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Determinants and characteristics of tuberculosis in liver transplant recipients

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Background/aim: Solid organ transplant (SOT) recipients have increased risk of tuberculosis (TB). We aimed to investigate the prevalence and features of TB in liver transplant (LT) recipients at our transplantation canter.

Materials and methods: All patients who underwent LT between January 2004 and December 2013 and whose data were accessible were included in the study. Demographic features, tuberculin skin test (TST) results, and TB prevalence were recorded. Characteristics of LT recipients who developed TB were evaluated.

Results: A total of 403 patients underwent LT during this period. Mean age was 47.27 ± 11.04 years; 280 (69.47%) were males. The TST was administered to 108 (25.91%) and the QuantiFERON-TB test to 1 patient. TST positivity was determined in 28 (25.93%). Latent TB infection (LTBI) treatment was not recommended to any of the LT candidates. In the posttransplant period, 5 patients (1.24%) developed TB over a median duration of 14 (min: 7, max: 84) months, 2 of whom were found to have had LTBI in the pretransplant period.

Conclusion: The prevalence of TB in LT recipients at our center was similar to that in the current literature. LTBI screening, including risk factor assessment and TST/QuantiFERON-TB testing, is necessary in the early diagnostic workup for TB in LT recipients.

Key words: Tuberculosis, liver transplantation, immune suppression, latent tuberculosis infection

1. Introduction

Active tuberculosis (TB) may develop in a minority of individuals whose immune systems fail to evolve adequate responses towards the *Mycobacterium tuberculosis* complex (1). Therefore, immunocompromised patients such as solid organ transplant (SOT) recipients possess increased risk for tuberculosis (TB), depending on the burden of the disease in their country of residence (2). The prevalence of TB in SOT recipients has been reported to be between 0.26% and 6.4% (3–6) in different settings, while in high-burden areas prevalence of up to 15% has been defined (7). Although the TB incidence rate has been decreasing in Turkey (22 per 100,000 population for 2012), it is higher than that of low-burden countries (7). TB prevalence in SOT recipients has been reported to be between 1.9% and 6.7% in our country in a few studies (8–10).

Posttransplant TB development risk depends not only on TB incidence in the population, but also on the number of transplantations performed in the center, prior TB infection or latent TB infection (LTBI) treatment in the pretransplant period, pretransplant tuberculin skin test (TST) results, and the recipient's age (1). Atypical presentations, delayed diagnosis, and drug interactions lead to high TB-related morbidity and mortality in SOT recipients (11). Therefore, we aimed to investigate clinical characteristics as well as risk factors associated with TB in liver transplant (LT) recipients and posttransplant TB prevalence in a tertiary teaching hospital located in a TB low-burden city in Turkey.

2. Materials and methods

We conducted a retrospective descriptive study and reviewed the data of LT recipients at our LT center for the 10-year period between January 2004 and December 2013. Our local ethics committee approved the study (4 September 2014, 2014/28-13).

Pulmonologists, infection diseases specialists, psychiatrists, anesthesiologists, and gastroenterologists had

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evaluated all patients routinely for their own specific risk factors prior to transplantation. Medical records obtained by pulmonology consultations, including pretransplant medical history, smoking status, previous TB contact, and Bacillus Calmette–Guérin (BCG) vaccination, were investigated. Radiological findings associated with LTBI (apical fibronodular lesions, calcified solitary nodules, calcified lymph nodes, or pleural thickening) and TST results were also recorded.

LT recipients who developed TB in the posttransplant period were identified and posttransplant TB prevalence was calculated. TB diagnosis in these patients depended on symptoms, signs, and radiological findings (cavities, consolidation, bronchopneumonia, lymphadenopathy) compatible with active TB infection, in addition to microbiological (demonstration of acid-fast bacilli or culture positivity of *M. tuberculosis* in specimens) and/or pathological (caseating granuloma) confirmation.

2.1. Immunosuppressive treatment

Tacrolimus, mycophenolate mofetil, and corticosteroids were the immunosuppressive drugs administered in the posttransplant period. Within a 20-day period, the drug doses were tapered.

2.2. Statistical analysis

Data were analyzed with SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Mean and standard deviation or median and minimum maximum values were expressed according to the distribution of the data. Variables were compared by Mann–Whitney U test for nonparametric values. Categorical data were evaluated by chi-square or Fisher's exact test. The relationship between independent variables was evaluated by Spearman correlation analysis. $P < 0.05$ was considered significant.

3. Results

Four hundred and three LTs were performed during the given period. Demographic and clinical features of the patients are shown in Table 1. The factors associated with likelihood of TB development—previous TB history, contact with an active TB patient, and smoking—were asked about for 214 (53.10%), 211 (52.35%), and 212 (52.61%) of the patients, respectively. BCG vaccination was recorded in 19 (8.81%) cases. Respiratory system physical examination was normal in 369 (91.57%). Chest X-ray was normal in 182 (84.7%) out of 215 interpretable radiographies. Pathological radiographic appearances included consolidation, pleural effusion, mass, fibrotic lesions, and nodules. One hundred and eight (26.79%) patients underwent the TST, and 28/103 (25.93%) were positive. Only one of the patients had the QuantiFERON-TB test, which was positive. The TST was applied to 3 of the patients who developed posttransplant TB infection, and TST positivity was obtained for one. TST median value was 7 (0–25) mm. LTBI treatment was not administered in the pre- or posttransplant period to patients who had tested positive with either the TST or QuantiFERON-TB.

