Case Report

Chronic organizing microangiopathy in a renal transplant recipient

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Introduction

Thrombotic microangiopathy (TMA), not an uncommon but potentially serious complication of transplantation, occurs in 3–15% of renal transplant recipients [1,2]. De novo post-transplant TMA is mostly due to calcineurin inhibitor toxicity. Histologically, TMA is characterized by glomerular endocapillary damage with subendothelial accumulation of amorphous material. Narrowing or occlusion of capillaries with intravascular fibrin thrombi and fragmented erythrocytes is common. Similar changes may involve arterioles and arteries. Post-transplant TMA can be isolated to the allograft or can present with clinical and laboratory evidence of systemic TMA, including fever, haemolytic anaemia and renal failure. Intravascular haemolysis leads to the presence of schistocytes on peripheral blood smear, increased lactate dehydrogenase (LDH), and decreased haptoglobin levels in the systemic form of post-transplant TMA, which is often referred to as haemolytic-uraemic syndrome (HUS). Both localized and systemic TMA can present with acute renal failure, and both have been associated with decreased graft survival [1,2]. Here we use the descriptive term TMA to refer to both localized and systemic forms of post-transplant TMA, as well as to systemic forms of TMA in the general population, including HUS and thrombotic thrombocytopenic purpura (TTP).

Recurrence of TMA following clinical resolution has been described in renal transplant recipients with pre-transplant TMA and in patients rechallenged with calcineurin inhibitors following an episode of calcineurin inhibitor-induced TMA [3]. The role of the initial endothelial insult in recurrent disease is unclear, and the significance of residual histological changes is not well described. Because the organizing phase of TMA may resemble chronic transplant glomerulopathy, it is unclear how often post-transplant TMA evolves into the fibrotic organizing phase. We present serial renal biopsies from a patient with acute humoral rejection and later development of malignant hypertension and systemic TMA, in whom intervening biopsies revealed fibrotic microvascular changes attributed to chronic organizing microangiopathy.

Case

A 46-year-old African-American female with end-stage renal disease attributed to hypertensive nephropathy underwent living-related donor renal transplantation from her 29-year-old daughter. The aetiology of native kidney disease was not confirmed by renal biopsy due to late referral; however, the patient had no proteinuria, haematuria or clinical manifestations of systemic illness prior to the initiation of dialysis. Initial complement-dependent cytotoxicity (CDC) T-cell cross-match was negative. CDC B-cell cross-match and flow cytometry T-cell and B-cell cross-match were positive, with a donor-specific anti-human leukocyte antigen (HLA) antibody (anti-A2) demonstrated by antigen-coated flow beads (Luminex). There were no pre-transplant anti-HLA class II antibodies. The addition of \textit{in vitro} intravenous immunoglobulin (IVIG) into test wells completely abrogated the CDC and flow cytometry cross-match positivity. The patient received induction therapy with IVIG (100 mg/kg for 3 days) and thymoglobulin (1.5 mg/kg for 5 days), which has been shown to permit the successful transplantation of patients with positive CDC B-cell and flow cytometry cross-match [4]. Maintenance therapy included cyclosporin microemulsion, (trough 166–195 ng/ml), prednisone and mycophenolate...
mofetil. The patient was discharged on post-operative day 4 with a creatinine of 1.2 mg/dl.

On post-operative day 7, the patient was readmitted with oliguria and creatinine of 4.4 mg/dl in the setting of a low cyclosporin trough (106 ng/ml). Renal biopsy showed neutrophilic infiltrates in the interstitium and interstitial capillaries, as well as acute microangiopathic glomerular changes, including swelling of glomerular capillary endothelial cells, segmental capillary dilatation and congestion, intracapillary thrombi and red blood cell fragments (Figure 1A). The vascular pole of some glomeruli showed endothelial damage, but the afferent arterioles and arteries were unremarkable. There was no evidence of arteriolar muscle cell degeneration or adventitial hyaline nodules. Interstitial capillaries were strongly positive for C4d (Figure 1B). Repeat CDC T- and B-cell cross-match and donor-specific antibody (anti-A2) were positive. The clinical and biopsy findings indicated acute humoral rejection, and the patient was treated with IVIG, plasmapheresis, OKT3 and rituximab. Cyclosporin was changed to tacrolimus for maintenance therapy. Subsequent renal biopsies on post-operative days 21 and 31 showed resolution of the acute microangiopathic glomerular changes and neutrophilic infiltrates but persistence of a strong C4d reaction in interstitial capillaries. Both biopsies demonstrated marked fibrous narrowing of the hilum of multiple glomeruli, attributed to organizing microangiopathy (Figure 2). Several immediately adjacent afferent arterioles displayed mild fibrous intimal thickening, but the glomerular capillaries and other arterioles and arteries were unremarkable. Renal function gradually improved, reaching a new baseline creatinine of 1.7 mg/dl.

