Case Report

Development of transplant renal artery thrombosis and signs of haemolytic-uraemic syndrome following the change from cyclosporin to tacrolimus in a renal transplant patient

Ahmet Alper Kiykim¹, Caner Ozer², Altan Yildiz², Naci Tiftik³, Mehmet Senli¹, Ebru Kelebek¹, Erdal Doruk⁴ and Erdem Akbay⁴

¹Division of Nephrology, Department of Internal Medicine, ²Department of Radiology, ³Division of Hematology, Department of Internal Medicine and ⁴Department of Urology, Faculty of Medicine, University of Mersin, Turkey

Keywords: haemolytic-uraemic syndrome; tacrolimus; transplant renal artery thrombosis

Introduction

The clinical presentation of post-transplantation thrombotic microangiopathy (TMA) is variable. Often, TMA will manifest systemically as haemolytic-uraemic syndrome (HUS), with classic findings of renal failure, haemolytic anaemia, schistocytes and thrombocytopenia [1]. Localized and systemic TMA represent a spectrum of severity of the same disorder, not two different disorders with distinct pathophysiological states. Pre-transplantation HUS, antecedent antiphospholipid antibodies, acute rejection, cytomegalovirus (CMV) and some medications are associated with the development of TMA. Herein we report a patient who developed the signs and symptoms of de novo HUS and transplant renal artery thrombosis following switching from cyclosporin to tacrolimus.

Case

The patient is a 38-year-old Turkish woman whose primary cause of renal failure was bilateral nephrolithiasis. She had a gradual development of end-stage renal disease (ESRD) without a previous renal history of thrombotic microangiopathy. She had been on haemodialysis for 10 months. The renal transplantation had been performed from a 2-antigen mismatched, 74-year-old living related donor (her mother) 10 months earlier. The transplanted kidney had immediate function with excellent urine output but a slowly dropping serum creatinine level. The patient did not require haemodialysis in the post-transplant period. Induction immunosuppressive protocol consisted of daclizumab and a total of 750 mg intravenous methylprednisolone. Maintenance immunosuppression included a prednisone tape, mycophenolate mofetil (MMF) at 1000 mg orally twice daily and cyclosporin at 200 mg orally twice daily. Her serum creatinine level at discharge, post-transplant day 20, was 1.4 mg/dl (normal: 0.8–1.2 mg/dl).

The patient was healthy, except for hypertension during 6 months post-transplant. Her serum creatinine level increased to 1.6 mg/dl gradually during this period, but we did not consider this due to rejection and structural abnormality in graft, guiding laboratory and clinical evaluation. Because the donor was an elderly person and resistant hypertension and cyclosporin nephrotoxicity were considered in the patient, cyclosporin was switched to low dose tacrolimus (4 mg/day, 0.08 mg/kg/day) in the sixth month post-transplant. Tacrolimus dose was subsequently increased to 6 mg/day (0.1 mg/kg) orally within 3 weeks.

The patient was admitted to our hospital at 24 days after switching to tacrolimus, with complaints of sudden and severe local graft pain, complete anuria and weakness for 25 h. At this time, the patient had no additional complaints. On admission, physical examination revealed no abnormal finding, except for elevated blood pressure (200/110 mmHg). There was no tenderness or swelling on the graft region. Obstructive uropathy was not determined. Renal artery blood flow was not observed by Doppler ultrasound examination. Selective transplant renal arteriography was performed. The main transplant renal artery and some peripheral branches were occluded by thrombi (Figures 1 and 2). The main renal artery stenosis and tortuous segmental arteries are shown in Figure 2.
Blood and urine tests that were obtained 25 h before admission were all normal, except the unchanged elevated serum creatinine (1.7 mg/dl). On admission, blood tests revealed the following results: haemoglobin 8.9 g/dl; platelet count 37 000/mm³ and blood smear revealed the features of microangiopathic haemolytic anaemia. Other values were serum glucose 99 mg/dl; blood urea nitrogen 127 mg/dl; serum creatinine 4.9 mg/dl; potassium 6.2 mEq/l; cholesterol 198 mg/dl; low-density lipoprotein 118 mg/dl; high-density lipoprotein 32 mg/dl. Because of anuria, urine tests could not be done. Lactate dehydrogenase (LDH) was 1840 U/l (normal: < 480 U/l), aspartate aminotransferase (AST) was 340 U/l (normal: < 32 U/l), alanine aminotransferase (ALT) was 42 U/l (normal: < 31 U/l) and creatine kinase (CK) was 580 U/l (normal: < 145 U/l). Arterial blood gas analysis revealed mild metabolic acidosis. Anticardiolipin antibody-IgG and -IgM were negative. Other antibodies (antinuclear antibodies, antit doubly-stranded DNA, antineutrophil cytoplasmic autoantibody) and lupus anticoagulant were all negative. Coomb’s test was negative. CMV-IgM was negative. Resistance to activated protein C was not determined.

