

Tuberculosis Post-Liver Transplantation: A Rare but Complicated Disease

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Abstract

Introduction: Tuberculosis is a rare but serious complication after transplantation. We report a case and discuss its presentation and management. **Clinical Picture:** A 60-year-old Indonesian male presented initially with fever, acute confusion and rapidly progressive right upper lobe pneumonia 3.5 months post-liver transplant, and was diagnosed with pulmonary tuberculosis by positive sputum smear for acid-fast bacilli and tuberculosis culture. **Treatment/Outcome:** Standard anti-tuberculosis therapy was administered but was complicated by interaction with cyclosporine and drug-induced cholestasis. **Conclusion:** A high level of suspicion, prompt anti-tuberculosis treatment and close follow-up are essential in management of post-transplant tuberculosis.

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Introduction

Tuberculosis (TB) is a serious opportunistic infection in transplant recipients, with an incidence in organ transplant recipients ranging from 0.35% in developed countries to 15% in endemic areas.¹ It carries a mortality rate of as high as 40%.² The majority of TB infection have occurred within 12 months of transplant. Reactivation of TB and, rarely, nosocomial acquisition or donor transmission are considered to be the most frequent modes of acquisition of TB.¹ We describe a case of pulmonary TB developing 3.5 months after orthotopic liver transplant (OLT).

Case Report

A 60-year-old Indonesian male underwent OLT for chronic hepatitis C (CHC)-related decompensated cirrhosis and hepatocellular carcinoma on 28 April 2000. He had no past or contact history of TB. His pre-transplant chest X-ray and computed tomography scan of the thorax revealed no abnormalities. Immunosuppression regimes consisted of intravenous basiliximab administered immediately and on day 4, tapering dose of prednisolone starting from 20 mg b.d. on day 0, and tapering dose of tacrolimus from 0.1 mg/kg/day from day 7 post-transplant.

His immediate post-transplant course was complicated by surgical wound infection and *Klebsiella pneumoniae*,

which resolved with parenteral antibiotics, and he was eventually discharged 24 days post-transplant with a clear chest X-ray (Fig. 1). He was later diagnosed with hepatitis C virus (HCV) recurrence at 10 weeks, which was treated with interferon- α 3 MU t.i.w and ribavirin 1 g daily. However, due to acute psychosis and severe depression, the antiviral treatment was stopped after 3 weeks, 13 weeks post-transplant.

Fifteen weeks post-transplant, the patient was again admitted for fever and acute confusion. Magnetic resonance imaging of the brain and lumbar puncture results were unremarkable. In view of the possibility of tacrolimus-induced neurotoxicity, tacrolimus was substituted with cyclosporine (Neoral[®], Novartis (Singapore) Pte Ltd, Singapore) 125 mg b.d. and azathioprine 75 mg om. Chest X-ray, however, showed an acute onset of right upper lobe pneumonia (Fig. 2). Sputum smear for acid-fast bacilli (AFB) and subsequent TB culture were both positive. Standard 6-month quadruple anti-TB therapy, consisting of rifampicin 450 mg/day, isoniazid 300 mg/day, ethambutol 800 mg/day and ofloxacin 400 mg/day were prescribed for 2 months, followed by isoniazid and ethambutol for 4 months. The patient's fever settled and he was discharged 10 days after admission.

During the 6-month course of anti-TB treatment,

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Fig. 1. Chest X-ray done 10 days post-transplant shows clear lung field.

prednisolone was gradually stopped, but cyclosporine dosage was increased from 125 mg b.d. to 175 mg b.d. due to his dropping cyclosporine level. Cholestasis occurred 7 weeks after anti-TB treatment, and rifampicin-induced cholestasis was suspected. Hence, rifampicin was substituted with streptomycin. However, subsequent ultrasonography of hepatobiliary system and endoscopic retrograde cholangiopancreatography showed a tight anastomotic biliary stricture, which was not amenable to endoscopic therapy. The patient then underwent laparotomy with creation of Roux-en-Y jejunobiliary anastomosis 9 weeks after anti-TB treatment, and 24 weeks post-transplant. Cholestasis resolved after the surgery. Rifampicin was not resumed.

After the 6-month course of therapy, his right upper lobe infiltrates resolved and he remained well with no respiratory symptoms until his last review, 40 months after the cessation of anti-TB treatment.

Discussion

TB has important implications in the care of transplant recipients. First, it causes significant mortality in transplant recipients as compared to the general population with TB.³ It is of concern that this high mortality rate has not varied in more recently published series, despite the decreasing incidence of TB recorded in many countries.³ Although only 1% of liver transplant recipients at the NUH Liver Transplant Programme had post-transplant TB, TB remains at the top of the watch list in the care of post-transplant patients.

