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High-resolution CT findings of pulmonary tuberculosis in liver transplant patients

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AIM: To assess the high-resolution computed tomography (HRCT) findings in liver transplant patients diagnosed with pulmonary *Mycobacterium tuberculosis* infection.

MATERIALS AND METHODS: The HRCT findings from 19 patients diagnosed with pulmonary tuberculosis infection after liver transplantation were reviewed. The patients included were 12 men and seven women, age range 23–65 years; mean age 57 years. The diagnosis was established with *Mycobacterium tuberculosis* detection in bronchoalveolar lavage, sputum, or biopsy. HRCT images were reviewed independently by two observers who reached a consensus decision. The HRCT findings were classified as (1) miliary nodules; (2) cavitation and centrilobular tree-in-bud nodules; (3) ground-glass attenuation and consolidation; and (4) mediastinal lymph node enlargement.

RESULTS: The time between the transplantation and the diagnosis of pulmonary tuberculosis ranged from 7 to 153 days with an average of 79 days. The main HRCT pattern was cavitation and centrilobular tree-in-bud nodules (79%) followed by mediastinal lymph node enlargement (10.4%), ground-glass attenuation or consolidation (5.2%) and miliary nodules (5.2%). None of the patients presented pleural effusion. The cavitation and centrilobular tree-in-bud nodules pattern had upper lobe predominance, and ground-glass attenuation and consolidation pattern had middle lobe/lingular segment predominance.

CONCLUSION: The main HRCT pattern of pulmonary tuberculosis in liver transplant patients was cavitation and centrilobular tree-in-bud nodules.

Introduction

Pulmonary infections are clearly a relevant cause of morbidity and mortality among solid-organ transplant recipients. The incidence of tuberculosis (TB) infection in transplant recipients are at least 20 times greater than the

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general population, in low endemic areas.[1,2] In 2013, Eyüboğlu *et al.*[3] reported an evaluation of pulmonary infections in solid-organ transplant patients, based on a 12-year review and found that TB was the most frequent infection involved in an endemic area, responsible for 6% of these infections.

Most transplant patients infected with TB manifest with clinical pulmonary TB, and symptoms such as fever, night sweats, and constitutional symptoms are masked by the immunocompromised state, which generates a wide range of differential diagnoses delaying the definitive diagnosis. High-resolution computed tomography (HRCT) is the imaging technique of choice for the evaluation of patients with suspected pulmonary TB in this scenario, and usually provides the first clue to the diagnosis of this disease. A range of radiographic manifestations including focal infiltrates, miliary pattern, nodules, pleural effusions, diffuse interstitial infiltrates, and cavitary disease has been described in solid-organ transplant recipients.[2,4]

There are few reports of HRCT findings in patients with pulmonary TB infection after liver transplantation. The aim of the present study was to describe the HRCT patterns in liver transplant patients with pulmonary TB.

Materials and methods

The study was approved by the institutional review board. This retrospective study reviewed data from all liver transplant recipients with pulmonary TB treated in three Brazilian hospitals, between January 2005 and January 2015. All patients underwent a tuberculin skin test before the transplant and were treated for latent TB infection if the skin test produced an area of swelling of >5 mm in diameter. The inclusion criteria for patients were positive *Mycobacterium tuberculosis* culture from sputum, bronchoalveolar lavage, or lung biopsy and performed HRCT in the same period of this microbiological investigation, with a maximum interval of 10 days between them. In the present study, at least one culture of *M. tuberculosis* was positive for each patient and only four had negative smear for pulmonary TB. The sample comprised 19 patients diagnosed with pulmonary TB infection from 1,853 liver transplant patients.

The technical parameters included inspiratory volumetric acquisition with 1 mm collimation at 1-mm increments using a high spatial frequency reconstruction algorithm. Images were obtained with mediastinal (width, 350–450 HU; level, 20–40 HU) and parenchymal (width, 1200–1600 HU; level, −500 to −700 HU) window settings. Reconstructions were performed in the axial and coronal planes.

