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BRIEF REPORT

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FK 506 as an alternative in cyclosporin-induced hemolytic uremic syndrome in a kidney transplant recipient

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Abstract We describe a patient who received a living related kidney transplant that worked very well initially but developed oliguria and renal failure within 1 week and required dialysis. Clinical and hemological changes, as well as renal biopsy, confirmed the diagnosis of cyclosporin-induced hemolytic uremic syndrome. The patient did not respond to antirejection therapy or plasma exchange but did respond to the withdrawal of cyclosporin A and the commencement of FK 506.

Key words Hemolytic uremic syndrome, CyA, FK 506 · CyA, hemolytic uremic syndrome, FK 506 · FK 506, hemolytic uremic syndrome, CyA

Introduction

Hemolytic uremic syndrome (HUS) is a recognized but uncommon complication of cyclosporin (CyA) therapy in organ transplantation. CyA may induce endothelial cell injury [9, 16], leading to uncontrolled platelet aggregation which, in turn, results in the formation of thrombi in the microcirculation. This leads to tissue necrosis and loss of renal function in more than half of the patients [11].

McCauley et al. salvaged an orthotopic liver transplant with CyA-induced HUS by discontinuing the CyA and using FK 506 as the main immunosuppressive agent [7]. In another paper, the same authors described, a patient who lost his first cadaveric renal transplant due to HUS, but whose second renal transplant was successfully maintained with FK 506 [8].

We believe our patient is the first case of successful substitution of FK 506 for CyA in the same renal allograft in a patient who became dependent upon dialysis due to CyA-induced HUS.

Case report

A 20-year-old girl was diagnosed in August 1991 as having end-stage renal failure (ESRF) due to chronic analgesic intake and was maintained on regular hemodialysis. In November 1992, she received a living related renal allograft from her mother. The patient's HLA typing was A1, A30, B27, B37, CW2, and DR2 and her mother's was A1, B37, A11, B35, CW4, and DR1. There were no HLA-related cytotoxic antibodies in the recipient, and the crossmatches for cold and warm antibodies were negative.

The patient's initial immunosuppression consisted of CyA, 6 mg/kg twice daily, and prednisolone, 30 mg daily. She was given routine I. V. methylprednisolone, 1 g, intraoperatively and again during the first 24 h postoperatively. She also received 0.5 g on the 5th postoperative day.

The 1st postoperative week was uneventful, with serum creatinine decreasing to 133 mmol/l by the 5th day. On the 7th postoperative day the patient became oliguric, with deterioration of renal function and perfusion index (on renography). CyA (measured by RIA Abbot in whole blood) was within the therapeutic range (500–800 ng/l; Fig. 1). The patient was given three boluses of methylprednisolone with no noticeable response. Her renal function continued to deteriorate during the 2nd postoperative week and onwards, with serum urea rising to 40 mmol/l and creatinine to 505 mmol/l. She became anuric and dependent upon dialysis. At the same time, the patient developed signs of microangiopathic hemolytic anemia and platelet consumption. Platelet count dropped to 80,000, prothrombin time and partial thromboplastin time were prolonged, was raised to 1 μg/l (normal range 0.0–0.5 μg/l), and fibrinogen was at the low level 1.3 g/l (normal range 2–6 g/l). Reticulocyte count was high (6.3 %) and schistocytes were observed in the peripheral blood smear. Hemoglobin decreased from 7.8 to 4.9 g/l. Urine culture was negative. CMV, H. simplex, and H. zoster antibody titers showed no increase. The patient did not develop any neurological symptoms.

