Thoracic and Abdominal Imaging Features as Predictors for Diagnosing Tuberculosis in Patients with AIDS and Disseminated Mycobacterial Disease: a retrospective cohort study

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Abstract

Background. Disseminated mycobacterial disease is an important cause of morbidity and mortality in patients with HIV-infection. Nonspecific clinical presentation makes the diagnosis difficult and sometimes neglected.

Methods. We conducted a historical cohort study to compare the presentation of disseminated Mycobacterial tuberculosis (MTB) and non-tuberculous Mycobacterial (NTM) disease in HIV-positive patients from 1996 to 2006 in Brazil.

Results. Tuberculosis was diagnosed in 65 patients (67.7%) and NTM in 31 (32.3%) patients. Patients with NTM had lower CD4 T cells counts (median 13.0 cells/mm$^3$ versus 42.0 cells/mm$^3$, $P=0.002$). Patients with tuberculosis had significantly more positive acid-fast smears (48.0% vs 13.6%, $P=0.01$). On chest X-ray, miliary infiltrate was only seen in patients with MTB (28.1% vs. 0.0%, $P=0.01$). Pleural effusion was more common in patients with MTB (45.6% vs. 13.0%, $P=0.01$). Abdominal adenopathies (73.1% vs. 33.3%, $P=0.003$) and splenic abscesses (38.5% vs. 0.0%, $P=0.002$) were more common in patients with MTB.

Conclusions. Miliary pulmonary pattern on X-ray, pleural effusion, abdominal adenopathies, and splenic hypoechoic nodules were imaging findings associated with the diagnosis of tuberculosis in HIV-infected patients. Recognition of these imaging features can lead to a tentative diagnosis so that appropriate therapy can be instituted before cultures results become available.
Background

The use of highly active antiretroviral (HAART) therapy has been associated with a marked decrease in the incidence of opportunistic disease in patients with AIDS.\textsuperscript{1, 2} The incidence of non-tuberculous mycobacteria especially \textit{Mycobacterium avium complex} (MAC) infections, the most common bacterial disease in developed countries,\textsuperscript{3, 4} has dramatically declined since 1995 because of HAART therapy.\textsuperscript{1, 5} For \textit{Mycobacterial tuberculosis} (MTB) infections, this reduction was not so dramatic,\textsuperscript{6} but observational studies have demonstrated a protective effect of HAART in patients infected with MTB.\textsuperscript{7, 8}

Universal access to antiretroviral medications has reduced the risk of tuberculosis in patients with AIDS in developing countries such as Brazil.\textsuperscript{9, 10} However, infections with \textit{Mycobacterium tuberculosis} (MTB) have reached endemic levels and continue to be a major public health problem in these countries.\textsuperscript{11, 12} Previous infection with \textit{Mycobacterium tuberculosis} is not associated with protection against subsequent MAC infection.\textsuperscript{13} On the other hand, the diagnosis of \textit{non-tuberculous mycobacterial} (NTM) disease is still neglected in these settings considering its variable prevalence.\textsuperscript{3, 4, 14, 15} In Brazil, the rate of NTM disease can vary from 0\% to 45\%.\textsuperscript{11, 16-18}

Rapid laboratorial detection of \textit{Mycobacterial} species is difficult due to its dependence on the growth of a usually slow growing microorganism. Speciation of a \textit{Mycobacterium} isolate using these standard methods is a lengthy process based on subjective data interpretation. Commercially available molecular methods for speciation represent a useful and promising tool but are expensive and do not cover the number of mycobacteria that can be reliably identified in clinical laboratories. In addition, diagnosis based
solely on the clinical presentation is unreliable considering that most HIV-infected patients with disseminated disease present systemic symptoms, such as fever, weight loss, and anorexia.\textsuperscript{19, 20}

Abdominal and chest imaging are the initial steps in the investigation of fever of unknown origin (FUO).\textsuperscript{21} Considering that Mycobacterial infections are the most common cause of FUO in patients with AIDS,\textsuperscript{22, 23} radiological manifestations might be an important clue for the early diagnosis of tuberculosis or NTM disease in HIV-infected patients.

The goal of our study was to determine the most common radiological findings in patients with AIDS and disseminated mycobacterial disease caused by NTM and MTB in a tertiary care-hospital in Brazil.

\textbf{Methods}

We performed a historical cohort study at Hospital de Clínicas de Porto Alegre, a 735-bed accommodation tertiary-care hospital located in southern Brazil. From 1996 to 2006 all patients with the diagnosis of HIV infection and disseminated mycobacterial disease were included in the study. Patients were selected by the review of data from the records of microbiology laboratory.

