Case Report

Cyclosporin-induced haemolytic–uraemic syndrome presenting as primary graft dysfunction

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Introduction

Although the efficacy of cyclosporin (CsA) as an immunosuppressant is undisputed, the problem of nephrotoxicity continues to cause concern. CsA can lead to a wide spectrum of renal damage. The development of cyclosporin-induced haemolytic–uraemic syndrome (HUS) was initially reported in bone marrow transplant recipients. De novo cyclosporin-induced HUS has also been described in a limited number of renal allograft recipients [1–4]. We report a patient who developed HUS after a single intravenous injection of CsA. A 1-h graft biopsy showed characteristic changes, and the patient recovered after CsA withdrawal.

Case

A 30-year-old male with chronic renal failure resulting from mesangio-capillary glomerulonephritis was referred to this centre for renal transplantation. He received eight sessions of haemodialysis prior to transplantation. No blood transfusions were given. Pretransplant evaluation showed a Hb of 8.0 g/dl, total leukocyte count of 6500/mm³ with a normal differential count and a platelet count of 1.9 × 10⁵/mm³. Blood group was A+ve and there were no cold agglutinins in the serum. The kidney donor was the patient’s 40-year-old brother, who had the same blood group with a 50% HLA match.

The patient received CsA 3 mg/kg i.v. 1 day pretransplant (D−1), on the day of transplant, after surgery (D 0) and 1st day post-transplant (D +1). From the 2nd day onwards, he was put on oral CsA 8 mg/kg. The patient also received azathioprine 1 mg/kg from D−1 onwards. On D 0, patient received dexamethasone 8 mg i.v. and subsequently oral prednisolone 30 mg daily. Warm and cold ischaemia time were 2 min and 45 min respectively. The renal vein was anastomosed (end to side) to the external iliac vein and the renal artery to the internal iliac artery. After declamping, two small patches of bluish discoloration of the graft were noted, which did not increase and there was adequate diuresis. One hour after the anastomosis, a graft biopsy was taken.

Post-operatively the urine output was 2100 ml on D 0, 1800 ml on D +1, decreasing to 700 ml on D +2, and subsequently the patient became oliguric. Serum creatinine increased from 6.0 mg/dl to 10.2 mg/dl and patient required dialytic support. Ultrasonography (USG) of graft revealed no abnormality. ⁹⁹ᵐ怵diethylene triamine penta-acetic acid scan showed normal perfusion. Prothrombin time (PT) was 13 s (control 17) and partial thromboplastin time was 35 s (control 50). Platelet count decreased to 50 000/mm³ and Hb dropped to 5.8 g/dl on the third day. Peripheral smear showed anisopoikilocytosis with fragmented red cells. Reticulocyte count was 10%. Serum fibrinogen was 300 mg/dl (normal 200–400 mg/dl), fibrin degradation products were not detectable, plasma Hb was 11 mg/dl (normal 1–5 mg/dl). Peroperative graft biopsy (report received on D +4 ) showed fibrin thrombi in all 25 glomeruli. There was mild interstitial oedema with normal tubules (Figure 1). Repeat USG did not reveal

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increasing graft size. A cross-match test was repeated and was negative. The patient was given injection methylprednisolone 500 mg for 3 days but graft function did not improve. On D + 6, when the PT and PTT normalized and platelet count was 90,000/mm³, a second graft biopsy was done. Biopsy showed 29 glomeruli, many of which showed segmental fibrinoid necrosis of the tuft along with few fibrin thrombi in capillaries. Endothelial cell swelling was seen in glomerular tufts. One of the afferent arterioles showed endothelial swelling with occlusion of the lumen. There was no interstitial oedema and no endovasculitis (Figure 2).

