of an underlying ILD may lead to misdiagnosis of TB either clinically or radiologically[40]. Lesions are, as usual, often located to the upper lobes. However, non-segmental consolidation, developing in fibrotic areas without centrilobular micronodules, is the most frequent sign[39].

Some ILDs may be misdiagnosed as TB if clinicians and radiologists are not aware of these conditions particularly in countries with high TB burden[41]. In fact, TB and silicosis may present with fibrotic lesions of the upper lungs, micronodules nodules and calcified lymph nodes making the radiological diagnosis difficult. Cavitation, hallmark of active TB, is also possible in silicosis. Co-occurrence of TB and silicosis, known as silicotuberculosis, is also frequently reported in miners and in countries with extractive industries whether they have a heavy burden of TB or not. Silicosis multiplies the risk for TB by 2.5, which is explained by the impairment of antibacterial mechanism by silica exposure[42,43] (figure 10).

Sarcoidosis is the second ILD that may mimic TB. In fact, lesions in the fibrotic form predominate to the upper lungs making distinction with TB sequels sometimes difficult. However, the proximal and peri-bronchovascular distribution of lesions as well as the presence of perilymphatic micronodules help diagnosis. Miliary sarcoidosis is the second presentation that may make the diagnosis confusing[36] (figure 11). Moreover, both diseases may be associated. As both diseases may share the same clinical, radiological and immunological features, sarcoidosis should be considered whenever TB is diagnosed and the patient does not improve under adequate and well-conducted treatment[44].

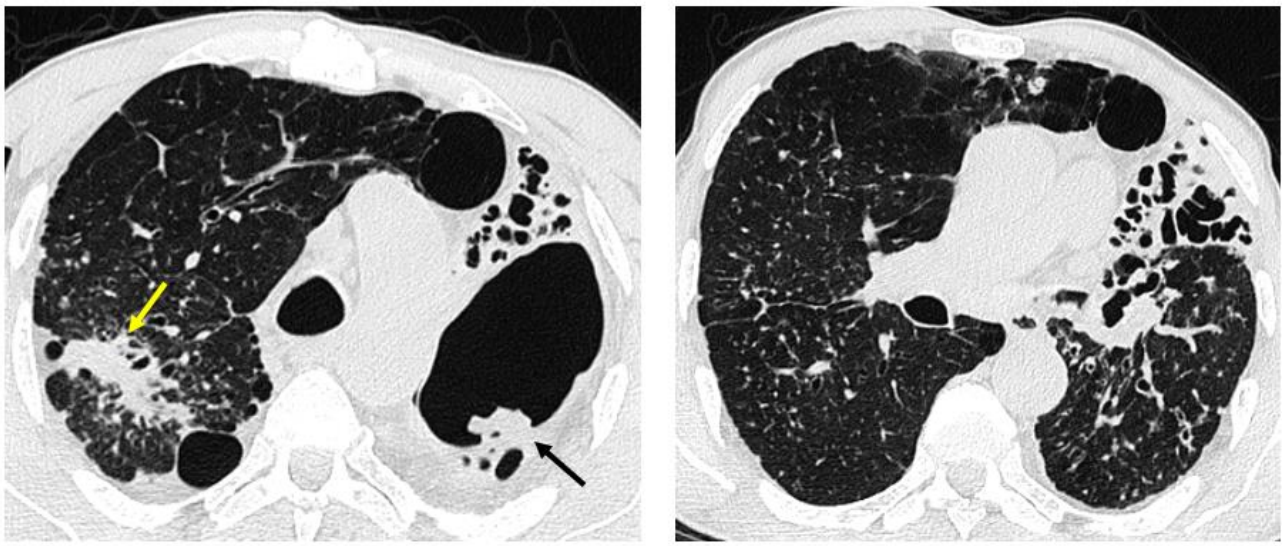

Figure 10: a 70 year-old men with silicotuberculosis. CT shows fibrotic mass of the right upper lobe (yellow arrow) with bilateral perilymphatic micronodules. Sequels of TB are obvious in the left upper lobe with aspergilloma development (black arrow)