Disseminated disease was characterized when we had a positive identification of MTB or NTM in either one of the following cultures: blood, bone marrow, or liver biopsies. For isolation of \textit{Mycobacterium} sp. a radiometric system (BACTEC 460 TB - Becton & Dickinson Diagnostic Instrument Systems, Sparks, MD, USA), and non-radiometric systems (BACTEC 9240 - Becton & Dickinson Diagnostic Instrument Systems, Sparks, MD, USA); and, BacT/Alert 240 (bioMérieux, Marcy-l'Étoile, France) were
used. For identification of MTB or NTM, NAP (\textit{p-nitro-alfa-acetylamino-beta-hydroxypropiophenone}) test was performed. In cases which NAP test could not be done, the identification of species were made by the visualization of the aspect of the colony – presence or absence of cord formation in liquid media – due to the high sensibility and specificity of this method. In fact, the sensitivity and specificity for identification of mycobacterial species in our study, by this method, was 98% and 96% (data not shown), respectively.

We included for analysis, the most recent CD4 lymphocyte count and HIV viral load test in a six-month period before the hospital arrival.

The imaging studies included – chest X-ray, abdominal ultrasound or computerized tomography (CT) – referred only to exams performed during the first 21 days of the patient’s hospital stay.

A descriptive analysis of all the variables collected from each patient was performed. The chi-squared test or Ficher’s exact test was used for univariate analysis of selected variables. Associations were considered statistically significant when P value was < 0.05. Data were compiled using Epi-Info 6.04 version and analyzed in SPSS 11.5 version program.

The study was approved by the ethic committee of Hospital de Clínicas de Porto Alegre. The authors signed a written commitment to guarantee the confidentiality of the data retrospectively collected.
Results

One-hundred and seven patients with disseminated mycobacterial disease were identified from 1996 to 2006. Eleven patients were excluded from the comparative analysis: six (5.6%) for incomplete data registry, three (2.8%) for simultaneous diagnosis of tuberculosis and NTM disease, and two (1.9%) patients because of lack of species identification. From the 96 remaining patients, sixty-five (67.7%) had the diagnosis of disseminated MTB and twenty-seven (32.3%) had NTM disease.

The characteristics of patients with tuberculosis and NTM are shown in Table 1. A lower CD4 lymphocyte count was associated with NTM infection. Black race was associated with the diagnosis of tuberculosis. There was no significant difference between tuberculosis group and NTM group with respect to any other parameter.

There was no statistical significant difference comparing the clinical presentation in both groups of patients. The most common clinical symptoms were as follows: weight loss (92.7%), fever (89.6%), respiratory symptoms, such as cough, hemoptysis, shortness of breath, and chest pain (75.0%), and gastrointestinal manifestations (68.8%).

Only 27 patients had positive results on acid-fast smear, of these, twenty-four (48.0%) in the tuberculosis group and three (13.6%) in NTM infection group (P=0.01).

The chest films and abdominal ultrasound or CT findings are shown in table 2 and 3, respectively. The chest X-ray was normal in ten (13.2%) patients, while in abdominal image the result was normal in five (7.7%) patients. There was no difference in terms of the presence or absence of
findings on chest X-ray or abdominal imaging comparing the patients with MTB or NTM disease. Seven patients (24.0%) with NTM infection and five (8.0%) patients with tuberculosis had normal chest X-ray findings (P=0.07). One patient (4.5%) with NTM and three patients (5.5%) with MTB infection had normal abdominal findings on ultrasound or CT (P=0.68).

The most common findings on chest X-ray of HIV-infected patients with disseminated mycobacterial disease were pulmonary interstitial infiltrate (51.3%), consolidation (37.5%), pleural effusion (36.3%), and adenopathies (31.3%). On abdominal image, adenopathies (61.6%), hepatomegaly (41.1%), ascites (34.2%), and splenic hypodense lesions (27.4%) were the most common abnormalities described in those patients. Micronodular infiltrate was identified in sixteen patients (28.1%) with MTB infection and in none with NTM disease (P=0.01). Pleural effusion was statistically significant more common in patients with tuberculosis (45.6% vs 13.0%. P=0.01). Other chest X-ray abnormalities were similar in both groups. Abdominal adenopathies were more frequent in patients with disseminated tuberculosis (73.1%, n=38) than patients with NTM disease (33.3%, n=7; P=0.003). Only patients with MTB infection presented splenic hypodense lesions (38.5%; n=20; P=0.002). The other abdominal findings were associated with neither TB nor NTM infection.

