Pulmonary involvement in pleural tuberculosis: How often does it mean disease activity?

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KEYWORDS
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Summary
Objective: To evaluate in chest X-rays and high-resolution computed tomographies of patients with pleural tuberculosis, the incidence of parenchymal and mediastinal lung lesions suggestive of active disease.
Methods: Prospective study (2008–2009) evaluating the radiographic and tomographic abnormalities of 88 HIV-negative patients with pleural tuberculosis (unilateral effusion). The images were reviewed by 3 independent specialists, and the observed changes were classified according to previously established criteria: presence or absence of signs suggestive of disease activity, and nonspecific findings.
Results: Abnormal changes were observed in chest X-rays of 22 (25%) patients and in the computed tomography of 55 (63%). Images compatible with active pulmonary tuberculosis were detected by radiography in 9 (10%) patients and by tomography in 38 (43%). Only 4 (4.5%) patients had tomography images suggestive of residual disease.
Conclusion: The present study demonstrates that pulmonary involvement is quite common in pleural tuberculosis. This finding is mainly observed in high-resolution computed tomography and has important epidemiological implications, since patients with pleural tuberculosis are significant sources of infection and disease dissemination.

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Introduction

Tuberculosis continues to be a significant public health problem especially in developing countries. The estimated number in 2008 was 9.4 million cases, most of them occurring in Asia (55%) and Africa (30%). With an approximate incidence of 39 cases/100,000 inhabitants, Brazil is one of the 22 countries responsible for 90% of all worldwide cases. Among the diverse clinical presentations, the frequency of the extrapulmonary form ranges from 9 to 46%. This form has become more frequent after the emergence of the human immunodeficiency virus (HIV) and the widespread use of immunosuppressive drugs. In Brazil, the extrapulmonary form accounts for 14–18% of diagnosed cases of tuberculosis, and pleural involvement is observed in about 50% of these patients. In this clinical presentation, the involvement of the pleural space occurs from pulmonary lesions with lymphatic and/or hematogenic dissemination, or as a result of rupture of a subpleural or nodal caseous focus. The presence of mycobacteria or their cellular wall antigens triggers a delayed hypersensitivity reaction that culminates in an exudative pleural effusion.

Traditionally, pleural tuberculosis is classified as primary when the disease develops after initial exposure to Mycobacterium tuberculosis. This form generally affects young adults living in regions with a high prevalence of disease. The post-primary form, which is associated with reactivation of a pre-existing focus, occurs after long periods of infection and is more frequent in elderly populations from regions with a low prevalence of the disease. This classification is currently controversial especially when we consider that the two forms have similar clinical manifestations. In addition, molecular evidence indicates simultaneous pleuropulmonary involvement. This fact has an epidemiological impact, given that many patients with pleural tuberculosis are not adequately evaluated regarding to the real intrathoracic compromising.

In medical practice, the chest X-ray is the first complementary exam requested when pleural tuberculosis is suspected. Besides confirming the presence of a pleural effusion, this method permits the investigation of associated intrathoracic lesions. Nowadays, the superiority of high-resolution computed tomography (HRCT) for identifying these lesions is well recognized. However, it should be highlighted that the radiological identification of anatomical abnormalities does not have sufficient specificity to characterize the clinical extent of the disease, i.e., what is active inflammatory disease and what is a fibrotic lesion resulting from a scarring process.

In this context, the objective of the present study is to identify by means of radiological methods, the presence of pulmonary and/or mediastinal abnormalities suggestive of disease activity in patients with pleural tuberculosis.

Methods

A prospective evaluation of a cohort of eighty-eight patients with pleural tuberculosis and negative serology for HIV was carried out between November 2008 and September 2009 at the Pleural Diseases outpatient clinic of the Pulmonary Division (HC-FMUSP). The study was conducted after patients signed a free informed consent and after the approval by the institutional review board.

On the first visit, the patients underwent clinical and radiological evaluation followed by thoracocentesis and pleural biopsy (Cope needle). Pleural fluid and blood samples were collected simultaneously for routine analyses. After the confirmation of pleural tuberculosis, patients underwent chest HRCT – axial thin (1 mm) sections (Tomoscan MX 800, Philips, Eindhoven, The Netherlands).