Two chest radiologists with >10 years of experience independently assessed the HRCT examinations. After the two radiologists had conducted independent analyses, the images were reviewed together with a third chest radiologist (with >40 years of experience) to reach a final consensus decision in only one case where the first two radiologists did not agree. For each patient, reviewers identified one of four predominant HRCT patterns: (1) miliary nodules; (2) cavitation and centrilobular tree-in-bud nodules; (3) ground-glass attenuation and consolidation; and (4) Mediastinal lymph node enlargement.

A nodule was defined as a rounded or irregular opacity that was well or poorly defined and ≤3 cm in diameter. Nodules were classified as small (diameter <10 mm) or large (diameter >10 mm). Miliary nodules were diagnosed when widespread, randomly distributed micronodules (≤3 mm) were observed. Mediastinal and hilar lymph nodes were considered normal up to the upper limit of 10 mm in short axis diameter.[5,6] A cavity was defined as a gas-filled space, seen as a lucency or low-attenuation area, within pulmonary consolidation, a mass, or a nodule. The tree-in-bud pattern refers to centrilobular branching structures that resemble a budding tree and are usually <10 mm in diameter. Ground-glass opacities were defined as hazy areas of increased opacity or attenuation, with no obscuration of the underlying vessels. Consolidation was defined as homogeneous opacification of the parenchyma with obscuration of the underlying vessels. The HRCT scans were assessed according to criteria defined in the Fleischner Society's Glossary of Terms.[6] The distribution of abnormalities was categorised as focal (unilobar) or diffuse (more than one pulmonary lobe) and stratified using the categories of upper, middle, and lower lung lobes.

Results

The sample included 12 men and seven women, with a mean age of 57 (range 23–65) years. The incidence of TB was 1% in liver transplant recipient patients and the mean interval between liver transplantation and infection diagnosis was 79 days (range 7–153 days).

The main symptoms reported were cough and asthenia, 16 patients (84%) had at least one of these complaints. Six patients had a known past history of TB, two patients were not known to have TB and had not received treatment, and 11 patients did not have this information in their electronic medical records.

According to these data and the imaging findings, the sample comprised patients with post-primary TB, and only two patients (10%), who presented with mediastinal lymph node enlargement, were diagnosed with probable primary TB (Table 1).

Table 1
Clinical characteristics of 19 liver transplant recipients with pulmonary tuberculosis.

Patients information	n=19 (%)
Mean age, years (range)	57 (23-65)
Gender, male	12 (63%)
Hepatitis C	14 (74%)
Use of corticosteroids	12 (63%)
Primary tuberculosis	2 (10%)
Cough or asthenia	16 (84%)
Mean time to tuberculosis diagnosis after transplantation, days (range)	79(7-153)

The underlying diseases that led to liver transplantation were hepatitis C in 14 patients (73%), hepatitis B in three (15.6%), autoimmune hepatitis in one (5.2%), hepatocellular carcinoma in two (10.5%). No patient had human immunodeficiency virus (HIV) infection. Regarding immunosuppressive therapy, 12 patients received prednisone (63%), five (26%) ciclosporin, four (21%) tacrolimus, two (10.5%) mofetil mycophenolate, and one (5.2%) sodium mycophenolate. Two patients had no pharmacological data recorded in the electronic medical files.

The main HRCT pattern, found in 15 (79%) patients, was cavitation and centrilobular tree-in-bud nodules (Fig 1). Mediastinal lymph node enlargement was observed in two (10.4%) patients (Fig 2). Ground-glass attenuation/consolidation and miliary nodes were present in one patient each (5.2%). There was no case of pleural effusion. These data are presented in Table 2.

Regarding distribution, cavitation and centrilobular tree-in-bud nodules were found in the upper lobes in all the 15 cases. In seven patients (45%), the lesions were bilateral, affecting both upper lobes; in five patients these findings were limited to the left upper lobe and two had lesions in the right upper lobe only. Ground-glass attenuation and consolidation pattern was found predominantly in the middle lobe and lingular segments.

