

Fatty liver due to high levels of serum tacrolimus after liver transplantation

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SUMMARY: Tümgör G, Arıkan Ç, Nart D, Kılıç M, Aydoğdu S. Fatty liver due to high levels of serum tacrolimus after liver transplantation. Turk J Pediatr 2007; 49: 223-225.

Tacrolimus has been used extensively for immunosuppressive therapy in pediatric liver transplant recipients. However, patients who are exposed to high levels of serum tacrolimus tend to be associated with a higher incidence of significant nephrotoxicity, neurotoxicity, pruritus, alopecia, diabetes and infection.

We herein report a child who developed increased serum transaminase levels and liver steatosis as a result of raised trough blood level of tacrolimus (30 ng/ml for 3 days) in association with rotavirus gastroenteritis.

Key words: tacrolimus, liver transplantation, fatty liver.

Tacrolimus (TAC) has been used extensively for immunosuppressive therapy in pediatric liver transplant recipients - it inhibits calcium-dependent signal transduction pathways in T cells and has been shown to reduce the incidence of acute rejection¹. Major side effects of TAC include increased incidence of lymphoproliferative disease, nephrotoxicity, neurotoxicity, pruritus, alopecia, diabetes and infection². No study has been conducted on the possible relationship between high levels of TAC in children and adults and the incidence of fatty liver.

In this paper, we describe a case of a liver transplant child who suffered increased morbidity caused by a raised trough blood level of TAC in association with acute rotavirus gastroenteritis (RV-AGE). Micro-macrovesicular steatosis (15-20%) with liver biopsy was demonstrated one month after gastroenteritis.

Case Report

The child, suffering from progressive familial intrahepatic cholestasis, received a left lateral liver segmental allograft from his mother at the age of 2½ years. Post-operative period was uneventful. Nine months after the transplantation the child acquired a rotavirus infection at home and she was rehospitalized.

TAC trough level increased to 30 ng/L on the following day. Despite the discontinuation of the drug, the TAC levels remained over 30 ng/L for three days. Fifteen days after the occurrence of RV-AGE, normal TAC levels were achieved with a dose of 0.03 mg/kg/day. It was observed that transaminase levels were 3 times greater 15 days after RV-AGE and 10 times greater after one month (Table I). Patient was evaluated for cause of elevated serum transaminase level including viral diseases (hepatitis A, B, C, Epstein-Barr virus, cytomegalovirus-CMV, Parvovirus B19, rubella virus, rubeola virus, varicella-zoster virus) and other liver toxic drugs. No specific agent was found. Liver Doppler ultrasonography (USG) was normal. Body mass index was 17. The blood biochemistry was normal except serum transaminase levels. Liver biopsy was taken because of the increased serum transaminase levels four weeks after diarrhea. There was no sign of a virus infection in biopsy specimen or of any rejection. The evaluation of a liver specimen showed balloon degeneration of the hepatocytes, micro and macrovesicular steatosis (15-20%) and Kupffer cell hyperplasia in biopsy specimen (Fig. 1a, 1b). The previous liver biopsy, which had been made three months before due to slightly higher transaminase level, was normal.

Table I. Blood Biochemistry

	Before RV-AGE	15 days after RV-AGE	One month after RV-AGE (liver biopsy: fatty liver)
Aspartate aminotransferase (AST) (U/L)	85	229	888
Alanine aminotransferase (ALT) (U/L)	136	309	950
Alkaline phosphatase (U/L)	1168	1285	1763
Gamma-glutamyl transpeptidase (U/L)	232	308	394
Total bilirubin (mg/dl)	0.5	0.4	0.5
Albumin (g/dl)	4.3	3.8	3.9
Uric acid (mg/dl)	5.5	5.1	5.7
Urea nitrogen (mg/dl)	54	46	48
Creatinine (mg/dl)	0.5	0.6	0.5

RV-AGE: Acute rotavirus gastroenteritis.

