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ORIGINAL ARTICLE

Evaluation of latent tuberculosis infection in liver transplant recipients

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ABSTRACT

Background and Objectives: Tuberculosis is one of the main reasons for mortality in liver transplant recipients. Since Iran is considered as a tuberculosis-endemic country, the present study aims to evaluate the outcome of latent tuberculosis infection in transplant recipients after liver transplantation.

Materials and Methods: The present analytical cross-sectional study was performed on transplanted patients in Imam Khomeini Complex Hospital in Tehran Iran from 2006 to 2016. All patients with positive tuberculin skin test were enrolled. Variables including demographic information, therapeutic and outcome data were gathered and analyzed.

Results: Among 675 transplant recipients, 100 patients had positive tuberculin skin test (14.8%). Sixty seven percent of recipients were men and the mean age was 72.67 ± 1.3 years. All patients' received Isoniazid prophylaxis before transplantation. The mean duration of anti- tuberculosis prophylaxis before and after transplant were 2.7 ± 1.9 and 3.6 ± 5.5 months, respectively. Tuberculosis has not been occurred in none of these patients after a mean follow up time of 45.21 ± 3 months. During the study period, four subjects infected by *Mycobacterium tuberculosis*, while their skin test was negative before transplant.

Conclusion: According to our study, tuberculin skin test is a reliable and sensitive test for diagnosis of latent tuberculosis in liver transplant candidates. Isoniazid prophylaxis is well tolerated in patients with end stage liver diseases and liver transplant recipients.

Keywords: Liver transplantation; Latent tuberculosis; Active tuberculosis

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INTRODUCTION

Tuberculosis (TB) is one of the main reasons for mortality in liver transplant (LT) recipients (1, 2). Infection is usually occurred through reactivation of latent infection or occasionally by the infected organ transplant (2). Diagnosis and treatment of TB after LT encounter several challenges. First, the diagno-

sis can be delayed due to subtle and unusual clinical manifestation and higher rate of extra-pulmonary TB (60%) in solid organ recipients, as well as lack of accurate diagnostic tools (3). Moreover, various adverse medical conditions could occur as a result of drug-drug interactions between anti tuberculosis therapy and cyclosporine. In addition, concerns regarding the hepatotoxicity of anti-TB drugs are also exist. The mortality rate related to TB infection has been estimated to be about 29% and thus remains as one of the most life-threatening infectious diseases in transplant recipients (4).

Immunosuppression is one of the well-known risk factors for TB recurrence. This infection occurs in 1.2-6.4% of transplant cases worldwide, although this rate has been reported to be 15% in endemic countries (5). The most common form of TB after transplant is the reactivation of latent infection (2). Approximately, 5-10% of immunocompetent patients who were exposed to *Mycobacterium tuberculosis* (MTB) will develop TB at some point in their lifetime. While this risk is estimated to be 10 to 70 folds higher in individuals who receive immunosuppression regimen (2, 6).

Currently, the gold standard tests for latent TB detection are tuberculin skin test (TST) that involves intradermal injection of purified protein derivative (PPD) along with interferon gamma release assays (IGRA). Despite the widely usage of TST, its accuracy in recognizing latent TB among LT candidates are unclear. Iran is one of the endemic countries with high incidence rate of TB infection. Considering the importance of latent TB among patients with liver cirrhosis, who are listed for LT, the present study aimed to identify and report the incidence rate of latent TB infection in transplant candidate patients. Moreover, the effectiveness of using isoniazid in preventing the recurrence of active TB infection after LT was measured.

MATERIALS AND METHODS

Patients. The present cross-sectional study was performed on transplanted patients in Imam Khomeini Hospital Complex, affiliated to Tehran University of Medical Sciences, from 2006 to 2016. The treatment outcome of the patients with positive TST was evaluated. The protocol for organ allocation in our center is based on deceased donors. The variables before transplantation included age, gender, model for end stage liver disease (MELD) score, and induration size of TST. The information after transplantation included time, type, and treatment duration of LTBI in patients with positive tuberculin skin test, radiological findings, the recurrence of tuberculosis and recurrence of underlying disease and survival rate of patients. A written informed consent was obtained from all patients prior to enrolling in the study. The protocol of the present study was in concordance with Declaration of Helsinki and other applicable guidelines laws and regulations (ethical code: IR.TUMS.IKHC.REC.1396.3891).

Measurements. TST was done by patient's residence laboratories through a standard method. To perform tuberculin test, 0.1 ml tuberculin was injected subcutaneously and marked with a pen. After 72 hours, the largest diameter of the knot was measured by a ruler. The second test was done for negative results with 7 days interval (Double Test). QuantiFERON-TB Gold test (QFT) was done for detection of *M. tuberculosis* in a valid laboratory setting. Induration more than 5 millimeters by TST or positive QFT was considered as diagnostic criteria for latent TB. In order to ruling out active TB, chest X ray (CXR) and/or chest computerized tomography (CT) scan were done for all patients. Ascites fluid analysis (including cell diff, glucose, protein, lactate dehydrogenase, adenosine deaminase and MTB PCR) and sputum smear and culture for MTB were performed. Chemoprophylaxis with isoniazid (INH) had been prescribed for 9 months for patients with latent TB infection. Patients received INH before transplantation and continued it after LT in case they did not complete the treatment duration. In emergency cases chemoprophylaxis was started after LT.

Statistical analysis. The results of quantitative variables were expressed by mean ± SD and for qualitative variables; they were expressed as a percentage. The comparison between quantitative variables was done by t-test and in the case of abnormal data distribution; it was performed by the Mann-Whitney U test. On the other hand, the comparison of qualitative variables was carried out using Chi-square test. Moreover, the correlation between quantitative variables was evaluated using the Pearson correlation coefficient and Spearman rank correlation tests. The statistical analysis of data was carried out using SPSS

V.16 (SPSS Inc., Chicago, IL, USA) and SAS v.9.1 software. The significant level was considered to be $P<0.05$.

