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CASE REPORT

Sirolimus-associated hepatotoxicity in the kidney graft recipient

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Summary

The aim of our paper was to describe hepatotoxicity of sirolimus (SRL) in a kidney graft recipient. We report the case of a 30-year-old male after kidney transplantation, treated with steroids, cyclosporin A and SRL, with steroid-resistant acute rejection in anamnesis. At 16th month after transplantation, elevation of serum aminotransfereases was observed. After exclusion of common reasons of this condition, liver biopsy was performed. Nonspecific changes were observed, with probability of drug-induced injury. SRL was changed to mycophenolate mofetil, which was followed by quick normalization of serum aminotransferase levels. Hepatoxicity is a rare complication of SRL therapy and may be connected with some diagnostic and/or therapeutic problems. Conversion to another immunosuppressant seems to be an appropriate procedure in this condition.

We report a case of 30-year-old White male with sirolimus (SRL)-associated hepatotoxicity. Because of end-stage renal failure due to chronic glomerulonephritis, renal transplantation was performed at 29 years of age. Initial immunosuppression included steroids, cyclosporin A (CsA) and SRL. Because of severe steroid-resistant acute rejection, triple immunosuppressive regimen was continued over third month post-transplant. Later, simvastatin (10 mg daily) was applied as the result of moderate mixed hyperlipemia and cilazapril (0.5 mg daily) due to slight proteinuria and polyglobulia. At 16th month post-transplant, serum aminotransferases increased. The patient was asymptomatic, with no significant abnormalities on physical examination and abdominal ultrasonography. Trough levels were CsA 165 ng/dl and SRL 6.3 ng/dl. Alcohol consumption, viral hepatitis and cytomegalovirus infection were excluded. Because of suspected Epstein–Barr virus infection, the patient received acyclovir. Subsequently, as the result of suspected atypical pathogen infection, doxycyclin was applied. As a result serum aminotransferases gradually increased (maximal levels: AspAT: 368 IU/l, AlAT: 579 IU/l). Nonspecific changes were observed most probably because of drug-induced injury when liver biopsy was performed. Steatosis was definitively excluded (Fig. 1). At 24-month post-transplant, SRL was changed to mycophenolate mofetil which was followed by quick normalization of serum aminotransferases.

Hepatotoxicity of SRL is underestimated, but it is not an unknown phenomenon. In clinical trials, in renal transplant recipients, elevated aminotransferases were more frequent in SRL versus CsA groups [1,2] and SRL versus SRL + CsA group [3]. SRL-associated hepatotoxicity was also reported in liver transplant recipients [4]. It is generally acknowledged that patients may benefit from synergistic actions of calcineurin inhibitor and SRL, combining effective prevention of rejection with the potential of reducing side-effects of both drugs [5,6]. There were no cases of severe SRL hepatotoxicity requiring discontinuation of SRL reported in kidney transplant recipients treated with SRL, CsA and steroids.

It is unlikely that, in our case, liver enzymes elevation was caused by other drugs. Although cilazapril and simvastatin had been withdrawn, aminotransferases did not decrease. Moreover, treatment with these drugs was star-

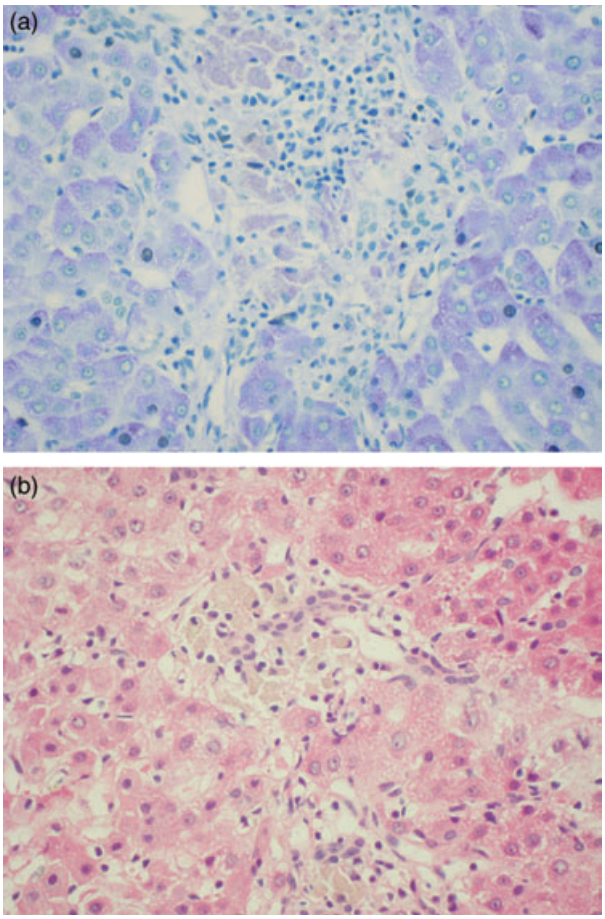

Figure 1 Histopathological findings in the liver biopsy specimen of kidney graft recipient in whom hepatotoxicity of SRL occurred. (a) Mild widening of portal area, lymphocytic infiltration. Few clumps of macrophages filled with weakly PAS (+) material. Mild interface activity. (PAS, magnification 200×). (b) Pericentral region. Small collection of macrophages filed with yellow–brown material (HE, magnification 200×). The inflammation is mostly portal, with weak interface activity and mild, focal lobular component.

ted again after normalization of liver enzymes which was not accompanied by liver damage. Acyclovir might also lead to the elevation of aminotransferases, but they were increased prior to its administration and persisted after its withdrawal. One might suggest that it was hyperlipemia which led to liver damage, but it is unlikely that moderate hyperlipemia could cause such severe effect. After SRL withdrawal, serum lipid levels improved, but few months later hypercholesterolemia appeared again and liver enzymes remained stable. The ultimate proof of SRL hepatotoxicity was biochemical normalization after SRL withdrawal.

Exact mechanisms leading to hepatotoxicity of SRL are unknown. The reason may be the influence of the drug on liver enzymes. In some cases, combination of SRL and CsA exacerbates these effects. It can be connected with accumulation of toxic metabolites in hepatocytes [7–9]. If even liver damage was a consequence of combined administration of CsA and SRL, SRL withdrawal solved the problem, and CsA continuation was harmless to the liver.

In conclusion, replacement of SRL with another immunosuppressant seems to be appropriate in SRL-associated hepatotoxicity.

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Conflict of interest

No conflict of interest.

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