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CASE REPORT

Cyclosporin-Associated Thrombotic Microangiopathy: Successful Retreatment with Cyclosporin

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ABSTRACT

This report describes a patient who developed cyclosporin-induced thrombotic microangiopathy in a renal allograft. Cyclosporin-induced thrombotic microangiopathy is considered by many as a contraindication to subsequent therapy with cyclosporin. This case is notable for successful treatment with cyclosporin following resolution of thrombotic microangiopathy in a renal allograft.

INTRODUCTION

Thrombotic microangiopathy (TM) is a severe form of cyclosporin (CsA) nephrotoxicity, frequently resulting in graft loss. The frequently catastrophic nature of this process has led, in some centers, to the policy of not rechallenging patients with CsA once this side effect has been documented. This position has led to many patients being denied an important immunosuppressive medication. This case and our review of the literature (1, 2) supports a possible dose-related effect and suggests that patients with CsA-induced TM can in some cases be successfully retreated with CsA.

CASE REPORT

Patient is a 35-year-old, obese, black female who at the age of 33 was noted to have renal insufficiency and proteinuria during her first pregnancy. The cause of her renal failure was not determined. Specifically, no renal biopsy was performed and there was no documented evidence of microangiopathic hemolytic anemia or red cell casts by urinalysis. Following a therapeutic abortion, the patient's edema improved; however, her renal insufficiency and proteinuria continued to worsen. A 24-h urine taken 6 months following her therapeutic abortion revealed 4.7 of protein. Within 2 years, her renal function

had deteriorated to the point of requiring hemodialysis. Over the subsequent 3 months the patient was evaluated for and underwent a 2AB/1DR match renal transplant from a living-related donor. The patient's only pretransplant CsA was 1 g p.o. (10 mg/kg) the night before surgery. The patient also received donor-specific transfusions. Following transplantation, the patient was started on steroids, azathioprine, and CsA 520 mg given i.v. over the first 48 h postoperation, then 1 g p.o. QAM. During the first four postoperative days, the patient's creatinine fell from 12.3 mg/dL to 5.4 mg/dL (Fig. 1). However, on day 5 the trend reversed, with the creatinine rising to as high as 6.3 mg/dL. Concurrent with this, the patient was noted to have a drop in her hematocrit and platelets with schistocytes noted on peripheral smear. The patient had no clinical evidence of infection and her blood pressure did not exceed 140/90. Twenty-four-hour trough levels of CsA were repeatedly greater than 400 ng/mL despite a reduction in dose. On the sixth postop day the patient underwent renal biopsy which revealed TM with focal cortical necrosis (Fig. 2). There was focal fibrinoid necrosis, without influx of leukocytes, in glomeruli, arterioles, and small arteries, sometimes associated with lumenal thrombosis. There was no evidence for rejection, including no tubulitis and no vascular mural influx of leukocytes. The patient's CsA was stopped, and her creatinine consistently fell from 5.7 mg/dL to 4.2 mg/dL over the next 3 days. However, over the subsequent 3 days the creatinine increased to 4.9 mg/dL. Another renal biopsy was performed which revealed moderately severe acute cellular tubulointerstitial rejection (Fig. 3).

Seven days of treatment with OKT3 resulted in a fall in creatinine to 3.7 mg/dL. The patient was subsequently restarted on CsA at a lower dose. The patient's creatinine continued to fall, and 4 days later she was discharged with a creatinine of 3.0 mg/dL. Eleven days later, the patient presented with a creatinine of 11.8 mg/dL. Renal biopsy at that time revealed severe acute cellular tubulointerstitial rejection, but no TM. CsA levels were therapeutic. The patient was treated with pulse steroids and remained on previous dosages of CsA and azathioprine. The patient's creatinine fell to 6.8 mg/dL within 5 days, and she was discharged. The patient has been followed as an outpatient with CsA trough levels between 143 ng/dL and 252 ng/dL on 470 mg of CsA per day, and creatinine levels in the 3.3 mg/dL to 3.6 mg/dL range.

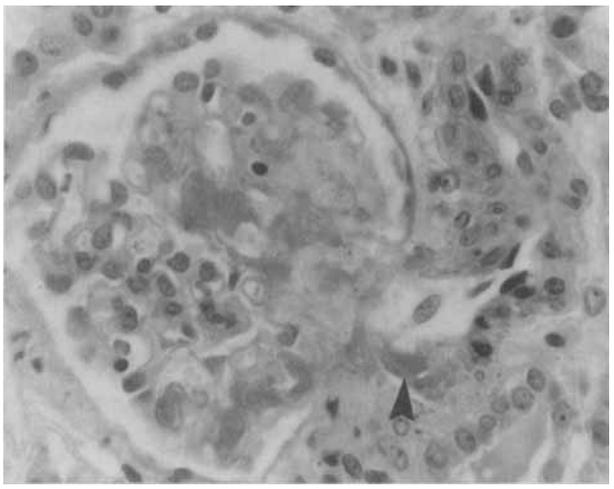

Figure 2. Renal biopsy with TM and focal cortical necrosis. Large arrow: fibrinoid necrosis of arteriole.

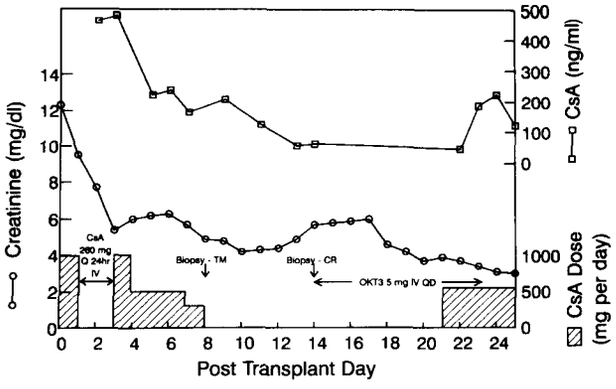

Figure 1. Creatinine levels and CsA dose posttransplant.