Discussion

The incidence of TB in Brazil is one of the world's largest and, among the Brazilian cities, Porto Alegre has the highest incidence rate, reaching 99 new cases per 100,000 inhabitants in 2014, whereas the national rate is 33.5 new cases per 100,000 inhabitants per year.[7] The low rate of primary versus post-primary TB is a reflection of the high endemic rate of TB infection in the country.

TB incidence in solid-organ transplant recipients can reach approximately 15% in high endemic areas.[8,9] Worldwide, liver transplant recipients have an incidence of 0.5–2% active TB.[2,4,5,10] In a retrospective study that included 319 patients who underwent liver transplantation in a Brazilian centre, the frequency of TB was 1.5%, which is within the range reported previously.[11]

The mean time from symptom onset to diagnosis of TB infection in liver transplant recipients in the literature is 1.1 months; therefore, knowledge regarding the most common HRCT patterns of TB in this population is of paramount importance.[12] In a large Spanish multicentre cohort, including 4,388 solid-organ transplant recipients, 95% of all TB cases occurred within the first year after the transplant, with a median time of onset of 183 days after transplantation.[4]

Diagnosis of active TB in these patients may be challenging because of the atypical clinical presentation and prolonged growth time in culture. Limitations to the diagnosis of TB are mainly related to diagnostic methods, as bacillus identification techniques, such as smear, culture, or even molecular techniques, have a low sensitivity rate. The sensitivity of diagnostic methods for TB is approximately 50% for sputum smears and can reach 80% for induced sputum in some references, further increasing with culture and other methods combined.[13]

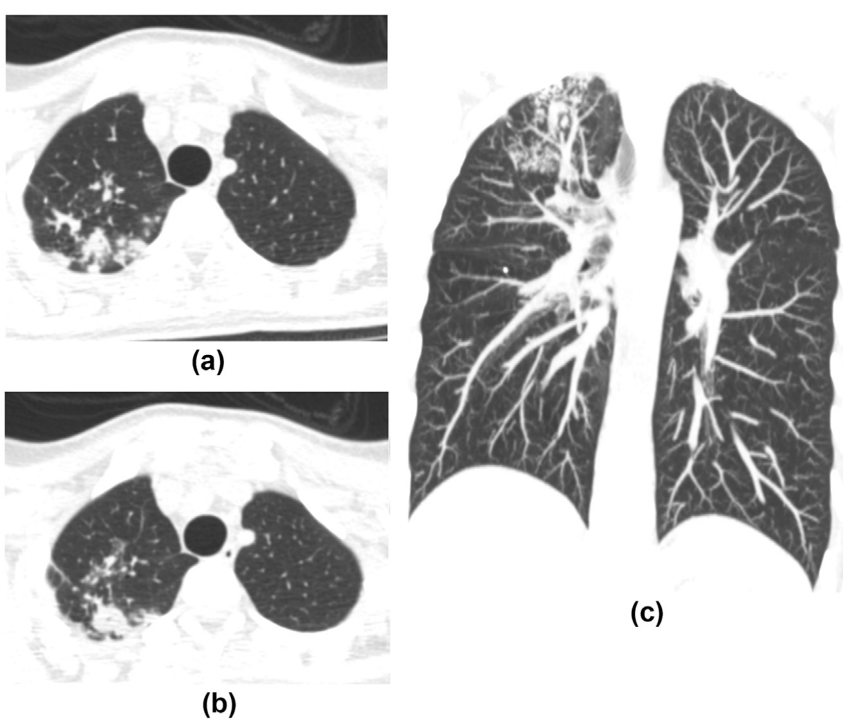

Figure 1 Active pulmonary TB in a 54-year-old woman with cough and fever. (a) Axial HRCT shows nodular and branching opacities, typical of endobronchial spread. (b) Small focal opacity with mild central cavitation in the posterior segment of the right upper lobe. (c) Coronal HRCT reconstruction (MIP) shows more evidently the tree-in-bud nodules pattern.