The criteria for the diagnosis of tuberculosis were: positive Ziehl–Neelsen stains or Lowenstein cultures (pleural fluid or tissue), and/or pleural biopsy showing typical granuloma and/or compatible clinical history associated with a lymphocyte rich exudate, elevated levels of adenosine deaminase (ADA) and a favorable clinical follow up after specific treatment.

Three independent specialists (KU, MS, and SB) evaluated the images according to the following criteria for: 1) lung: presence of cavitations, nodules, consolidations, and fibrotic bands; 2) bronchus: presence of wall thickening, dilatations, and the tree-in-bud pattern, and 3) mediastinum: presence of lymphadenomegaly. The presence of pulmonary consolidation, thick-walled cavity, centrilobular or confluent nodules, and tree-in-bud pattern are signs indicative of active disease. The presence of solitary nodules, lymphadenomegalia, cylindrical bronchiectasis, and bronchial wall thickening are considered nonspecific signs. Finally, the presence of parenchymal fibrotic bands and traction bronchiectasis are considered indicative of residual scarring.

Statistical analysis

All variables considered in the radiologic analysis were binary (yes/no) and were depicted throughout the text and tables as total numbers and proportions. The differences between findings in chest radiographies and chest CT scans were analyzed through the chi-square test or Fisher exact-test; the latter was used when expected frequencies were \( \leq 5 \). To compensate the multiple testing situations, the \( p \) value was adjusted by using the Bonferroni procedure, and we considered results with a \( p \leq 0.05 \) to be statistically significant. All tests were performed in STATA 11.0.

Results

Sixty-seven (76%) of the 88 patients (age 16–99; median: 47 years) included were males. Pleural effusions were unilateral in all patients, right-sided in 33 (37.5%), and left-sided in 55 (62.5%). Most of the patients presented moderate pleural effusion with a mean fluid withdrawn of 500 mL at thoracentesis. Associated to the pleural effusion, 22 (25%) patients had other radiographic changes, and in 55 cases (63%) tomographic abnormalities were observed (Table 1 and Figs. 1 and 2).

According to the radiologic criteria, the chest X-ray revealed suggestive signs of active disease in 9 (10.2%) patients, a number significantly lower (\( p = 0.0001 \)) than those obtained by tomography (40/88; 45.5%). Although no statistical difference had been observed concerning to the presence of consolidation and thick-walled cavities by the
two methods, these alterations were more frequently observed in CT scans. Centrilobular nodules (27/88; 30.7%), confluent nodules (24/88; 27.3%) and the tree-in-bud pattern (9/88; 10.2%) were only detected by computed tomography, demonstrating the superiority of this method over the chest X-ray.

The finding of nonspecific signs showed a clear balance between chest X-ray and HRCT (12/11; p = 0.823). Solitary nodules (18/39; p = 0.001) and lymphadenomegaly (0/8; p = 0.007) were more frequently detected by tomography. The observation of cylindrical bronchiectasis (4/88; 4.5%) and bronchial wall thickening (8/88; 9.1%) was discrete and restricted to tomography. Agreement among observers was around 90% in most cases; conflicting diagnoses were resolved by consensus. No significant differences between the 2 radiologic methods were observed when signs suggestive of residual scarring were analyzed (1/4; p = 0.368), including the presence of parenchymal fibrotic bands (2/8; p = 0.099) and traction bronchiectasis, which were detected by tomography in only one of the 88 patients.

Discussion

The present study conducted in a high-prevalence tuberculosis region demonstrates that patients with the pleural form frequently have intrathoracic abnormalities characterized by pulmonary or mediastinal involvement, mimicking the form traditionally called post-primary. In addition, the clear superiority of high-resolution computed tomography in the identification of these lesions was confirmed. Finally, we observed that approximately half the patients with pleural tuberculosis had signs suggestive of extrapleural inflammatory activity.

