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Hemolytic-uremic syndrome in association with both cyclosporine and tacrolimus

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**Abstract**  Hemolytic-uremic syndrome (HUS) is a well-recognized complication of cyclosporine (CyA) therapy. Transplant recipients with this complication are frequently switched to tacrolimus, although this drug has also been implicated. We report a case of a renal transplant recipient who developed severe graft dysfunction due to biopsy-proven HUS after receiving CyA. Renal function and hemolytic parameters improved with discontinuation of the drug, but they deteriorated again after commencement of tacrolimus 15 days later. A second transplant biopsy demonstrated fresh lesions diagnostic of HUS. Hemolytic parameters resolved with discontinuation of tacrolimus. This is the first report of metachronous HUS being caused in a renal transplant by both CyA and tacrolimus. We therefore believe that caution should be exercised when using tacrolimus as rescue therapy in patients with CyA-induced HUS.

**Keywords**  Renal transplant  
Hemolytic-uremic syndrome  
Cyclosporine  
Tacrolimus

**Abbreviations**  CyA Cyclosporine  
HUS Hemolytic-uremic syndrome  
LDH Lactate dehydrogenase  
PGI2 Prostacycline  
TMA Thrombotic microangiopathy

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**Introduction**  In the management of renal transplant recipients, cyclosporine (CyA) has significantly reduced the incidence and severity of acute rejection. Unfortunately, the drug is associated with a variety of side effects, including acute nephrotoxicity, chronic renal damage, and hypertension. Rarely, CyA can cause an acute hemolytic-uremic syndrome (HUS) characterized by microangiopathic hemolysis and graft dysfunction [16]. Sommer et al. reported on 15 cases of CyA-induced HUS in renal transplant recipients [14]. They found an overall incidence of 4.5 %, with irreversible graft failure occurring in all but one patient. Singh et al., in a review of 91 solid organ recipients developing HUS, reported an associated mortality of 13 % [13]. In addition, the incidence of subclinical hemolysis after CyA use, as detected using serial measurements of haptoglobin level, may be as high as 25 % [10]. As well as reducing or discontinuing CyA, various strategies have been proposed to improve the poor prognosis associated with CyA-induced HUS. One such intervention is the replacement of CyA with tacrolimus [6] on the basis of in vitro studies which have suggested that tacrolimus causes less endothelial damage at equivalent immunosuppressant doses [3].

We report here the first case of HUS in a renal transplant recipient initially treated with CyA in whom biopsy-proven HUS recurred after rescue therapy with tacrolimus. The implication of this finding is discussed.

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**Case report**  A 58-year old female with end-stage renal failure due to adult polycystic kidney disease received a cadaveric renal transplant...
(1–1–1 HLA mismatch) after 6 months of regular hemodialysis. The intraoperative course was uneventful. Immunosuppression induction was with 5 mg/kg per day azathioprine i.v., 8 mg/kg per day methylprednisolone i.v., and an overlap of 10 mg/kg per day microemulsion CyA (Neoral) with 1.5 mg/kg per day of intravenous CyA. She was then maintained on 1.5 mg/kg per day oral azathioprine, adjusted to blood counts, 5 mg/kg CyA b.d., adjusted according to trough blood levels (target 230–300 ng/ml, Instar CYCLO-Trac RIA, Minn.), and 20 mg per day prednisolone. In addition, she received 960 mg sulphamethoxazole daily, 800 mg acyclovir daily, and 150 mg ranitidine b.d. The graft functioned promptly, and serum creatinine fell to 384 μmol/l by day 7. However, during this time there was a reduction in platelet count from 136 × 10^9/l to a nadir of 87 × 10^9/l, and the hemoglobin level had fallen from 13.0 g/dl to 9.6 g/dl by day 5 after transplantation. Blood films performed on days 3 and 7 after transplantation revealed no abnormalities. The 12-hour trough level of CyA varied from 654 to 320 ng/ml.