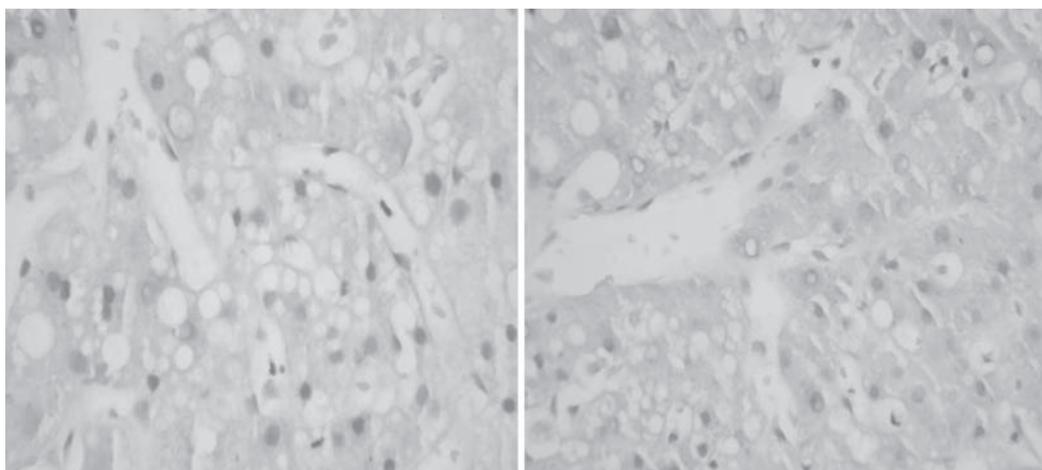


Fig. 1a, 1b. Macro- and microvesicular steatosis and Kupffer cell hyperplasia seen in hematoxylin-eosin sections. Nuclear polymorphism is also seen.

Discussion

Tacrolimus is a product of the fungus *Streptomyces tsukubaensis*, and although it is a macrolide-like cyclosporine, it differs in its chemical structure and cytosolic binding site². While it is well known that diarrhea may result in decreased trough levels of cyclosporin A, experience with levels of TAC and diarrhea is limited³. Possible explanations for the rise in blood levels of TAC during acute diarrheal illness include hemoconcentration, fasting, increased absorption as a result of increased intestinal permeability, or reduced hepatic metabolism caused by reduced hepatic blood flow or hepatic dysfunction^{4,5}. Despite the extensive use of TAC for almost a decade, until recently little was known about the important role that the intestine plays in its metabolism⁶.

Hypercholesterolemia, diabetes mellitus, hypertension, and obesity, which are risk factors for fatty infiltration of the liver after transplantation, were not determined in this patient. Both corticosteroids and calcineurin inhibitors may promote hypertension and hypercholesterolemia. Prednisone is a known risk factor for fatty liver⁷. Our patient was using low dose prednisolone (5 mg/day); however, the biopsies of the liver three months before RV-AGE and after one month of prednisolone treatment were the same.

In some studies it has been determined that rotavirus infection could affect the liver^{8,9}. In particular, a relation has been shown between rotavirus infection and Reye syndrome¹⁰. There were no findings associated with Reye syndrome or rotavirus infection in the liver biopsy of our patient.

We think the fatty liver and elevated liver enzymes are of a secondary importance to TAC toxicity because serum TAC levels were above 30 ng/dl following a rotavirus-associated diarrhea three weeks previously. TAC is primarily metabolized by the cytochrome system. Fatty liver can be a feature of drug toxicity because the drugs undergo phase I metabolism through the cytochrome P-450 enzyme system. In cases of drug toxicity, mitochondrial function is presumably affected, resulting in microvesicular steatosis¹¹. In addition, no viral etiology was found for elevated liver enzymes and liver Doppler USG was normal. Liver biopsy performed one month after last biopsy revealed improvement (1-2%) in fatty liver and this supports our suggestion.

In conclusion, increased levels of TAC can be observed in children after RV-AGE. High levels of serum TAC can cause fatty liver. Close TAC monitorization should be done in patients with RV-AGE.

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