When patients were stratified for the lowest CD4 lymphocyte count strata (CD4 ≤ 50 cels/mm³), all the imaging abnormalities previously associated to the diagnosis of disseminated tuberculosis (miliary infiltrate, pleural effusion, abdominal adenopathies, and splenic hypodense nodules) remained statistically significant for the diagnosis of tuberculosis.
Discussion

We identified relevant imaging features that could help to distinguish tuberculosis from NTM in patients with AIDS and disseminated mycobacterial disease. The presence splenic hypoechoic nodules or micronodules suggestive of microabscesses on abdominal ultrasound and CT scan were highly specific for tuberculosis in HIV-patients with disseminated mycobacterial disease, considering it was not seen in patients with NTM infection. Studies have demonstrated a higher prevalence of splenic lesions in HIV-infected patients with disseminated tuberculosis compared with those with disseminated NTM.\textsuperscript{31, 32} Bernabeu-Wittel et al have shown, in 36 patients with HIV infection and splenic microabscesses, that tuberculosis and NTM were the etiology of 43% and 15% of patients respectively.\textsuperscript{31} Radin found that 30% of patients with tuberculosis and 7% of patients with MAC had focal lesions in the spleen.\textsuperscript{32}

Previous non-comparative studies\textsuperscript{33, 34} have shown the association between \textit{tuberculosis} and abdominal adenopathies. Monill-Serra, for instance, found that out of 76 patients with tuberculosis, twenty-seven had the presence of retroperitoneal and mesenteric adenopathies on sonographic imaging. Although some authors have advocated that virtually 100% of HIV-infected patients with MAC presented abdominal adenopathies,\textsuperscript{32, 35, 36} in our population the presence of adenopathies were predominantly seen in HIV-infected patients with tuberculosis.

Considering intrathoracic lymphadenopathy, Jasmer et al\textsuperscript{37} evaluated the imaging features of 318 HIV-infected patients, mostly with disseminated mycobacterial disease. The majority of HIV-infected patients (74%) diagnosed
with tuberculosis had intrathoracic lymphadenopathy on chest CT scan compared with 50% of the patients with NTM infection. Our data did not demonstrate statistically significant difference in our patients, probably because we evaluated only the chest X-rays in contrast to the CT scan findings, which have a higher sensibility for the detecting intrathoracic adenopathies.

Miliary infiltrate was highly associated with diagnosis of tuberculosis, considering that our HIV-infected patients with NTM did not present miliary pattern on chest X-ray. Hsieh et al\textsuperscript{38} have found that none of their HIV-infected patients with MAC presented miliary pattern on chest X-ray. However, three HIV-infected patients with tuberculosis presented with miliary infiltrate on chest x-ray.

In patients with AIDS, atypical radiographic presentation of tuberculosis in severe immunossuppressed patients seems to occur frequently, and an interstitial diffuse infiltrate is one of the most common radiographic abnormality\textsuperscript{38} as described in our patients. Significant pulmonary involvement has not been seen commonly in disseminated MAC infection,\textsuperscript{39} and a miliary pattern on X-ray is rarely seen in those patients.\textsuperscript{40-43} It has been mainly reported in patients with infection by non-tuberculous mycobacteria other than MAC such as patients with \textit{Mycobacterium xenopi} infection.\textsuperscript{44} In patients with AIDS and disseminated mycobacterial infection, the presence of pulmonary disease and miliary changes on X-ray strongly suggests the diagnosis of tuberculosis. However, consolidations or nodular infiltrates, interstitial infiltrate, pulmonary mass and cavitation have been occasionally reported in HIV-infected patients with MAC infection.\textsuperscript{43}
We have found that pleural effusion was associated with the diagnosis of tuberculosis. In contrast to disseminated MAC disease, pleural effusions have been frequently described in patients with disseminated tuberculosis. In fact, Hsieh et al, found no patient with MAC and pleural effusion in their study.\textsuperscript{38}

Infections due to MAC are related to more immunosuppressed states.\textsuperscript{45, 46} Whereas MTB infections can affect patients with higher levels of CD4 counts, and is associated with a greater inflammatory response and granuloma formation. In fact, HIV-infected patients with disseminated tuberculosis had a higher median CD4 lymphocyte count compared with patients with disseminate NTM. However when we controlled our results for the lowest CD4 count strata (CD4 < 50 cels/mm\textsuperscript{3}), all the imaging differences associated with the diagnosis of tuberculosis remained statistically significant. Although some have advocated that the manifestations of tuberculosis in abdomen are related to the immunologic state of the patient,\textsuperscript{35, 36} our data suggest that even in the lowest strata of CD4 counts, patients with tuberculosis still seem to have more exuberant disease presentation with abdominal lymphadenopaties and granuloma formation than NTM disease.

