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Characteristics, management, and outcome of tuberculosis after liver transplant: a case series and literature review

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ABSTRACT

Background: Liver transplant recipients are at risk of tuberculosis, which is particularly difficult-to diagnose and to treat in this population.

Methods: Retrospective study of all cases of tuberculosis diagnosed during from 2007 to 2022 in the French network of liver transplant sites.

Results: Twenty-three liver transplant recipients were diagnosed with tuberculosis (six females, median age 59 years [interquartile range, 54-62]), with a median time lapse of 10 months [5-40.5] after transplant, and 38 days [26-60] after symptom onset. Primary modes of pathogenesis were latent tuberculosis reactivation (n=15) and transplant-related transmission (n=3). Even though most patients with pre-transplant data had risk factors for tuberculosis (11/20), IFN-gamma release assay was performed in only three. Most cases involved extrapulmonary tuberculosis (20/23, 87%). With median follow-up of 63 months [24-108], five patients died (22%), including four tuberculosis-related deaths.

Conclusions: Extrapulmonary tuberculosis is a severe disease in many liver transplant recipients. Systematic pre-transplant screening of latent tuberculosis may prevent most of them.

Keywords: liver transplant; tuberculosis; latent tuberculosis; pre-transplant screening; prevention

1. Introduction

Tuberculosis (TB) is a feared complication of solid organ transplantation (SOT), especially insofar as it is difficult to diagnose and treat. The risk of TB in immunocompromised patients is closely related to the incidence of TB in the countries where donors and recipients live, estimated at 0.7% (0.4-2.3%), 2.2% (0.2-8.5%), and 2.7% (1.5-16%) respectively, in hematopoietic stem cell recipients in regions with low, intermediate, and high TB incidence [1,2]. Incidence of active TB is 20-74 fold higher in SOT than in the general population [3–5]. The main risk factors are lung transplantation, intensive immunosuppressive regimens and comorbidities [4,6,7]. While most cases of active TB following SOT are related to reactivation of latent TB, transplant-transmitted TB and TB acquisition after SOT have been reported [2–4].

Active TB in SOT, as in other immunocompromised patients, is associated with diagnostic challenges ascribable to atypical features, high prevalence of extra-pulmonary TB [8–10], and poor outcome [2]. In liver transplant recipients, treatment of active TB is particularly challenging due to interactions between immunosuppressive agents and anti-tuberculosis treatment, entailing increased risk of liver toxicity [11]. We report on a case series of active TB cases following liver transplant, with two main objectives: i) to better characterize and raise awareness about this highly severe and largely neglected complication; ii) to identify cases that could be prevented by pre-transplant screening for latent TB.

2. Methods

We conducted a retrospective study of all patients diagnosed with active TB following liver transplantation from 2007 to 2022 in the French network of liver transplant sites (n=18). We selected 2007 as the start date because that year the nationwide rules for selection of liver transplant candidates were modified, and thereafter primarily based on MELD score. All patients who fulfilled the nationwide criteria for mandatory active tuberculosis case notification of active TB could be enrolled: Briefly, this definition includes: i) patients with documented *Mycobacterium tuberculosis* complex infection, detected by PCR or cultures; ii) patients treated for active TB with at least three drugs, whether the diagnosis was supported by microbiological data (acid-fast bacilli after Ziehl-Nielsen staining or immuno-fluorescence), histological findings (granulomas), or by epidemiological, clinical and/or imaging features alone. Patients for whom anti-tuberculosis treatment was prematurely discontinued due to alternative diagnosis, or failure to improve, were excluded. Cases were categorized as transplant-transmitted when the per-transplant graft biopsy and/or donor history was suggestive, as post-transplant acquired when post-transplant exposure was reported, and otherwise as reactivated pre-transplant latent TB.

Patients were identified through the computerized database of each site. Data were collected on a standardized questionnaire by the principal investigator (RNV). The study was approved by the CER-MIT review board, the national research ethics committee specialized in infectious diseases (approval number 2022-0101). Informed consent was waived, due to the retrospective collection of data. Non-opposition of participants was obtained by sending a

letter to patients or relatives. Due to the study design and limited sample size, we only performed descriptive analysis. Quantitative variables are expressed as median with interquartile range [IQR], qualitative variables by numbers (%).