After the clotting disturbances were corrected, the patient underwent renal biopsy. Histology showed prominent intravascular

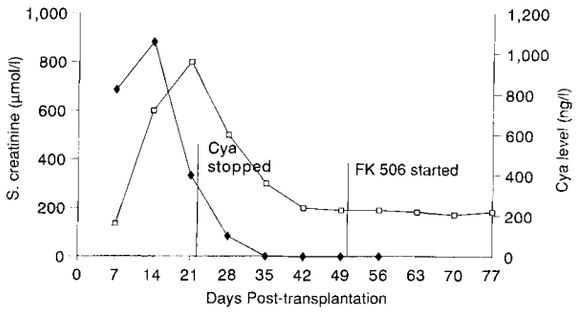

Fig. 1 Reversal of severe CyA-associated hemolytic uremic syndrome (□ creatinine level, ◆ CyA level)

sludging with fibrin clots without any neutrophilic response. A few arterioles also showed pink staining material in their walls with occlusion of the lumen. The interstitium showed focal, but moderately heavy, infiltration of mononuclear cells with some disruption of the tubules. In view of the hematological picture and the historical findings, the CyA dose was reduced. Plasma exchange was started and continued for a total of 14 exchanges. (Three titers were exchanged during each session and replaced by fresh frozen plasma.) There were no improvements and the patient continued to be dependent upon dialysis. Finally, the CyA had to be discontinued 8 weeks post-transplantation. The patient could not tolerate azathioprine because of leukopenia.

Renal function started to improve 2 weeks after CyA was stopped, at which time the hematological picture normalized. Serum creatinine stabilized at 190 μmol/l and the patient was maintained on prednisolone, 60 mg/day, for 3 weeks. A second renal allograft biopsy was performed 3 weeks after stopping CyA; this showed acute cellular rejection, but the signs of thrombotic microangiopathy were no longer present. The patient was given three boluses of methylprednisolone and was started on FK 506, 5 mg twice daily. The prednisolone dose was gradually reduced to 10 mg/day. Renal function continued to improve with serum creatinine decreasing to 140 mmol/l. A third renal allograft biopsy was performed 8 weeks after starting FK 506 and showed normal-looking glomeruli and vessels with no cellular infiltration and no fibrinoid changes.

Discussion

CyA-induced HUS is a rare, but serious, complication of CyA therapy, resulting in graft failure in many cases [2, 4, 5, 12]. Recently, it has been found that patients who have been sensitized as a result of previous transplantation, who have had high cytotoxic antibodies for other reasons, or who have received grafts from nonheart-beating donors are at a higher risk of developing HUS [4].

It is not clear how CyA induces HUS. Experimental studies suggest that CyA may interfere with the complex mechanism that promotes the generation of prostaglandin I2 (PGI2) [9, 11, 13, 16] or the lowering of red blood cell arachidonic acid [10], resulting in endothelial cell injury and precipitating platelet aggregation and the formation of microthrombi.

Experimental evidence suggests that the effect of CyA on the microcirculation is a dose-dependent, cytotoxic effect on the endothelial cells [11, 15, 16]. In addition, there is some clinical evidence suggesting that the microangiopathic process can be reversed with a moderate dose reduction of CyA [3, 14]. However, it seems likely that there are other contributing factors since, despite the wide usage of CyA, the condition is still regarded as relatively rare [11] and since, as in our case, the reduction of CyA did not ameliorate the microangiopathic process. This only disappeared after the CyA was discontinued, suggesting that, in addition to the dose-related effect of CyA, there could be an idiosyncratic reaction-like effect.

Both plasma exchange [6] and the infusion of fresh frozen plasma [1] have been successfully applied in renal and liver allograft recipients who developed CyA-induced HUS. Our patient had 14 sessions of plasma exchange with no noticeable response.

McCauley and colleagues have suggested that FK 506 may be an effective substitute therapy in CyA-induced HUS [8], but we are not aware of any previous report about the successful substitution of FK 506 in one and the same renal allograft.

It is now 5 months since we substituted FK 506 in our patient. She has stable graft function and a normal hematologic picture. This case suggests that the best treatment for CyA-induced HUS is the discontinuation of CyA and that FK 506 is a safe, alternative drug that can be used as the main immunosuppressant in such cases.

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