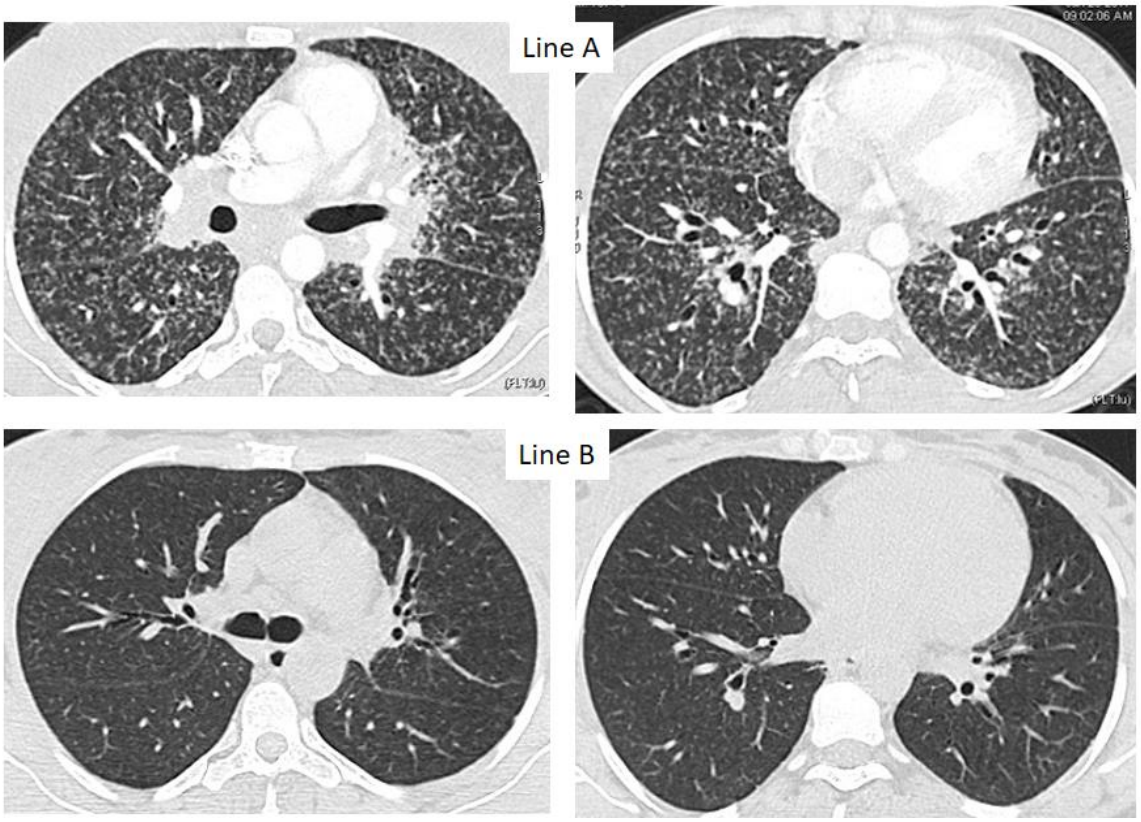

Figure 11: Miliary feature in a 32 year-old woman with mediastinal and hilar enlarged lymph nodes (line A). Bronchial biopsy showed tuberculoid granuloma with tiny necrosis. The patient didn't improve under anti-tubercular treatment and improved under corticosteroids.

3. LUNG CANCER

The association between tuberculosis and cancer is not fortuitous. Chronic inflammation and the process fibrous healing causes metaplasia predisposing to malignant transformation[45]. Two recent meta-analysis demonstrated that TB increases the risk of lung cancer development with an odds ratio of 1.74 and 2.09. This risk is high in the first 2 years after TB and decreases thereafter. It is also higher in young people[46,47]. A relationship has been found between pulmonary tuberculosis and EGFR mutations in patients with lung adenocarcinoma. The diagnosis is difficult due to the existence of sequelae lesions. Occurrence of lung cancer is suggested on CT by the modification of pre-existing lesions, the convexity of their contours, the appearance or existence of pleural extension and bone lysis. When a patient first presents with lung cancer, coexistence of TB is suggested when there is an association of tree-in-bud feature, acinar nodules, cavitary consolidations and nodules in relevant areas[45].

V. Conclusion

Atypical imaging findings are far to be uncommon in pulmonary TB, which may lead to delay in diagnosis and treatment. CT scan plays an essential role in the diagnosis of these forms that can occur in conditions affecting cell-mediated immunity. Therefore radiologists should be aware of these unusual imaging features to avoid misdiagnosis and to guide bacteriological sampling and, if necessary, biopsies with histological and bacteriological study.

Conflicts of interest:

All authors declare that they have no conflict of interest in relationship with this work.

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