On day 8 after transplantation, graft function began to deteriorate. Serum creatinine rose from 384 μmol/l to 542 μmol/l by day 10. Concurrently, she developed laboratory evidence of intravascular hemolysis. The total bilirubin level rose (from 9 μmol/l to 25 μmol/l), serum haptoglobin level fell from 5.3 g/dl to undetectable levels, and the serum lactate dehydrogenase (LDH) level rose to 2136 IU/l. In addition, examination of a blood film revealed schistocytes on day 9. During this time the patient remained afebrile, and blood pressure ranged from 130/80 mmHg to 150/95 mmHg. Cultures of blood and urine were sterile, a Coomb's test was negative, and liver enzymes remained within normal limits. Viral studies were negative. A transplant biopsy was performed on day 10 and revealed that more than 50% of the glomeruli contained fibrin thrombi within the arterioles (Fig. 1) and prominent tubular necrosis was present. There were no signs of rejection, and in the absence of clinical or laboratory evidence of infection or severe hypertension, a diagnosis of CyA-induced HUS was made. CyA was stopped on day 10 and replaced a day later with 8 mg tacrolimus b.d. Drug dosage was adjusted to maintain levels between 10–15 ng/l. At the same time plasmapheresis was begun with fresh frozen plasma and saline. The patient received four exchanges over the next 7 days.

With these measures, the indices of hemolysis improved. After these sessions of plasmapheresis, the haptoglobin and bilirubin levels had normalized to 2.4 g/dl and 12 μmol/l, respectively, and the platelet count rose to 121 × 10^9/l. Serum LDH levels fell to 983 IU/l and serum creatinine fell to 480 μmol/l (Fig. 2). After an initial level of 23.1 μg/l, tacrolimus levels varied between 9.2 μg/l and 14.3 μg/l (Abbott IMx Tacrolimus II assay). On day 17 after transplantation (day 6 of tacrolimus), hemolytic parameters improved once more, with a fall in platelet count (to 82 × 10^9/l), a rise in LDH level (to 2367 IU/l), a decline in haptoglobins (to 0.38 g/dl), recurrence of schistocytes, and mild hypertension. Repeat cultures of blood, urine, and stool were negative. Serum creatinine rose progressively to 618 μmol/l by day 25, at which point a repeat transplant biopsy was performed. On histological examination, a fresh area of infarction involving 7 of 18 glomeruli and 40% of the cortical tubules was noted. There were fresh fibrin thrombi within the arterioles (Fig. 3a), some appearing as recent as 1–2 days old. In addition, lesions associated with an organizing thrombotic microangiopathy (TMA) were present. These included occlusive mucoid fibro-intimal proliferation (Fig. 3b), capillary loop double contour formation, and segmental mesangiolysis. These latter lesions were not evident in the first biopsy. There was no evidence of acute rejection.

The presence of discrete new lesions in connection with the clinical features described above indicated recurrence of HUS. As the patient had been on tacrolimus for 15 days with CyA levels repeatedly undetectable prior to the second biopsy and since no other possible etiological factor was identified, a diagnosis of tacrolimus-induced HUS was made. On day 30 after transplantation, tacrolimus was stopped (19 days after it was commenced) and azathioprine was replaced with mycophenolate mofetil. Three days after discontinuing tacrolimus, the serum haptoglobin level had recovered to a normal value of 2.38 g/dl. This was accompanied by the disappearance of schistocytes on blood film analysis and a rise in Hb from 6.0 g/dl to 8.7 g/dl. Repeated Doppler ultrasound studies and isotope renograms of the transplant kidney showed no evidence of thrombosis of the renal artery or vein. At the time of discharge from our care some 11 weeks after her transplantation, the serum creatinine was 305 μmol/l.

**Discussion**

In this case, microangiopathic hemolytic anemia occurred in association with histological evidence of TMA occurring after the use of CyA. These features confirm a diagnosis of HUS. This pathological process can be caused by conditions such as malignant hypertension, acute humoral rejection, scleroderma, and a number of different drugs and infections, such as cytomegalovirus [17]. However, in our patient the only possible etiological factor identified was CyA. Clinical and biochemical parameters improved after cessation of CyA treatment and the initiation of a short course of plasmapheresis. However, after 6 days of treatment with tacrolimus there was a clear re-emergence of intravascular hemolysis with further deterioration in graft function. A second transplant biopsy, performed 15 days after discontinuation of CyA, revealed fresh TMA lesions which were considered to be only a few days old. It is thus highly improbable that CyA was the cause of these lesions. Furthermore, hemolysis resolved soon after the discontinuation of tacrolimus. Consequently, we have concluded that the recurrence of HUS was caused by...