RESULTS

Demographic, clinical and laboratory findings of the patients are summarized in Table 1. In the present study, 100 out of 675 LT recipients had positive TST (14.8%). The most common etiology of cirrhosis was cryptogenic (20%), followed by hepatitis C (19%), and hepatitis B infection (13%). Forty eight percent of patients were transplanted because of other indications. One patient was treated with azathioprine (1%), six patients with prednisolone (6%) and six of them with combination of prednisolone and azathioprine (6%) before LT.

Seventy patients (70%) had scar of Bacillus Calmette–Guérin (BCG) vaccination on their arms. Five patients (5%) diagnosed with latent TB had a history of tuberculosis before transplantation. A total of 56 (56%) patients received chemoprophylaxis with INH prior to LT. The mean time of anti-TB prophylaxis before and after transplants were 2.7 ± 1.9 and 3.6 ± 5.5 months, respectively. The total mean duration of INH prophylaxis was 6.9 ± 3.4 months (range: 1-9 months). Eight patients completed 9 months INH prophylaxis.

Increasing in liver enzymes was observed only in 2 (2%) patients that led to the discontinuation of drug after 3 (post transplantation prophylaxis 3 months) and 9 months (pre-transplantation prophylaxis 1 month, post transplantation 8 months) of treatment. However it is important to mention that the exact complications related to INH prophylaxis had not registered at the patients files.

After LT, no cases of active TB were found among patients with positive TST during a mean follow up of 45.21 months. Moreover, Cytomegalovirus (CMV) viremia occurred in 29 subjects (29%), although only 4 of them (4%) had developed CMV disease. Organ rejection was observed in 13 cases (13%) during follow up.

Among 675 LT recipients four patients had active tuberculosis, while their skin test was negative before transplant. Clinical, laboratory and outcome of these patients are shown in Table 2. Due to low number of patients with tuberculosis we did not do any analysis between different variables and TB infection.

Table 1. Baseline information of patient with latent tuberculosis.

Variables	Mean	Std. Error
Weight	72.67	1.305
Age	47.76	1.301
PPD	10.36	0.5015
prophylaxis after transplantation (month)	5.68	0.350
prophylaxis before transplantation (month)	1.96	0.279
prophylaxis duration (month)	7.22	0.317
MELD	19.01	0.467
number of rejects	0.13	0.039
Follow up duration (months)	45.21	3.009

Abbreviation: Purified protein derivative (PPD), model for end stage liver disease (MELD).

Table 2. Information of patient with active TB disease.

Patient	Weight	Age	PPD	MELD	Time of TB	Rejection	Follow up	Type TB	Outcome
1	73	62	<5	22	9	Yes	76	vertebral	alive
2	47	31	<5	22	2	No	68	vertebral	alive
3	70	70	<5	7	10	Yes	69	pulmonary	alive
4	63	47	<5	16	12	no	78	lymphadenitis	alive

Abbreviation: Purified protein derivative (PPD), model for end stage liver disease (MELD), Tuberculosis (TB).

DISCUSSION

Iran is an endemic country for tuberculosis, with the rate of 14 out of one hundred thousand TB-infected cases and is among the regions with high risk of TB infection (7). This condition is a challenging concern for patients with immunocompromised condition as seen in transplanted individuals. The frequency of TB among the organ receivers is 20 to 74 times more than the normal population. Moreover, patients, who were treated with immunosuppressive drugs before transplant, were experienced TB after transplantation 6 times more than others (8). This issue shows the necessity of screening before transplantation.

Latent TB infection screening before transplantation is a challenging examination that has been done differently by various centers. Interferon gamma release assay test intensifies the complexity of screening. This issue leads to an increase in the complexity of screening and indistinctive effectiveness on outcome of LT recipients. In a retrospective study, the positive rate of QFT before LT was 13.5% while none of them experience active TB (8). Despite the complexity of diagnosis and treatment of latent TB, most transplant centers including our center do latent TB screening with treatment of patients. The positive TST results in previous study in our center in cirrhotic patients on the waiting list was 15.9% (9), while in comparison with reports from positive TST in liver recipients in Canada (24.2%) and Italy (40%) (10, 11). However, in the present study, the rate of latent TB infection was 14.8%.

The treatment of latent TB is necessary in high risk patients including solid organ transplant recipients (12). In the present study, all patients with positive PPD test were received prophylaxis, which led to a significant reduction in active TB after LT. Thus active TB was not seen in any of the patients with latent TB after transplantation. The daily consumption of isoniazid for 9 months is recommended to treat latent TB before organ transplantation, but the reports on chemical toxicity of isoniazid are controversial (13).

Hepatotoxicity risk from isoniazid prophylaxis appears to be low in transplant recipients without pre-existing liver disease and may even be well tolerated in selected LT candidates with compensated liver disease (14, 15). Several studies recommended that in LT candidates with advanced liver disease, which has a higher risk for tuberculosis, prophylaxis may delay with isoniazid after LT, the time that patient is stable clinically (16). In our study, we were able to treat latent TB before LT with isoniazid without complications.

CONCLUSION

The present study showed that the rate of active TB was lower than in endemic areas. It seems that the difference can be due to the use of anti-TB prophylaxis in patients with latent TB. Furthermore, considering the well tolerated INH treatment before LT in our study patients with decompensated cirrhosis and drug interaction between anti-TB with immunosuppression agents after LT, we recommend the use of INH prophylaxis before transplant.

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