3. Results

During the study period, 23 liver transplant recipients fulfilled the criteria for active TB (16 men, 7 women). Patient characteristics are summarized in Table 1. The main indications for liver transplant were cirrhosis (21/23, 91%), with hepatocellular carcinoma for 7/23 (30%), primarily related to alcohol abuse (11/23, 48%), and viral hepatitis (9/23, 39%). Although 11/23 (48%) had epidemiological risk factors for TB before transplant (mostly prolonged stay in highly endemic countries, n=10), pre-transplant IFN-gamma release assay (IGRA) was reported in medical files for only three patients, and found positive in two, who received incomplete treatment for latent TB, by isoniazid (n=1), or by the combination of isoniazid and rifampin (n=1), both of which were prematurely discontinued due to liver toxicity.

Patients were diagnosed with TB after a median time of 10 months [5-40.5] following liver transplant, and 38 days [26-60] after symptom onset (Table 2). Median age at TB diagnosis was 59 years [54-62], and the main comorbidities were chronic kidney disease (11/23, 48%), diabetes (9/23, 39%), and smoking (4/23, 17%). Immunosuppressive regimen included tacrolimus (18/23, 78%) and mycophenolic acid/mycophenolate mofetil (18/23, 78%). Half of the patients presented with fever (12/23, 52%), while altered general status was the primary clinical sign (14/23, 61%). Most of the patients (20/23, 87%) had extra-pulmonary TB, including 12 with disseminated TB (at least two organs affected). Thoracic CT scan identified pulmonary lesions in 11/23 patients (48%), but only two presented with cavitory lesions. Microbiological documentation was obtained by PCR (n=12) and/or cultures (n=12) for 17 patients, all of whom patients had multi-susceptible TB documented by phenotypic (n=12), or genotypic (n=5) drug-susceptibility testing. TB was categorized as related to latent TB reactivation in 15 patients (68%), transplant-transmitted in three, post-transplant exposure in two, and undetermined in three.

First-line anti-TB treatment was mostly a four-drug combination of isoniazid, rifamycin, pyrazinamide, ethambutol (13/23, 59%), the rifamycin being rifampin in ten patients, and rifabutin in three. Nine patients (39%) presented with treatment-related adverse events, which required treatment changes in five. For six patients, the immunosuppressive regimen was modified as a consequence of drug-drug interactions or cumulative toxicity. Median duration of anti-TB treatment was 9 months [6-12.5]. With median follow-up of 63 months [24-108] following TB diagnosis, 17/23 patients (74%) were cured, 2/23 (9%) had a new episode of documented TB, and 5/23 (23%) died, including 4 deaths attributed to TB (Table 1). All of the four patients who died had a disseminated TB. One patient who died had received a treatment without pyrazinamide, while the others had received a standard regimen (Table S1).

4. Discussion

The main findings of this retrospective multicenter study of active TB following liver transplant in France are the following: i) as expected in a low-endemicity country, active TB following liver transplant is a rare event; ii) in a country with low probability of TB exposure, most cases were due to reactivation of latent TB undetected before transplant; iii) the characteristics of TB in SOT are similar to findings in other immunocompromised patients [12,13], primarily with extra-pulmonary and disseminated TB, and low prevalence of classical TB signs (only 50% with fever, 10% with cavitary lesions on CT scan, much lower than in immunocompetent subjects [14]); iv) management of TB in liver transplant recipients is complex, with high incidence of treatment-related adverse events, and a need to adjust immunosuppressive regimens, and/or anti-TB treatment; v) the prognosis is poor, with incidence of a new TB diagnosis, and occurrence of death at 9% and 23%, respectively, after median follow-up of 5 years post-TB diagnosis.

As it was retrospective, with no active surveillance during the study period, and given the non-participation of one of the largest liver transplant sites in the country, our study was not powered to provide reliable estimates of TB incidence in liver transplant recipients. However, the identification of only 23 cases over 16 years through a network involved in >90% of liver transplants performed in France confirms the rarity of this complication. During the study period, some 19,375 liver transplants were performed in the country (source, French Agency for Biomedicine, <https://rams.agence-biomedecine.fr/greffe-hepatique-0>). Of note, TB incidence following liver transplant may be highly heterogeneous, even within low-endemicity countries: recent estimates were 541 (CI 95% 269-1065) per 100,000 persons per year in Spain, and 38 (23-63) cases in Australia [1,3,5], although TB incidence in the general population is similarly low in these two countries (<10 per 100 000 inhabitants per year).