She was diagnosed as systemic TMA and HUS, with classic findings of renal failure, haemolytic anaemia, severe thrombocytopenia, elevated LDH, AST and CK and peripheral blood smear that revealed microangiopathic haemolytic anaemia. We did not find other conditions proposed by some to trigger TMA, such as pre-transplantation HUS, anticardiolipin antibodies, acute rejection or CMV. The patient was not on other medications known to be a significant risk for causing medication-induced thrombotic microangiopathy at this time.

Tacrolimus trough levels were not found higher than 13.9 ng/ml during the treatment period. Believing tacrolimus was possibly the inducing agent for this thrombotic microangiopathy, it was discontinued at once. Immunosuppressive therapy was continued with MMF and high dose (1 mg/kg/day) oral steroid. Percutaneous transplant renal angioplasty (PTRA) was performed successfully after thrombolysis (direct infusion into the thrombus of three bolus doses of 5 mg rt-PA followed by 1 mg/h infusion for 8 h) to the stenotic and occluded segments (Figures 1–3). Low dose rt-PA was administered because of the presence of thrombocytopenia and uraemia. The patient needed to be treated by haemodialysis three times. We could not perform plasmapheresis for considered HUS due to technical insufficiency.

Urine output started at once after the thrombolysis and PTRA. Her serum creatinine decreased gradually and was 2.2 mg/dl after 2 weeks. Her blood pressure control was acceptable with a beta-blocker (nebivolol) monotherapy. Platelet count increased to 138 000/mm³. Blood smear findings and the serum levels of LDH, AST, CK and ALT returned to normal. The patient was discharged with the treatment regimen, which consists of MMF (2000 mg/day), prednisolone (15 mg/day), acetylsalicylic acid (100 mg/day), dipridamole (225 mg/day), nebivolol (10 mg/day) and simvastatine (20 mg/day). The patient was healthy and serum creatinine was 2.1 mg/dl after 3 months.

Discussion

TMA and renal artery thrombosis is a very rare condition. Rates of de novo TMA after renal trans-
With HUS [2], as in our patient. It has been demonstrated that there is no association of HLA mismatch, recipient sensitization or ischaemic time with the risk of TMA [2]. The peak risk of both de novo and recurrent HUS is early (this early period extended for at least 3–6 months). Patients with systemic TMA have a greater incidence of both acute renal failure requiring dialysis therapy and graft loss than patients with localized TMA.

Several immunosuppressive medications, including OKT-3, thymoglobulin, sirolimus, tacrolimus and cyclosporin, have been documented to be associated with the development of post-transplant HUS. Tacrolimus and, especially, cyclosporin cause endothelial dysfunction and increase platelet aggregation, particularly via inhibition of prostacyclin. It has been believed that the risk of HUS is higher with cyclosporin than with tacrolimus [3]. It has been demonstrated that switching from cyclosporin to tacrolimus in stable renal transplant patients has a beneficial effect on renal function and blood pressure [4]. Furthermore, it has been claimed in a recent study that blood thrombogenicity is significantly reduced in cardiac transplant patients receiving FK506 as compared with those receiving cyclosporin [5]. Although we switched from cyclosporin to tacrolimus, which is known to have less adverse effects than cyclosporin, transplant renal artery thrombosis in combination with systemic HUS was developed.

Treatment of transplant-associated HUS can be somewhat different from idiopathic HUS. Temporary calcineurin-inhibitor withdrawal was the mainstay of therapy for HUS [6]. Some authors have suggested that high-dose steroids can have favourable responses, especially in those with mild symptoms and no neurological complaints. In our patient, the immunosuppressive regimen continued with MMF and high dose (1 mg/kg) oral steroid, after tacrolimus was discontinued. Plasma exchange or infusion have been tried to treat for some severe systemic cases of HUS. Lin et al. [7] suggested that morbidity and mortality due to systemic TMA are high without intensive plasma exchange therapy. There are no large series to confirm the benefit of plasma exchange in this setting, although it is used commonly. Recommendations are based on a single institution’s experiences, anecdotal reports and small series of patients. Despite the discrepancy in outcome between low-risk TMA and high-risk patients, there are no large series to recommend a different therapeutic approach. In patients with TMA, the switching of calcineurin inhibitors to MMF-based immunosuppression may be alternative therapies [8]. It remains to be seen whether TMA also occurs with the same frequency in patients treated with calcineurin-inhibitor-free immunosuppression regimens. It has been documented in some cases developing TMA that switching patients to another calcineurin inhibitor results in recurrence of TMA [9]. Furthermore, Furlong et al. [10] suggested that conversion from cyclosporin to tacrolimus is not an effective treatment approach in cases with post-transplantation HUS.
In conclusion, to the best of our knowledge, this is the first report of a patient who developed acute transplant renal artery thrombosis and the signs of de novo HUS and who was treated by the combination of PTRA and thrombolytic therapy. Instead of invasive and expensive treatment procedures, such as plasma exchange, calcineurin inhibitor-free regimens with administration of modestly increased dose of steroids for a short period of time may be preferred in patients with signs of de novo HUS.

Conflict of interest statement. None declared.

References


Received for publication: 7.1.04
Accepted in revised form: 28.5.04