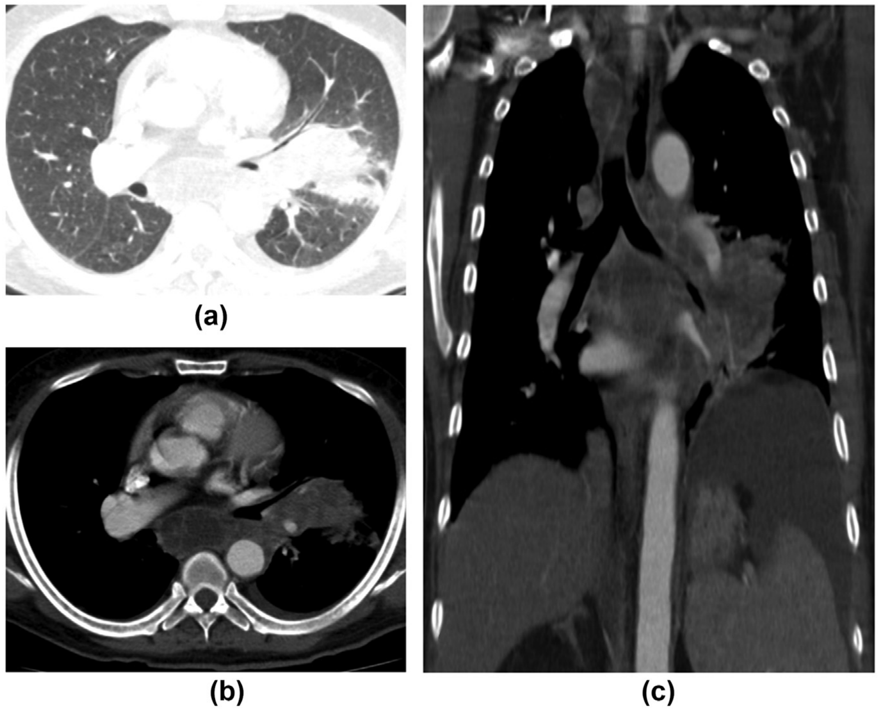

Figure 2 A 61-year-old man with tuberculous lymphadenopathy. (a,b) Contrast-enhanced CT at the level of the carina shows low-density, rim-enhancing mediastinal enlarged lymph nodes, associated with pulmonary consolidation. (c) Coronal reconstruction shows enlargement of other lymph nodes at the level of the great vessels.

Chest radiography also has limitations: in up to 15% of cases, signs of the disease might not be shown. Determining disease activity may be difficult as the abnormalities found are similar to those found in other diseases, such as bacterial infections, *Pneumocystis* pneumonia, cytomegalovirus pneumonia, neoplasia, sarcoidosis, and fungal infections, particularly aspergillosis and invasive candidiasis.[7,8]

The presence of cavitation is an important sign of disease activity and HRCT can demonstrate small cavities in the midst of consolidations that are not seen on radiographs, as occurred in the present study. Im *et al.*[14] in their paper on CT findings of TB in non-immunocompromised patients found that chest radiography was able to identify cavitation in only nine of 24 cases with cavitation seen at CT.

Tozkoparan *et al.*[15] reviewed the role of HRCT in assessing activity of disease in 85 patients with suspected smear-negative pulmonary TB, none with immunosuppression or history of transplantation reported, and found that HRCT had good diagnostic value in detecting activity of smear negative pulmonary TB. In their series, the sensitivity, specificity, positive predictive value, and accuracy of HRCT in detecting disease activity were 88%, 88%, 92%, and 88%, respectively. They concluded that HRCT alone had relatively good sensitivity for the diagnosis.

