TRANSPLANT INTERNATIONAL

LETTER TO THE EDITORS

Tacrolimus induced hepatotoxicity in a patient with bilateral lung transplant

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Dear Sirs,

Tacrolimus-induced hepatotoxicity has been reported in solid organ recipients [1–4]. We report a case of idiosyncratic tacrolimus-induced hepatotoxicity in a lung transplant recipient with no response to dose reduction.

A 43-year-old man with a history of cystic fibrosis presented with chronic respiratory failure. The patient also had a history of long standing hepatitis C (RNA load of 51 000 IU/ml), pancreatic insufficiency, and chronic sinusitis. He had normal liver function and minimal fibrosis on a pretransplant liver biopsy. The immediate postoperative course was complicated by pericardial tamponade on postoperative day (POD) 2 that required an emergency pericardial window. He developed transient liver and renal failure from the hypotension requiring dialysis for short period of time. Renal and liver function normalized by POD-26 with total bilirubin of 0.1 mg/dl [normal value <1.3], aspartate aminotransferase (AST) of 38 IU/l [normal value <35], alanine aminotransferase (ALT) of 40 IU/l [normal value <42], and alkaline phosphatase of 803 IU/L [normal value <360].

Post-transplant screens were negative for hepatitis B virus, cytomegalovirus (CMV), Epstein–Barr virus (EBV), herpes simplex virus, or aspergillus infection. The patient received tacrolimus, mycophenolate mofetil, and methyl prednisone on POD 1. He made steady progress, and was doing well until POD 119 (17 weeks) when he developed abnormal liver function tests, with total bilirubin of 1.6, AST of 68, alkaline phosphatase of 1187, and a normal coagulation profile. Tri-phasic computer tomography (CT) scan of the liver demonstrated patent liver vessels and no evidence of cirrhosis. Magnetic resonance images and Doppler ultrasonography showed normal blood flow in the hepatic artery, portal veins, and hepatic veins. No evidence of intra- and extra-hepatic biliary dilation or inflammatory change was noted. The patient showed no signs of sepsis or portal hypertension. Real-time PCR tests indicated that he did not have an acute infection of EBV and CMV.

A right heart catheterization on POD 126 (18 weeks) and transjugular hepatic biopsy showed normal right atrial pressure of 6 mmHg (normal = 4–6 mmHg), and slightly elevated hepatic venous pressure gradient of 9 mmHg (normal = 1–5mmHg), respectively. The HCV-RNA viral load increased to greater than 69 million IU/ml. A liver biopsy on POD 126 showed ground glass hepatocytes with the presence of prominent pale eosinophilic round-to-oval intracytoplasmic bodies that occupied most of the cell and displaced the nuclei toward the periphery. Some of these cytoplasmic bodies had a kidney-shaped appearance that encroached the nucleus of the hepatocytes and others had a crescent shaped halo that separated them from the cell membrane. The glassy hepatocytes were mostly in clusters, located predominately in the periportal areas, and involved approximately 30% of the tissues. The inclusions were strongly positive for periodic acid-Schiff (PAS) stain, but negative after diastase digestion. They were negative for hepatitis B core and surface antigens by immunohistochemistry. There was minimal nonspecific portal chronic inflammation with no significant fibrosis. Reticulin stain showed normal pattern. These findings were suggestive of tacrolimus-induced liver toxicity.

On POD 135 (19 weeks) total bilirubin was 3.4, AST was 77, alkaline phosphatase was 1140, and gamma GTP was 8400 IU/L [normal value <40]. Tacrolimus dose was reduced without much improvement in liver enzymes, therefore was discontinued. Cyclosporine was given for less than 1 week, but it was stopped due to rising liver enzymes during that period. The patient was started on sirolimus and mycophenolate mofetil on POD 148. Liver enzymes improved 3 weeks after starting sirolimus (Fig. 1). The rest of his stay was uncomplicated and he was discharged home on POD 167 (24 weeks).

The patient last was seen in the clinic 8 months after transplant with near normal LFT. Unfortunately, the patient had community-acquired pneumonia 10 months after lung transplantation and expired.

Common side effects of tacrolimus, include nephrotoxicity, neurotoxicity, hepatotoxicity, and new onset diabetes [1–4]. These side effects are usually dose-dependent. Tacrolimus has been shown to induce cholestasis by inhibiting biliary excretion of glutathione [2]. The reported incidence of tacrolimus-induced cholestatic syndrome was 5.4% in pediatric liver transplant patients [1]. However, tacrolimus-induced hepatotoxicity has rarely been described in lung transplant recipients. Our patient developed tacrolimus-induced cholestasis that was not dose-dependent, as

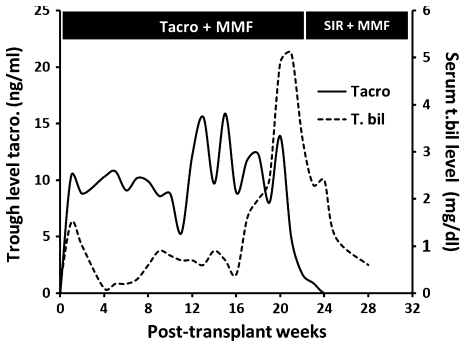

Figure 1 Course of tacrolimus level and total bilirubin after bilateral lung transplant. (tacro. – tacrolimus, MMF – mycophenolate mofetil, SIR – sirolimus, t. bil – total bilirubin).

reduction of tacrolimus did not improve liver function. This is the second reported case in which there is tacrolimus-induced hepto-toxicity in a lung recipient followed by normalization of liver function values after cessation of tacrolimus. The course of abnormal liver enzymes in our patient is similar to that of the case reported previously by Oto and associates [4]. In both cases, liver function promptly normalized after cessation of tacrolimus.

Very little data exist regarding HCV infection and lung transplantation. The HCV seropositive rate among potential lung transplant candidates is 1.9%. It has been reported that the presence of HCV infection does enhance the risk of hepatotoxicity by immunosuppressants [5]. It has been shown that HCV replication is increased in liver, kidney, and lung transplant recipients who are carriers of HCV before transplant [6]. In our patient, the HCV viral load increased significantly after transplant, but did not have inflammatory changes consistent with reactivated HCV infection in liver biopsy. We concluded that our patient's hepatic dysfunction was due to tacrolimus toxicity because of the following: (i) extensive hepatic work-up that exclude all other etiologies including hepatic veno-occlusive disease, (ii) the ground glass hepatocytes found on transjugular liver biopsy [9], and c) the rapid reversal of LFT after tacrolimus was stopped. Ground-glass hepatocytes have been described earlier with other causes, such as chronic hepatitis B infection, Lafora's disease, type 4 glycogenosis, cynamide alcohol aversion therapy, and fibrinogen storage disease. There has been report of patients with glycogen inclusions in hepatocytes in patients on multiple immunosuppressive medications, which included tacrolimus [7–10].

In conclusion, idiosyncratic tacrolimus-induced hepatotoxicity may be a cause of significant liver impairment in transplant patients. This toxicity is promptly reversible with cessation of tacrolimus. The ground-glass appearance of hepatocytes on liver biopsy can be an early diagnostic marker of drug-induced hepatotoxicity, including tacrolimus toxicity.

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