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BRIEF REPORT

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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 · PGI_2 Prostacyline · *TMA* Thrombotic microangiopathy

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.

Case report

A 58-year old female with end-stage renal failure due to adult polycystic kidney disease received a cadaveric renal transplant

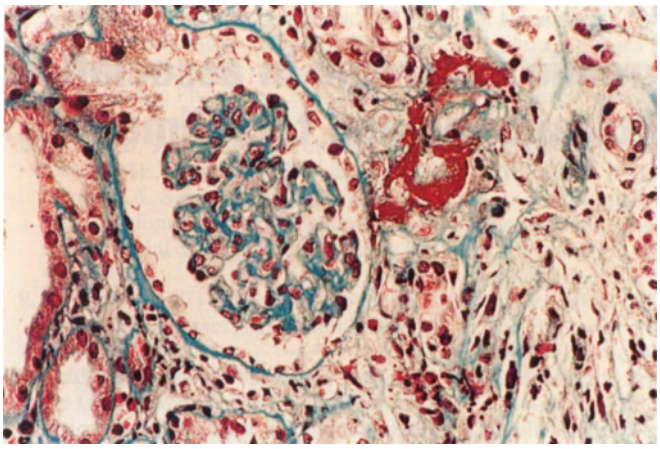

Fig. 1 Biopsy at day 9 post-transplantation; acute thrombotic lesion in an arteriole (Masson Trichrome × 90)

(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, Incstar 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 three 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 disimproved 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. 3 a), 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. 3 b), 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 transplantion, 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

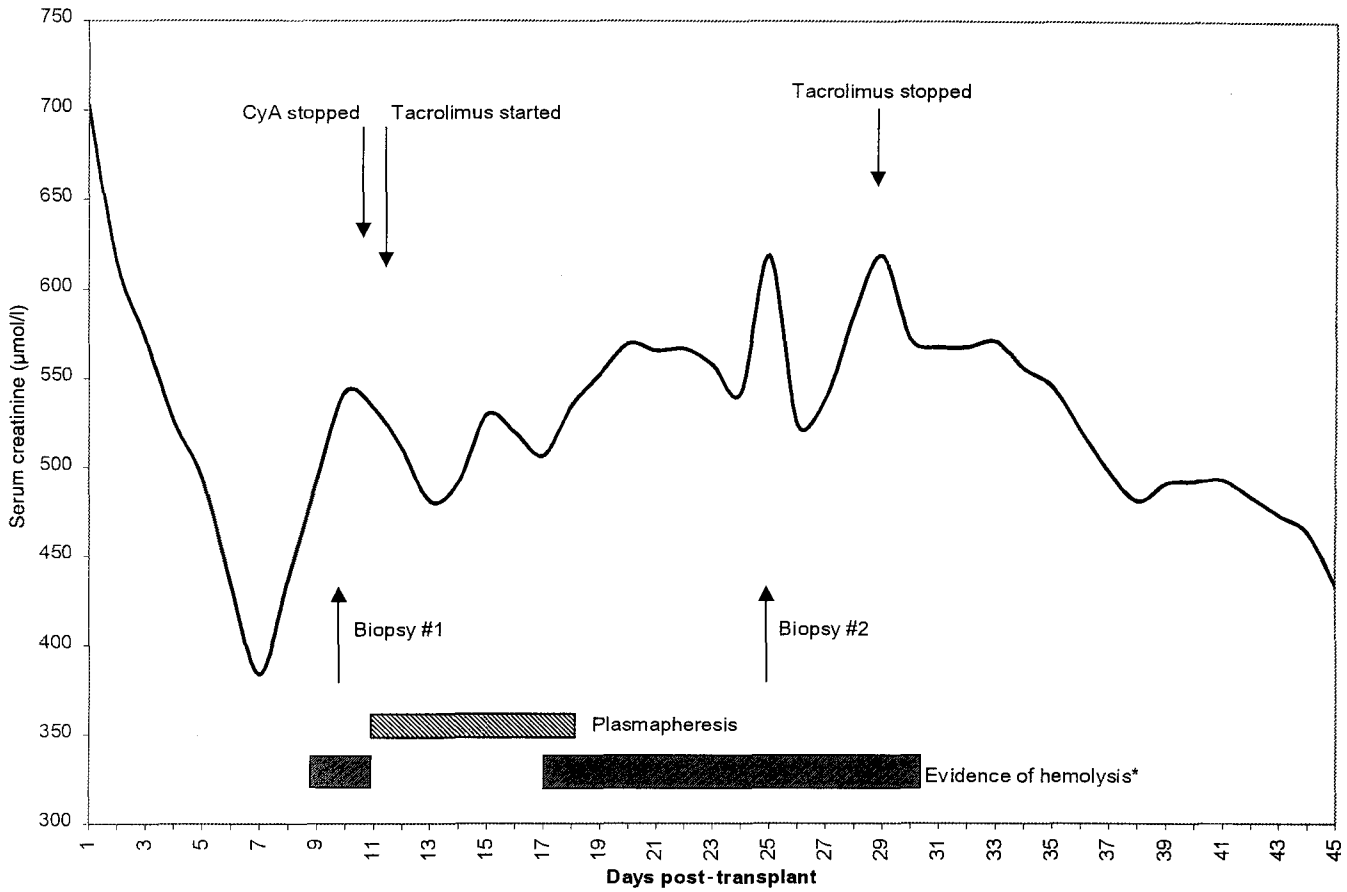

Fig. 2 Changes in graft function and hemolytic parameters with time. * Schistocytes on blood film, lactate dehydrogenase > 1300 IU/l + /- undetectable haptoglobins

the latter drug; this is the first time that metachronous HUS induced by both CyA and tacrolimus in the same renal allograft has been reported.