Table 1. Characteristics of liver transplant recipients.

Characteristics		n (%)
Sex	Male	280 (69.47)
	Female	123 (30.52)
Child classification (n = 379)	Child A	41 (10.81)
	Child B	186 (49.07)
	Child C	152 (40.10)
Donation type (n = 399)	Living donor	227 (56.89)
	Cadaveric	172 (43.11)
Etiology	Hepatitis B	88 (21.83)
	Hepatitis C	36 (8.93)
	Cryptogenic	32 (7.80)
	Other	247 (61.56)
Previous TB history (n = 214)		5 (2.33%)
Contact with active TB patient (n = 211)		5 (2.36%)
Smoking history (n = 212)		108 (50.94%)
Diabetes mellitus (n = 385)		76 (19.79%)
TST positivity (n = 108)		28 (25.93)
		Mean ± SD
Age (years)		47.27 ± 11.04
MELD score		16.30 ± 6.54

TB, Tuberculosis; MELD score, Model for End-Stage Liver Disease.

The median duration of follow-up was 5 years in the posttransplant period (min: 6 months, max: 10 years) until 2013. Following the transplant, 5 patients (1.24%) had active TB diagnoses, one of which was extrapulmonary. The median duration of TB development after transplantation was 14 months (7–84 months). Among these patients, TST positivity was determined in one and QuantiFERON-TB test positivity was also found in one. Characteristics of these patients are shown in Table 2.

Age, body mass index (BMI), and Model for End-Stage Liver Disease (MELD) scores of the TB patients were similar to those of other patients ($P > 0.05$).

4. Discussion

SOT recipients are prone to opportunistic infections due to intense immunosuppression in the posttransplant period. Reactivation of LTBI is a challenging problem in

Table 2. Characteristics of patients who developed active TB in the posttransplant period.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age–Sex	59–M	52–M	60–M	28–F	67–F
Primary disease	HBV, HCC	HBV, HCC	HBV	HBV, HDV	HCV
Donation type	Cadaveric	Living	Living	Living	Living
Posttransplant TB development time	9th month	24th month	84th month	14th month	7th month
TST / QuantiFERON-TB test	10 × 11 mm	20 × 23 mm	Not applied / +	Anergic / not applied	Not applied
TB contact	-	-	+	-	-
Symptoms	-	Night sweats	Weight loss, cough, sputum	Fatigue, cough, fever	Fever, mouth ulceration
Clinical signs	-	-	Crackles	Fever, crackles	Fever, mouth ulceration
Radiology	Fibrotic changes	Nodule	Nodule bronchiectasis cavity	Consolidation atelectasis	Normal

HBV, Hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis D virus; HCV, hepatitis C virus; TB, tuberculosis; TST, tuberculin skin test.

posttransplant settings. Predictors and prevalence of TB infection in SOT recipients have been investigated in different regions of the world, and a 20–74 times increased risk with respect to the general population has been defined (3,12). In our study, a tertiary hospital experience for LT recipients revealed risk factors for LTBI in 2 out of 5 TB diagnosed patients and a TB prevalence similar to that of the current literature on LT recipients.

We found hepatitis B infection as the most common etiology for LT in both patients with and without TB. In other studies, hepatitis C was defined as the most common etiology (13,14). The findings of our study were attributed to the high prevalence of HBsAg positivity in our country (15).

Pretransplant LTBI screening in SOT recipients is strongly recommended in transplantation guidelines (1). However, risk factors for LTBI, such as previous TB and contact with an active TB patient, had only been evaluated in approximately 50% of the patients in our cohort. This was due to the lack of a multidisciplinary approach and organization, as well as inappropriate systematic follow-up of LT candidates. We recognize that pulmonologist evaluations and TB records were properly organized after the year 2007.

The predictors of TB development in SOT recipients are defined as follows: graft from a cadaveric donor, intense immunosuppression, use of T cell-depleting antibodies, diabetes mellitus, increased age of the recipient, TST positivity, and risk factors or evidence for LTBI (1,12,16). In our study, living donor LT (59%) was more frequent than cadaveric donation, and 80% of the TB-diagnosed patients had living-donor grafts. This is compatible with our country's data. The absence of TST results for the donors is one of the limitations of our study. Among other risk factors for posttransplant TB development, we found that one of the TB-diagnosed patients had close contact with an active TB patient, one was older than 65, and 2 had positive TST or QuantiFERON-TB results.