DISCUSSION

TM has been reported in renal transplant patients with a prior history of hemolytic-uremic syndrome (HUS) (3); and in renal (4), bone marrow (5), and liver (6) transplant patients treated with CsA. It has also been reported in bone marrow transplant patients with no prior history of TM and no exposure to CsA (7). Moreover, HUS is a syndrome which can be mimicked clinically by a variety of situations in the renal allograft recipient, such as severe acute vascular rejection and malignant hypertension. It has also been suggested that rejection can trigger HUS (8). Clinically, the reported cases of transplant-associated TM uniformly present without gastrointestinal symptoms, and only one reported case had neurologic symptoms.

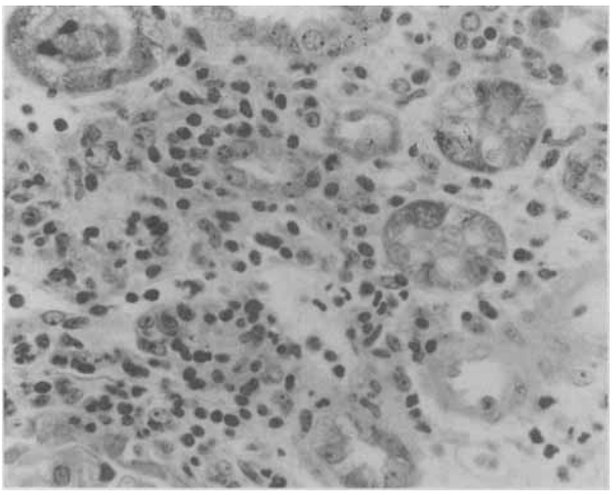

Figure 3. Renal biopsy with acute cellular tubulointerstitial rejection.

In the largest series published to date, 5 of 11 patients whose original disease was TM had definite recurrence of disease in their allograft, and 3 of 11 had a suggestion of recurrence of disease (3). Patients with HUS as their pretransplant disease have been successfully treated with CsA, although the literature would suggest the recurrence rate is high, especially with living-related donors (3). Ours is the first reported case of a patient with biopsy-proven allograft TM while on CsA that, following resolution, was successfully retreated with CsA at a lower dose.

The etiology of TM is unknown. TM is known to occur without an identifiable predisposing factor; and in association with malignancy, infection, pregnancy, severe hypertension, collagen vascular disease; and with exposure to certain drugs, specifically, birth control pills, mitomycin, and CsA. Though the mediators of CsA nephrotoxicity are unknown, the renin–angiotensin system, sympathetic nervous system activation, and intrarenal eicosanoids have been implicated. Treatment with prazosin or renal denervation has been shown to improve depressed renal hemodynamics seen with CsA toxicity (9). CsA is known to have damaging effects on endothelia. Hampel et al. (10) demonstrated induction of endothelial cell DNA damage with CsA and this damage was preferential for glomerular epithelial cells. Recently, Kon et al. (11) demonstrated CsA-induced vasoconstrictive effects on glomerular hemodynamics which were blocked with anti-porcine endothelin serum. CsA has been shown to inhibit production of PGI_2 (12) and PGE_2 (13) and to stimulate $TBXA_2$ (14). This could lead to unopposed vasoconstriction and could stimulate platelet degranulation and adhesion. Elzinga et al. (15) demonstrated that CsA-associated reductions in GFR could be attenuated by substituting the usual olive oil carrier for eicosapentaenoic acid which was shown to concurrently lower renal cortical levels of $TBXA_2$. The prostaglandin E_1 analog misoprostol has been shown to reverse CsA-induced reductions in glomerular hemodynamics (16). However, Cooper et al. (17) demonstrated increases in urinary excretion of both vasoconstrictive and vasodilatory species following 10 days of treatment with CsA in rats with a fall in GFR following only 5 days of treatment when prostanoid levels were unchanged. MacIntyre et al. (18) described a factor normally present in plasma that powerfully stimulated prostacyclin synthesis. Later studies (19, 20) demonstrated increased activity of this factor in renal failure. Of interest, Remuzzi et al. (21) reported a lack of this same factor in patients with HUS, and postulated that a lack of this plasma factor would place patients at risk for microvascular thrombosis. Recently it has been suggested that the presence of platelet-aggregating factor in renal transplant recipient serum can identify patients at risk for TM, with 6 of 7 patients with TM being positive for this factor preoperatively compared to only 4 of 11 positive in subjects without TM (22). No studies to date have evaluated the effects of CsA on von Willebrand factor multimers, abnormalities of which have been associated with drug-related TM (23). Triggering factors of infectious origin that have been asssociated with HUS have not been systematically evaluated in renal transplant populations.

The heterogeneous spectrum of TM has made the development of specific treatment protocols difficult. Though allograft recurrence rates are high for patients with HUS, these patients have been successfully transplanted, with one reported case of treatment with CsA (24). Plasma infusion/exchange has been used successfully in several uncontrolled trials and case reports involving HUS, including recurrent HUS following transplantation. Others (4, 23) have suggested cessation of CsA as therapy for TM. There is *in vitro* evidence (2) that CsA-mediated vascular injury is both dose and time dependent. Our experience would suggest that a reduction in dose or temporary cessation of therapy can in some patients resolve TM, and that further use of CsA should not be precluded.

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