One of the main drivers of discrepancies regarding TB incidence in SOT may be the heterogeneity of pre-transplant screening for latent TB [1,15–17]. Scientific societies and experts recommend that all SOT candidates be screened for latent TB through routine risk assessment (exposure), clinical examination, thoracic imaging (chest X-ray +/- CT scan), and immunological testing, *i.e.* tuberculin skin test (TST) +/- IGRAs [6]. In countries where the BCG vaccine is part of routine immunization programs, as was the case for France until 2007, IGRA tests are associated with elevated positive predictive value for the diagnosis of latent TB, but the risk of indeterminate results may be as high as 25% in patients with advanced liver diseases, a common feature in candidates for liver transplant [17,18]. Our findings, which show that pre-transplant screening using IGRA was reported in only 3/23 patients with active TB following liver transplant, even though 11 had pre-transplant risk factors for TB exposure, illustrate both the sub-optimal implementation of relevant guidelines in France, and the high proportion of post-transplant TB that might be prevented through systematic screening and treatment of latent TB prior to SOT. Both the complexity of TB diagnosis and treatment in SOT recipients [19,20] and the dismal prognosis call for intensified efforts to prevent this dreadful complication.

Our study has limitations. First, due to the retrospective design, with no active surveillance, we may have missed some cases. This limitation is critical given the complexity of TB diagnosis in SOT, which implies that active TB may remain unrecognized. Second, we only collected data in one country, hence our findings may not be generalizable to other settings, with different TB epidemiology and different practices for pre-transplant screening of latent TB, or implementation of immunosuppressive regimens following liver transplant.

Third, due to limited sample size, our study was underpowered to detect uncommon features and prognostic factors. However, this case series is the largest to date to report original data on active TB following liver transplant, and the involvement of a large network of sites with expertise in liver transplant is another strength.

In conclusion, active TB is a rare and severe complication of liver transplant. A high proportion of cases may be prevented through systematic screening and treatment for latent TB before transplant.

Conflicts of Interest. All authors, none.

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Journal Pre-proofs

RNV contributed to study design, collected data, performed primary analysis and wrote the first draft; FL, and PT designed the study, contributed to study analysis, and critically reviewed the manuscript; PHD, DE, JD, AP, GB, FD, LS, VLM, and NK collected data, contributed to patient care, reviewed and approved the manuscript.

Journal Pre-proofs

HIGHLIGHTS:

- Tuberculosis is a severe disease in liver transplant recipients, difficult to diagnose and difficult to treat
- As in other immunocompromised populations, most patients in this case series (20/23, 87%), had extra-pulmonary tuberculosis
- Median time from liver transplant to tuberculosis diagnosis was 10 months [5-40.5]; median time from first symptoms to diagnosis was 38 days [26-60]
- Even though most patients had pre-transplant risk factors for tuberculosis, screening by IFN-gamma release assay was performed in only three patients

Table 1. Characteristics of patients with active tuberculosis following liver transplant

| Variable | Data (n=23) |
|------------------------------------------------------------------|--------------------|
| Age, years | 59 [54-62] |
| Women | 7 (30%) |
| <u>Reason for transplant</u> | |
| - Cirrhosis | 21 (91%) |
| - Hepatocellular carcinoma | 7 (30%) |
| - Fulminant hepatitis | 1 (4%) |
| <u>Underlying liver disease</u> | |
| - Alcohol abuse | 11 (48%) |
| - Viral hepatitis ¹ | 9 (39%) |
| <u>Immunosuppressive treatment</u> | |
| - Prednisone | 8 (35%) |
| - Tacrolimus | 18 (78%) |
| - Ciclosporin | 4 (17%) |
| - Mycophenolic acid or mycophenolate mofetil | 18 (78%) |
| - Everolimus | 1 (4%) |
| <u>Pre-transplant risk factors for tuberculosis ²</u> | 11 (55%) |

| | |
|-----------------------------------------------------------------|----------|
| Prolonged stay in high-endemicity area ³ | 10 (50%) |
| Previous contact with contagious tuberculosis | 2 (10%) |
| Low socio-economic status | 4 (20%) |
| <u>Pre-transplant investigations for latent TB ²</u> | |
| IFN-gamma release assay (IGRA) ⁴ | 3 (15%) |
| Thorax CT scan | 11 (55%) |
| - Possible sequelae of tuberculosis | 2 |
| - Pleural effusion | 2 |
| <u>Comorbidities at the time of tuberculosis diagnosis</u> | |
| | 9 (39%) |
| - Diabetes | 11 (48%) |
| - Chronic kidney disease | 1 (4%) |
| - HIV | 4 (17%) |
| - Active smoking | 3 (13%) |
| - Uncontrolled cancer or malignant hemopathy | |