TST and/or interferon-gamma release assays (IGRAs) are the recommended laboratory tests for LTBI screening. However, false negative results due to underlying liver disease and/or immunosuppression and false positive results associated with high prevalence and prior BCG vaccination limit the value of TST screening in SOT patients (17). In these circumstances, radiological studies are recommended. Turkey is an intermediate-burden country and BCG vaccination is routine in childhood; therefore, chest X-rays were administered to all our patients, and most of the radiographs that we could access in the database were normal (84.71%).

After excluding active TB disease, positive immunologic test results should indicate treatment for LTBI (1). In our study, the TST was positive in 28 (25.93%) of 108 patients to whom it was administered, and the QuantiF-

ERON-TB was positive in the one patient who underwent this test. We attributed the TST positivity rates to our country profile. Considering prior BCG vaccination, the QuantiFERON-TB test might be a better choice for SOT recipients in our country. However, it is still a sophisticated and expensive diagnostic test. Among the 5 patients who developed TB in the posttransplant period, only 1 of them was positive for the TST. In some studies, TST positivity has not been defined as a risk factor for TB infection, based on the fact that active TB develops in only 0.9% of TST-positive patients (11). Only one of our TST-positive patients developed TB in the posttransplant period.

Although it is strongly recommended, drug toxicity and/or interactions restrict the administration of LTBI treatment in LT candidates. Isoniazid (INH) for 6–9 months of duration is the recommended choice (1,18). Although most of the studies investigating INH for LTBI treatment in LT candidates reported that the drug was safe, the practical implementation is controversial (13,18). Sidhu et al. evaluated 200 of 461 SOT candidates in a TB screening program during a 10-year period (18). Eleven of the patients refused the treatment and most of the remaining patients (64.5%) completed the therapy, although LT candidates or recipients were less compliant. Active TB was not detected in any patients in either the treatment or treatment-rejected groups during the follow-up period (18). While there are expert opinions and recommendations for LTBI screening and treatment in SOT, national LTBI screening programs for LT candidates are not defined in some countries. Therefore, some centers avoid medication based on the hypothesis that the risks of LTBI treatment might outweigh the benefits (12,19). We were also of that opinion, so we did not recommend LTBI treatment in either the pre- or posttransplant periods; we also considered the relatively low compliance rates of LT patients to LTBI treatment and the conflicting results about drug safety. However, after we determined that 40% of our TB patients had a positive TST or QuantiFERON-TB test, we decided to review our practice of not recommending LTBI treatment. Some authors recommend LTBI treatment in LT candidates only with compensated cirrhosis, recent TST conversion, previous inadequately treated TB, or exposure to active TB (20,21).

We identified 5 (1.24%) TB cases out of 403 LT recipients. The incidence of TB in SOT recipients has been reported to be between 0.45% and 3.5% in Europe (11,12,22,23). Our prevalence rate is relatively low, considering that Turkey is an intermediate-burden country. Among the previously defined risk factors, 2 of the TB-diagnosed patients had positive TST/IGRA results and one of them had a previous active TB contact; however, all had normal radiograms in the pretransplant period. Only one of our TB patients had extrapulmonary involvement. The extrapulmonary TB rate was defined as 16% in one series, which is higher than that for the general population (3,23). TB infection generally occurs in the first year after transplantation, but a peak after 2 years has also been defined (5,21). In our study, we found median duration of TB infection development after transplantation to be 14 months (7–84 months). All transplant recipients except one presented in the first 2 years. Constitutional symptoms related with TB including night sweats, weight loss, and fever are common in TB patients with SOT (1). All of our TB patients had these symptoms (Table 2).

Diagnosis of TB in SOT recipients is similar to that in immunocompetent patients with positive smears for acid-fast bacilli and/or mycobacterial culture or histopathological confirmation. A pyrazinamide-free regimen can be preferred in nonsevere hepatic disease; in severe hepatic disease, a regimen that is both isoniazid- and pyrazinamide-free is recommended (22). The doses of calcineurin inhibitors, mTOR, and corticosteroids should be increased with a rifamycin-inclusive regimen. (24). Fluoroquinolones might be used as a first-line agent when a standard regimen cannot be used (25). All of our patients were treated with standard TB medication, except for one to whom moxifloxacin instead of rifamycin was administered. One of our patients worsened during the course of therapy; fever and lymph node enlargement developed. This clinical deterioration was explained by immune reconstitution inflammatory syndrome and high-dose systemic corticosteroids were given. One of our patients died in the first month of the treatment due to acute rejection. Drug interactions between immunosuppressive and antituberculosis drugs might end with graft rejection, as in our patient (20). A mortality rate of up to 40% has been described in SOT recipients with TB (2,3,11,21).

We determined a relatively low prevalence of TB in the LT recipients at our center, although only half of the recipients were evaluated for LTBI. This is due to suboptimal recording and preoperative evaluation in the first years of our center's transplantation practice. Two of our TB-diagnosed patients had LTBI screening test positivity and one stated a close contact with an active patient. Therefore, pretransplant LTBI screening should be performed, and LTBI treatment might be offered in LT recipients with stable disease after considering the risk/benefit ratio. Standard TB treatment was successfully administered to our patients.

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