At this stage CsA-induced HUS was suspected. CsA was stopped on the 10th post-transplant day and azathioprine was increased to 2.5 mg/kg. Urine output improved gradually and was 1800 ml on 18th post-transplant day. On the 22nd day the patient had a sudden decrease in urine output along with graft tenderness. Kidney biopsy was undertaken, and showed only one glomerulus, which was unremarkable. There was interstitial oedema, lymphomononuclear infiltrate, and marked tubulitis, suggesting acute rejection. A large artery included in the biopsy did not show evidence of vasculitis. The patient was given injection methylprednisolone 500 mg i.v. for 3 days. Gradually the serum creatinine decreased to 2.3 mg/dl on 31st post-transplant day and patient was discharged. At discharge, Hb was 8.8 g/dl, platelet count was $2.5 \times 10^5$/mm³. Two and a half years post-transplant, serum creatinine is 1.9 mg/dl and Hb is 13.0 g/dl, with a normal platelet count.

**Discussion**

In the immediate post-transplant period, it is very difficult to differentiate accelerated rejection from *de novo* HUS, both clinically as well as histologically. In both, the major damage occurs in blood vessels. Haemolysis and some degree of thrombocytopenia can be present secondary to rejection. In acute vascular rejection, the most striking feature is an endovasculitis characterized by intimal mononuclear cell infiltration, subendothelial foam cells, and myeloblastic proliferation [2]. In the present case these features were not seen. There was no evidence of infection, malignant hypertension, or systemic illness like scleroderma which could have caused HUS. The patient developed HUS possibly as a side-effect of CsA treatment.

The development of post-transplant HUS seems to have been a rare event prior to the use of CsA. Giroux *et al.* [2] did not observe a single case of *de novo* HUS in renal allograft recipients receiving azathioprine and prednisolone. Only eight cases of graft failure associated with microangiopathic haemolytic anaemia (MAHA) have been reported prior to the use of CsA in renal-transplant recipients, and the MAHA seemed to be secondary to acute rejection in all but one case [5–7]. Since the introduction of CsA the number of cases described has increased [1–4]. CsA has been shown to be directly toxic to cultured endothelial cells, and the reduction of prostacyclin and increased thromboxane A2 and endothelin by CsA may contribute to the development of HUS [8].

CsA-induced HUS can present over a variable period of time. It is commonly seen between the 2nd to 4th week post-transplant [2]. Van Buren *et al.* [1] described a case who was diagnosed on the 3rd post-operative day. In our patient the peroperative graft biopsy done 1 h after the anastomosis showed fibrin thrombi. Prior to this, the patient had received a single dose of CsA 3 mg/kg i.v. He also had primary graft failure associated with MAHA and thrombocytopenia. The presence of thrombi on peroperative biopsy and subsequent detection of MAHA cannot be dissociated in the present case. Although glomerular thrombi can be seen on peroperative graft biopsy in patients receiving CsA in the absence of HUS, development of primary graft dysfunction has so far only been reported in such instances in association with acute vascular rejection or ABO incompatibility [9,10]. We therefore feel that our patient developed HUS after a single intravenous injection of CsA; this has not previously been described in the literature. The changes of HUS were also present in the second graft biopsy, done on the 6th post-operative day when the patient was still on CsA. HUS resolved only after withdrawal of the drug.

CsA-induced HUS generally occurs during the first few weeks after transplantation when higher doses of CsA are administered [2]. An association between high panel-reactive antibody levels and thrombotic microangiopathy has been reported [11] but this was not tested in the present case. Intravenous CsA preparations contain cremophor EL (polyoxyethylated castor oil), which has been reported to cause anaphylactoid reactions; other adverse effects are the same as those of the oral preparation. CsA-induced HUS can be a devastating complication, as it may fail to resolve after CsA withdrawal [2]. Some cases have improved following either withdrawal or even reduction in dosage of the drug. Thrombocytopenia, the severity of which usually corresponds with the degree of anaemia, may

![Figure 2. A glomerulus with segmental tuft necrosis (×) (H&E × 550).](image-url)
improve independently of renal function and may display spontaneous resolution long before the recovery of renal function [1]. CsA has also been successfully re instituted in patients in whom thrombotic microangiopathy occurred due to CsA [11]. We have described a patient who developed HUS following a single dose of parenteral CsA. To conclude, CsA-induced HUS can present in the immediate post-transplant period, simulating accelerated rejection. Timely detection and withdrawal of CsA may prevent graft loss.

References


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