Quantitative data are presented as medians [interquartile range], qualitative data as numbers (%)

CT, computed tomography

¹ HCV (n=7), HBV (n=2); ² data available for only 20 patients; ³Africa (n=9), Asia (n=1); ⁴ Two IGRAs returned positive, and were prescribed treatment for latent tuberculosis

Table 2. Characteristics of tuberculosis following liver transplant

| Variables | Data |
|---------------------------------------------------------------|-------------|
| <u>Clinical signs</u> | |
| - Fever | 12 (52%) |
| - Altered general status | 14 (61%) |
| - Dyspnea | 7 (30%) |
| - Neurological disorders | 5 (22%) |
| - Enlarged lymph nodes | 6 (26%) |
| | 4 (17%) |
| Time from liver transplant to tuberculosis diagnosis (months) | 10 [5-40.5] |
| Time from symptom onset to tuberculosis diagnosis (days) | 38 [26-60] |
| <u>Suspected mode of tuberculosis pathogenesis</u> | |
| - Latent TB reactivation | 15 (68%) |
| - Transplant-related transmission | 3 (14%) |
| - Post-transplant exposure | 2 (9%) |
| <u>Tuberculosis characteristics</u> ¹ | |
| - Pulmonary tuberculosis | 11 (48%) |
| - Extra-pulmonary tuberculosis | 20 (87%) |
| - Disseminated (at least 2 organs affected) | 12 (52%) |
| <u>Thoracic CT scan</u> ² | 11 (55%) |
| - Pulmonary lesions ³ | |
| - Pleural effusion | |
| - Enlarged lymph nodes | 11 (55%) |

| | |
|-----------------------------------------------|----------|
| - Pericardial effusion | 7 (35%) |
| <u>Microbiological tests for tuberculosis</u> | 7 (35%) |
| - Positive microscopic examination | 2 (10%) |
| - Positive PCR | |
| - Positive cultures | |
| <u>Histology</u> | 7 (30%) |
| - Granuloma | 12 (52%) |
| - Necrosis ⁴ | 12 (52%) |
| | 10 (43%) |
| | 7 (30%) |

Quantitative data are presented as medians [interquartile range], qualitative data as numbers (%)

¹ Extra-pulmonary sites: pleura, pericardium, peritoneum, lymph nodes, liver, digestive tract, central nervous system, bone; ² Data available for only 20 patients; ³ including two with cavitory lesions, ⁴ Two cases with caseous necrosis

Table 3. Treatment of active tuberculosis post-liver transplant (n=22) ¹

| Variables | Data |
|-------------------------------------------------------------------------------------|-------------|
| <u>First-line anti-tuberculosis treatment</u> ³ | |
| - isoniazid, rifampin, pyrazinamide, ethambutol | 10 (45%) |
| - isoniazid, rifabutin, pyrazinamide, ethambutol | 3 (14%) |
| - isoniazid, rifampin, pyrazinamide | 3 (14%) |
| - fluoroquinolone-containing regimen ² | 6 (27%) |
| <u>Treatment-related adverse events</u> ³ | |
| - Liver toxicity | 3 (14%) |
| - Renal toxicity | 2 (10%) |
| - Neurological toxicity | 4 (19%) |
| Change in tuberculosis treatment due to adverse events ³ | 5 (24%) |
| Change of immunosuppressive regimen due to adverse events or drug-drug interactions | 6 (27%) |
| Graft rejection under anti-TB treatment ⁴ | 2 (9%) |
| Total duration of anti-tuberculosis treatment, months | 9 [6-12.5] |
| <u>Outcome</u> | |
| Time to last follow-up after tuberculosis diagnosis, months | 63 [24-108] |
| Cure | 17 (77%) |

| | |
|-------------------------------|---------------------|
| New diagnosis of TB | 2 (9%) ⁵ |
| Deaths | 5 (23%) |
| - tuberculosis-related deaths | 4 (18%) |

Quantitative data are presented as medians [interquartile range], qualitative data as numbers (%)

¹ For one case we had information about diagnosis but no data for treatment and follow-up;

² Fluoroquinolones were always associated with at least two drugs among first-line anti-TB drugs (isoniazid, pyrazinamide, rifampin); ³ data available for only 21 patients; ⁴ one was directly linked to resumed alcohol consumption, the other rejection was not directly associated with TB treatment; ⁵ TB diagnosed 8 months, and 12 years after completion of first TB treatment