Among different imaging methods, chest X-ray plays an unquestionable role in the diagnosis of pulmonary tuberculosis because of its ease of use, good performance, and low cost. However, this method lacks diagnostic sensitivity in the presence of pleural effusion, mainly due to difficulties in the visualization of the lung parenchyma and mediastinal structures. This fact is important when considering that parenchymal or mediastinal involvement is observed in 17–36% of patients with pleural tuberculosis.15–18 Similar results were obtained in the present study, with approximately one-fourth of the patients presenting images compatible with active or scarring pulmonary lesions on conventional chest X-rays. However, the superiority of chest HRCT in the demonstration of these lesions should be emphasized.15,18,19 This study also showed similar results, with 38% of the patients without radiographic evidence of parenchymal or mediastinal lesions having tomographic abnormalities. Furthermore, about two-thirds of the patients (62.5%) had intrathoracic abnormalities concomitant with the pleural effusion. Taken together, chest HRCT is a more accurate imaging method for suggesting the presence of pleuropulmonary tuberculosis.

These observations require discussion of clinically important issues. If it is unequivocal that HRCT adds sensitivity to the diagnosis, we should consider that the inclusion of this method in the clinical routine considerably increases the cost of public health. It is important to highlight that neither the chest HRCT nor the chest X-ray permits recognition of the presence of active lesions. However, the presence of abnormalities suggesting inflammatory activity allows the identification of patients with pleural tuberculosis capable of disease transmission. This point is epidemiologically relevant, because additional care should be taken with these patients, particularly in relation to contact investigation.

Therefore, as there are no pathognomonic findings that characterize active pulmonary tuberculosis, it is recommended that once the diagnosis of pleural tuberculosis has

### Table 1 Radiologic findings and evidence of pulmonary inflammatory activity in 88 patients with pleural tuberculosis.

<table>
<thead>
<tr>
<th>Imaging findings and inflammatory activity</th>
<th>Chest X-ray</th>
<th>Chest HRCT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrathoracic and extrapleural changes</td>
<td>22 (25.0%)</td>
<td>55 (62.5%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Activity signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>9 (10.2%)</td>
<td>40 (45.5%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Parenchymal consolidation</td>
<td>8 (9.1%)</td>
<td>17 (19.3%)</td>
<td>0.052</td>
</tr>
<tr>
<td>Thick-walled cavity</td>
<td>2 (2.3%)</td>
<td>8 (9.1%)</td>
<td>0.099</td>
</tr>
<tr>
<td>Centrilobular nodules</td>
<td>No detectable</td>
<td>27 (30.7%)</td>
<td></td>
</tr>
<tr>
<td>Confluent nodules</td>
<td>No detectable</td>
<td>24 (27.3%)</td>
<td></td>
</tr>
<tr>
<td>Tree-in-bud pattern</td>
<td>No detectable</td>
<td>9 (10.2%)</td>
<td></td>
</tr>
<tr>
<td>Nonspecific</td>
<td>12 (13.7%)</td>
<td>11 (12.5%)</td>
<td>0.823</td>
</tr>
<tr>
<td>Solitary nodules</td>
<td>18 (20.5%)</td>
<td>39 (44.3%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Lymphadenomegaly</td>
<td>0 (0%)</td>
<td>8 (9.1%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cylindrical bronchiectasis</td>
<td>No detectable</td>
<td>4 (4.5%)</td>
<td></td>
</tr>
<tr>
<td>Bronchial wall thickening</td>
<td>No detectable</td>
<td>8 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1 (1.1%)</td>
<td>4 (4.5%)</td>
<td>0.368</td>
</tr>
<tr>
<td>Parenchymal bands</td>
<td>2 (2.3%)</td>
<td>8 (9.1%)</td>
<td>0.099</td>
</tr>
<tr>
<td>Traction bronchiectasis</td>
<td>No detectable</td>
<td>1 (1.1%)</td>
<td></td>
</tr>
</tbody>
</table>