The most common HRCT pattern of primary pulmonary TB in the general population are hilar or paratracheal lymphadenopathy, generally unilateral.[16] Cavitation and centrilobular tree-in-bud nodules, are the hallmark of post-primary TB, present in approximately 50% of immunocompetent patients, mostly affecting the upper and posterior lung segments. This pattern of pulmonary involvement is similar to those found in the current study where cavitation and centrilobular tree-in-bud nodules were present in 79% of cases, with this finding located in upper lobes in all of them.

Multiple diffuse nodules from 1–3 mm in size, in random distribution, are characteristic of miliary TB, which can occur in both primary and post-primary TB. Pleural TB can be seen as fluid in the pleural cavity and pleural layer enhancement after contrast medium administration.[17] The latter are less common patterns and there was only one case of miliary TB in the present study (5%), which is in line with the literature.[18] Although some references demonstrate higher rates of pleural TB we had no case of pleural effusion or pleural enhancement.

There are few reports of pulmonary TB findings in HRCT in liver transplant recipients. Recently, a South Korean study submitted 10 patients to HRCT, before and after liver transplant, and showed that only two patients (20%) had the miliary form of TB and eight (80%) presented with

Table 2
High resolution computed tomography (HRCT) findings of pulmonary tuberculosis in liver transplant patients.

HRCT findings	Patients	Distribution
Cavitation and centrilobular tree-in-bud nodules	15 (79%)	Upper lobes in 100%.
Mediastinal lymph node enlargement	2 (10.4%)	-
Ground-glass attenuation and consolidation	1 (5.2%)	Middle lobe/lingular segments
Miliary nodules	1 (5.2%)	-

typical pulmonary TB lesions in the upper lobe of the lung, which corroborates the findings observed in the present study.[19]

Studies involving renal transplant patients demonstrate a greater tendency of non-cavitary forms of TB.[20] The study by Pereira *et al.* showed the CT findings of 40 patients with pulmonary TB after renal transplantation and 16 patients (40%) demonstrated miliary nodules.[20] This pattern of pulmonary involvement may be related to a higher degree of immunosuppression in these patients, similar to what occurs in patients with other types of immunosuppression.[21] As renal transplantation was one of the first to be developed, immunosuppression in the initial era of transplantation was more intense; this may be an explanation for the forms linked to greater immunosuppression in these patients. In addition, isoniazid prophylaxis for kidney transplant recipients reduced the risk of developing TB post-transplant and was recently introduced.[22] Transplant recipients in settings that have a high prevalence of TB who receive isoniazid during the first year following transplant have a lower incidence of TB. The present patients received isoniazid prophylaxis, and this could have some influence regarding TB incidence and presentation, when compared with older studies.[20,23]

Historically, steroids have been the first-line immunosuppressive therapy in solid-organ transplant. Steroid withdrawal includes long-term (6–12 months), early (3 months), very early withdrawal (2 weeks), steroid partial avoidance (within 1 week) and steroid complete avoidance.[24–27] The improvement in this therapy, with very early steroid withdrawal, may be the most important reason for the similarity of the HRCT findings in liver transplant recipients and immunocompetent patients.[25–27] Another possible explanation for the predominance of cavitation and centrilobular tree-in-bud nodule pattern is that the infections were due to reactivation of healed TB.[19] It is worth noting that pulmonary TB should be suspected in any transplant recipient with cough, asthenia, unexplained fewer, weight loss, or respiratory symptoms, and HRCT should be considered.[28,29]

The present study has several limitations: the design was retrospective; the number of patients included was relatively small, due to restricted inclusion criteria; and sputum, bronchoalveolar lavage, and lung biopsy culture for *M. tuberculosis* has limited sensitivity. For the reasons, the results could not be statistically validated. Despite these limitations, the present study included the largest series of pulmonary TB in liver transplant patients, all with microbiological confirmation.

In conclusion, despite immunosuppressive therapy, the main HRCT pattern of pulmonary TB in liver transplant patients was cavitation and centrilobular tree-in-bud nodules. The miliary pattern had a very low incidence in this sample.

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