Of interest, the sensibility of acid-fast smears for the diagnosing disseminated disease was low in our patients with disseminated NTM and tuberculosis mycobacteria. Smith et al. have shown that positive acid-fast smears were frequently found in patients with disseminated tuberculosis disease and HIV (96%), and there was no difference related to HIV-status or level of immunosupression to the yield of acid-fast sputum smears.\textsuperscript{28} However, Samb et al. evaluated factors associated with negative sputum
smears in patients with HIV infection and disseminated tuberculosis and pulmonary involvement. Absence of cavitation, lack of cough, HIV seropositivity, CD4 count above 200 cels/mm³, and age over 40 years was associated with smear negativity. In disseminated MAC infection, the sensibility of acid-fast smears and cultures from the respiratory tract was characteristically low. Although, considering the low sensibility for diagnosing tuberculosis in HIV-infected patients, the specificity of the acid-fast smear for the diagnosis of tuberculosis in our study was 83%, compared to patients with NTM disease.

In summary, miliary pulmonary pattern, pleural effusion, abdominal adenopathies, and splenic hypoechoic nodules were imaging findings associated with the diagnosis of disseminated tuberculosis in HIV-infected patients. Our results emphasize the importance of imaging studies as valuable tool to help differentiate MTB and NTM disseminated infections in HIV-infected patients, considering the similar clinical presentation of both diseases. Recognition of these imaging features can lead to a tentative diagnosis so that appropriate therapy can be instituted before the results of mycobacterial cultures become available.
Competing interests

All authors no competing interests

Authors' contributions

RPS: conceived of the study, participated in the design of the study, participated in data collection and wrote the manuscript.

KLS: participated in data collection and helped to draft the manuscript.

DMCW: helped to draft the manuscript.

LZG: conceived of the study, participated in the design and coordination of the study, helped to draft the manuscript.
References


13. Sterling TR, Moore RD, Graham NM, et al. Mycobacterium tuberculosis infection and disease are not associated with


### Table 1 - Demographic characteristics of the HIV-infected patients with disseminated Mycobacterial disease

<table>
<thead>
<tr>
<th></th>
<th>All Patients(^1) (n=96)</th>
<th>MTB (n=65)</th>
<th>NTM (n=31)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32.0</td>
<td>32.0</td>
<td>34.0</td>
<td>.43</td>
</tr>
<tr>
<td>Men</td>
<td>71 (74.0)</td>
<td>49 (75.4)</td>
<td>22 (71.0)</td>
<td>.83</td>
</tr>
<tr>
<td>Race(^2)</td>
<td></td>
<td></td>
<td></td>
<td>.05</td>
</tr>
<tr>
<td>White</td>
<td>63 (66.3)</td>
<td>39 (60.9)</td>
<td>24 (77.4)</td>
<td></td>
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<tr>
<td>Black</td>
<td>23 (24.2)</td>
<td>20 (31.3)</td>
<td>3 (9.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (9.5)</td>
<td>5 (7.8)</td>
<td>4 (12.9)</td>
<td></td>
</tr>
<tr>
<td>HIV exposure</td>
<td></td>
<td></td>
<td></td>
<td>.34</td>
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<tr>
<td>Sexual</td>
<td>46 (57.5)</td>
<td>28 (52.8)</td>
<td>18 (56.7)</td>
<td></td>
</tr>
<tr>
<td>IV drug use</td>
<td>34 (42.5)</td>
<td>25 (47.2)</td>
<td>9 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Median CD4 (cels/mm(^3)) (No. of patients)</td>
<td>42.0</td>
<td>13.0</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Median viral load (log/mL) (No. of patients)</td>
<td>5.2</td>
<td>4.7</td>
<td>.83</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C serology</td>
<td>26 (35.6)</td>
<td>18 (37.5)</td>
<td>8 (32.0)</td>
<td>.83</td>
</tr>
<tr>
<td>Hepatitis B serology</td>
<td>6 (8.8)</td>
<td>4 (8.5)</td>
<td>2 (9.5)</td>
<td>.74</td>
</tr>
</tbody>
</table>

Note. Data are no. (%) of patients, unless otherwise indicated. MTB, *Mycobacterium tuberculosis*; NTM, *non-tuberculous mycobacteria*; IV, intravenous.