"Zero": potentially visible but absent; "No detectable": not possible to be recognized.
been established, parenchymal and mediastinal lesions should be stratified according to possible evidence of active disease. In the present study, lesions classified as highly suggestive of disease activity were detected in 10% of patients by chest X-ray and in 45.5% by HRCT. The most frequent finding was pulmonary consolidation (homogenous opacity reflecting granulomatous inflammation of the parenchyma) detected by radiography in 9.1% of

Figure 1  (A): Chest radiograph shows ill-defined nodules and moderate pleural effusion on the left side; (B): CT scan at the level of the intermedius bronchus shows a solitary nodule in the superior segment of the right lower lobe, which was not clear on the chest radiograph and (C): CT scan at the level of the inferior pulmonary veins demonstrates nodular foci of consolidation and bronchial wall thickening in the left lower lobe and a moderate loculated left pleural effusion.

Figure 2  CT scan images (A): Bronchial wall thickening and bronchiectasis associated with irregular nodular lesions in the right upper lobe are observed at a level just above the aortic arch; (B): Centrilobular nodules, tree-in-bud opacities and a thick-walled cavity are seen in the right upper lobe at the level of the aortic arch; (C): At the level of carina, multiple confluent centrilobular nodules and tree-in-bud opacities are observed in the posterior segment of the right upper lobe and in the superior segments of the lower lobes. Note also small foci of consolidation in the posterior segment of the right upper lobe; (D): Multiple centrilobular nodules and tree-in-bud opacities in the anterior segment of the right upper lobe, lingula and superior segments of the lower lobes are seen at the level of the bifurcation of the intermedius bronchus.
patients and by tomography in 19.3%. Chest X-ray and HRCT demonstrated parenchymal cavities with thickened walls, resulting from the coalescence of multiple inflammatory foci that necrose and drain into the airways,\(^5\) in 2.3% and 9.1% of patients, respectively. Finally, only HRCT permitted the identification of centrilobular and/or confluent nodules and the tree-in-bud pattern, findings highly suggestive of inflammatory activity. The tree-in-bud pattern reflects endobronchial dissemination of caseous necrosis and granulomatous inflammation that fills and surrounds the alveolar ducts and respiratory bronchioles.\(^5\) These features were observed in 30% of the patients included in this study.

Approximately 13% of the patients had nonspecific abnormalities upon radiography and computed tomography. There was a clear predominance of solitary nodules detected by radiography in 18 (20.5%) patients and by tomography in 39 (44.3%). These nodules appear as focal round opacities with relatively well-defined contours and size < 3 cm and generally result from coalescence or clustering of small nodules.\(^5\)\(^,\)\(^11\) Lee et al.\(^11\) characterized these lesions as nonspecific, because many nodules can persist after specific treatment despite an accentuated reduction in their number and less frequently, in their size. Lymphadenomegaly, cylindrical bronchiectasis, and bronchial wall thickening, findings observed in less than 10% of the patients by HRCT, are also considered as nonspecific because they can be observed both in the active phase and after specific treatment.\(^20\)

Finally, it should be mentioned that less than 5% of patients with pleural tuberculosis had radiographic or tomographic changes suggestive of residual disease. This condition is generally associated with the presence of parenchymal fibrotic bands or traction bronchiectasis, which are rarely present alone and are observed in a small number of cases (less than 10% upon tomography). These sequelae generally reflect previous parenchyma or bronchial involvement.\(^5\)\(^,\)\(^11\)

In conclusion, the present study supports the recommendation for a more rigorous diagnosis of patients with pleural tuberculosis, especially those living in high prevalence regions. Chest X-ray, the most common imaging method, failed to demonstrate pulmonary involvement in 75% of patients. However, this percentage decreased to 40% when high-resolution computed tomography was associated. Similarly, when we consider the possibility of concomitant pulmonary disease, only 10% of the patients fulfilled this criterion under radiographic examination. In contrast, computed tomography showed up almost 50% of patients exhibited lesions highly suggestive of active pulmonary disease. This finding is of great clinical and epidemiological relevance because it provides a basis for establishing guidelines for patients with pleural tuberculosis regarding prophylactic actions, since these patients may represent an important source of tuberculous dissemination.

Conflicts of interest
None declared.

References