Research into the pathogenesis of HUS has focused on the role of endothelial injury as an initiating factor, regardless of the underlying etiology. CyA-induced endothelial damage predates thrombosis and is probably the initiating insult of CyA-induced HUS [19]. CyA causes detachment of endothelial cells from the basement membrane and, in higher doses, endothelial cell lysis [19]. The denuded basement membrane is a focus for platelet adhesion. Vasoconstriction of the afferent and efferent glomerular arterioles [15], sheer stress [7], von Willebrand factor multimers [7], and imbalance between prostacycline (PGI_2) and thromboxane production [2] may also contribute to the pathogenesis.

It is postulated that tacrolimus causes HUS through similar mechanisms [15]. Both CyA and tacrolimus act by inhibition of interleukin-2 production in activated T lymphocytes by inhibition of calcineurin phosphatase. However, some authors have shown that, in comparable immunosuppressive doses, tacrolimus causes less suppression of PGI_2synthesis than CyA [3]. It has therefore been argued that tacrolimus can attain comparable levels of immunosuppression with lower endothelial toxicity. This hypothesis has some clinical support, with one series finding an incidence of 1% for tacrolimus-induced HUS [11], compared to 3–5% for CyA-induced disease [13]. It is important to emphasize, however, that tacrolimus has only been in clinical use for a relatively short period of time and that comparisons with CyA in this respect may not be valid.

There is a reported case of CyA and tacrolimus causing microangiopathic hemolytic anemia in the same patient (a bone marrow transplant recipient), although the authors were unable to demonstrate histological evidence of fibrin thrombi in the small vasculature [9]. In addition, in a recent case report Franz et al. described a patient who developed de novo tacrolimus-induced HUS with resultant graft loss, subsequently developing CyA-induced HUS in the second graft [4].

The clinical evidence for replacing CyA with tacrolimus for CyA-induced HUS is limited. A case report by McCauley et al. in 1989 reporting the successful replacement of CyA with tacrolimus after the former had

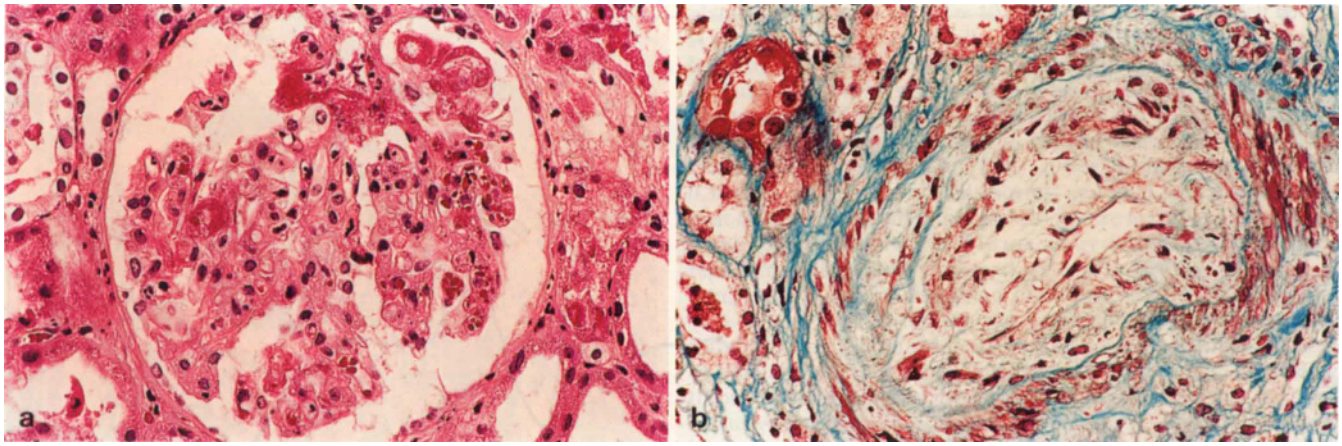

Fig. 3 a, b Biopsy at day 25 post-transplantation (**a**) Acute thrombotic microangiopathy affecting the glomerulus (H&E × 180) (**b**) Organizing thrombotic lesion in a small artery (Masson Trichrome × 180)

caused HUS [6] was followed by similar case reports by Abdalla et al. [1] (the case was a living related kidney recipient), Kaufman et al. [5] and Richardson et al. [12]. These initial favorable reports prompted more widespread use of this approach. In the paper by Franz et al., 2 of 3 patients developing CyA-induced HUS benefited from conversion to tacrolimus. In a clinical trial of aspirin, pentoxyfilline, and isradipine in the treatment of post-transplant HUS [18], all 3 of the patients that were switched to tacrolimus because of the recurrence of HUS after reintroduction of CyA remained off dialysis, albeit with impaired graft function. After switching 5 patients with CyA-induced HUS to tacrolimus, Morris-Stiff et al. reported that 4 experienced a rapid resolution of the hemolytic process while the fifth improved after several weeks [8]. However, to date only a small number of patients have been reported as actually benefiting from conversion to tacrolimus in the setting of CyA-induced HUS. On the other hand, in those patients losing the graft after such a strategy, the reason for their eventual graft loss has not been elucidated. Our case raises the question as to whether deterioration of graft function after institution of tacrolimus may well be due to further aggravation of the hemolytic process by this drug.

Consequently, we believe that the recurrence of biopsy-proven HUS in our patient should instill a strong element of caution when considering replacing CyA with tacrolimus when the former has caused HUS. In any patient who fails to improve after following this course of action, a detailed search for recurrence of TMA is warranted.

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