\(^1\) Patients diagnosed with tuberculosis, *non-tuberculous mycobacteria* infection.

\(^2\) \(P\) value related to black and white race groups comparison.

### Table 2 - Chest X-ray abnormalities in HIV-infected patients with disseminated mycobacterial disease

<table>
<thead>
<tr>
<th></th>
<th>All Patients(^1) (n=80)</th>
<th>MTB (n=57)</th>
<th>NTM (n=23)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse infiltrate</td>
<td>41 (51.3)</td>
<td>28 (49.1)</td>
<td>13 (56.5)</td>
<td>.72</td>
</tr>
<tr>
<td>Consolidation</td>
<td>30 (37.5)</td>
<td>21 (36.8)</td>
<td>9 (39.1)</td>
<td>.92</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>29 (36.3)</td>
<td>26 (45.6)</td>
<td>3 (13.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Adenopathies</td>
<td>25 (31.3)</td>
<td>21 (36.8)</td>
<td>4 (17.4)</td>
<td>.15</td>
</tr>
<tr>
<td>Miliary infiltrate</td>
<td>16 (20.0)</td>
<td>16 (28.1)</td>
<td>0 (0.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>3 (3.8)</td>
<td>2 (3.5)</td>
<td>1 (4.3)</td>
<td>.63</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>3 (3.8)</td>
<td>2 (3.5)</td>
<td>1 (4.3)</td>
<td>.63</td>
</tr>
<tr>
<td>Cavitation</td>
<td>3 (3.8)</td>
<td>3 (5.3)</td>
<td>0 (0.0)</td>
<td>.63</td>
</tr>
<tr>
<td>Nodules</td>
<td>3 (3.8)</td>
<td>3 (5.3)</td>
<td>0 (0.0)</td>
<td>.63</td>
</tr>
</tbody>
</table>

Note. Data are no. (%) of patients, unless otherwise indicated. MTB, *Mycobacterium tuberculosis*; NTM, *non-tuberculous mycobacteria*.

\(^1\) Patients diagnosed with tuberculosis, and *non-tuberculous mycobacteria* infection.
<table>
<thead>
<tr>
<th></th>
<th>All patients(^1)</th>
<th>MTB (n=52)</th>
<th>NTM (n=21)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=73)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenomegalies</td>
<td>45 (61.6)</td>
<td>38 (73.1)</td>
<td>7 (33.3)</td>
<td>.003</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>30 (41.1)</td>
<td>19 (36.5)</td>
<td>11 (52.4)</td>
<td>.32</td>
</tr>
<tr>
<td>Ascities</td>
<td>25 (34.2)</td>
<td>18 (34.6)</td>
<td>7 (33.3)</td>
<td>.86</td>
</tr>
<tr>
<td>Splenic hypodensities</td>
<td>20 (27.4)</td>
<td>20 (38.5)</td>
<td>0 (0.0)</td>
<td>.002</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>20 (27.4)</td>
<td>15 (28.8)</td>
<td>5 (23.8)</td>
<td>.88</td>
</tr>
<tr>
<td>Biliary tract alterations</td>
<td>19 (26.0)</td>
<td>12 (23.1)</td>
<td>7 (33.3)</td>
<td>.54</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>18 (24.7)</td>
<td>13 (25.0)</td>
<td>5 (23.8)</td>
<td>.84</td>
</tr>
<tr>
<td>Liver echotexture alteration</td>
<td>13 (17.8)</td>
<td>7 (13.5)</td>
<td>6 (28.6)</td>
<td>.86</td>
</tr>
<tr>
<td>Liver hypodensities</td>
<td>8 (11.0)</td>
<td>5 (9.6)</td>
<td>3 (14.3)</td>
<td>.74</td>
</tr>
<tr>
<td>Pancreatic lesions</td>
<td>3 (4.1)</td>
<td>3 (5.8)</td>
<td>0 (0.0)</td>
<td>.63</td>
</tr>
<tr>
<td>Intestinal abnormalities</td>
<td>2 (2.7)</td>
<td>2 (3.8)</td>
<td>0 (0.0)</td>
<td>.90</td>
</tr>
<tr>
<td>Abdominal Abscess</td>
<td>1 (1.4)</td>
<td>1 (1.9)</td>
<td>0 (0.0)</td>
<td>.63</td>
</tr>
</tbody>
</table>

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\(^1\) Patients diagnosed with tuberculosis, and *non-tuberculous mycobacteria* infection.