Secondly, symptoms of TB are insidious, often causing delay in diagnosis and resulting in a poor prognosis.⁴ In our patient, pulmonary TB presented initially as fever and



Fig. 2. Chest X-ray done upon readmission for febrile delirium shows new onset of right upper lobe opacification.

acute confusion without overt respiratory symptoms. His concurrent problems of interferon-induced psychosis and tacrolimus-induced neurotoxicity have complicated the differential diagnoses. TB was suspected once the right lung upper lobe infiltrates occurred, even though there was no past or contact history of TB, or radiological evidence of prior pulmonary TB on pre-transplant chest X-ray, the presentation being acute. Both sputum smear for AFB and TB culture were performed to increase sensitivity of diagnosis.⁵ Nishizaki et al⁵ showed that 3 of 12 patients had positive sputum TB culture despite a negative sputum AFB stain. As TB culture often takes about 6 to 8 weeks, molecular methods like transcription-mediated amplification or polymerase chain reaction may allow for early diagnosis of TB, but their accuracy may be dependent on the expertise of the respective laboratories.⁴

The treatment of TB in liver transplant recipients is more difficult than other transplant recipients due to potentially increased sensitivity of the hepatic allograft to anti-TB agents.³ Schluger et al⁶ reported that 5 (38%) of 13 patients given isoniazid for either TB therapy or prophylaxis developed biochemical and histological evidence of isoniazid-induced hepatotoxicity. Hepatotoxicity is also more likely to occur if isoniazid is combined with rifampicin. Diagnosis of anti-TB treatment-induced hepatotoxicity is difficult, as other causes such as acute cellular rejection, biliary stricture and recurrence of viral hepatitis may manifest in the same manner.⁷ When our patient presented with jaundice 7 weeks after the commencement of anti-TB medication, drug-induced cholestasis from rifampicin was initially suspected, but cholestasis was finally attributed to anastomotic biliary stricture after imaging. Therefore, strong clinical suspicion, virological markers, biliary tract imaging

and liver biopsy are necessary in the evaluation of the cause of elevated liver enzyme levels before stopping anti-TB treatment.^{1,7}

Interaction between anti-TB drugs and immunosuppressants raised another concern. Both rifampicin and isoniazid upregulate the cytochrome P450 function, causing an increase in the metabolism of calcineurin inhibitors such as cyclosporine, thus decreasing their levels in the blood and increasing the risk of allograft rejection.^{3,4} In one Egyptian study which followed 45 patients with TB after renal transplant, chronic rejection occurred in 25 (55.6%) patients, resulting in graft loss in 16 (36%) patients.⁸ Hence, regular monitoring of level of calcineurin inhibitors is important. We also experienced a decrease in cyclosporine level in our patient, requiring an increase of cyclosporine dose during the anti-TB drug treatment.

CHC was the most common coexisting infection with post-transplant TB. Pre-existing viral hepatitis has been considered a risk factor for hepatotoxicity of anti-TB drugs in patients with chronic HCV infection.⁴ Ungo et al⁹ reported the relative risk of developing drug-induced hepatitis being fivefold in patients with CHC infection as compared to controls. However, Sayiner et al¹⁰ did not find any statistical difference between those with or without CHC infection in TB drug-induced hepatotoxicity. Sadaphal et al¹¹ further reported rate of elevation of transaminases in CHC patients of 22%, which was similar to that of the general population. A recent Spanish study on patients given isoniazid prophylaxis suggests it was chronic hepatitis, either from alcohol consumption or other viral infection, rather than HCV infection per se that increased the risk of hepatotoxicity.¹²

As TB can seriously affect the outcome of liver transplantation, preventive measures such as screening and contact avoidance should be considered as part of the post-transplant care. Screening of latent TB is generally performed by tuberculin testing or screening chest X-ray. However, tuberculin testing for latent TB infection is not applicable in our local population as it lacks the sensitivity to distinguish between BCG-vaccinated and TB-infected populations.¹³ As chest X-ray is routine in patients evaluated for liver transplant, this can effectively diagnose any radiological evidence of past pulmonary TB. Sputum examination should be done if the chest X-ray is suspicious.¹⁴ During the post-liver transplantation period, TB screening can be included in the follow-up visit for high-risk individuals. New diagnostic tests including enzyme-linked immunosorbent assay, the Gen-Probe Amplified Mycobacterium tuberculosis Direct Test, DNA hybridisation, the Mycobacteria Growth Indicator Tubes System and the strand displacement amplification system are currently under evaluation, but their applicability in post-transplant

patients or other immunosuppressed patients remained to be studied.¹⁵ Avoidance of exposure to TB-infected persons should be strictly observed by the patient and family members.¹⁶

In conclusion, pulmonary TB is a rare post-transplant infection with high rates of mortality and morbidity. Its seriousness warrants a high level of suspicion. Early diagnosis and treatment are crucial for this rapidly progressive disease. Awareness of drug-induced hepatotoxicity and drug-drug interaction in anti-TB treatment ensures better prognosis.

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