Over the next 9 months, tacrolimus trough levels were maintained between 7 and 10 ng/ml, and blood pressure was well controlled on combination beta-blocker and calcium channel blocker therapy. Renal function remained stable until 1 year post-transplant, when the creatinine rose to 2.6 mg/dl in the setting of cytomegalovirus (CMV) viraemia. Repeat CDC and flow cytometry cross-match was negative. Renal biopsy demonstrated mild interstitial fibrosis and tubular atrophy (Banff 97: ci1, ct1), with no evidence of acute rejection or active microangiopathy by light microscopy. Persistent fibrosis at the glomerular hilus represented chronic organizing microangiopathy. Light microscopy did not disclose glomerular capillary TMA changes; however, electron microscopy demonstrated scattered glomerular capillary subendothelial widening and mild organizing subendothelial damage. Interstitial capillaries were negative for C4d, and there was no histological or immunohistological evidence of CMV or polyoma virus infection. Arterioles contained focal hyalinization, including an area of adventitial hyalinization consistent with calcineurin inhibitor toxicity. Arteries were unremarkable (Banff 97: g0, i0, ah2, cg0, ci1, ct1, cv0). The patient’s renal insufficiency (creatinine 2.4–2.6 mg/dl) persisted over the next 9 months.
2 months, at which time a repeat renal biopsy again showed chronic organizing microangiopathy without active microangiopathic changes or acute rejection. Tacrolimus trough levels were again maintained between 7 and 10 ng/ml, and blood pressure was well controlled on the same regimen.

Three weeks later, the patient was admitted with fever and malaise. Admission laboratory analyses were notable for creatinine 3.1 mg/dl, tacrolimus trough 16.6 ng/dl, haemoglobin 8.9 g/dl (baseline 10–11 g/dl), leukocyte count 5.4 $\times\ 10^3$ and platelet count 214 000. Repeat CMV viral load was undetectable. During evaluation for occult infection or malignancy, mycophenolate mofetil and tacrolimus were withheld initially, and tacrolimus was subsequently resumed to maintain lower trough levels of 4–6 ng/dl. Two weeks into the hospital course, the patient developed rapidly progressive renal failure and accelerated hypertension, which was difficult to control with multiple antihypertensive medications. Plasma creatinine increased to 3.7 mg/dl, and haemodialysis was initiated for oliguria and refractory volume overload. Laboratory tests were remarkable for a haemoglobin of 7.1 g/dl (baseline 10 g/dl) and platelet count of 148 000. Further findings of schistocytes, LDH of 533 U/l and red cell distribution width of 18% were consistent with intravascular haemolysis. Renal biopsy demonstrated extensive acute TMA with erythrocyte fragmentation, endothelial disruption, focal glomerular microaneurysm formation and capillary fibrin deposition. Arterial lumens were severely narrowed by myxoid intimal thickening with small focal intravascular thrombi (Figure 3A and B). There were no neutrophils in the interstitium or interstitial capillaries, and C4d staining was negative. Repeat CDC and flow cytometry cross-match was negative, although donor-specific anti-HLA antibodies (anti-A2) were still detectable by antigen-coated flow beads. Despite substitution of sirolimus-based immunosuppression and treatment with IVIg and plasmapheresis, allograft function did not recover. The allograft was removed and showed extensive thrombotic micro- and macroangiopathic changes without acute cellular rejection. The interstitial capillaries of the nephrectomy specimen were C4d negative. The patient is currently on haemodialysis awaiting retransplantation.

**Discussion**

*De novo* post-transplant TMA is usually triggered by calcineurin inhibitor treatment [1–3], and less frequently by viral infections [5,6]. The updated Banff classification of renal allograft rejection defined three types of antibody-mediated acute humoral rejection, ATN-like, capillary-glomerulitis and arterial [7]. The capillary-glomerulitis type acute humoral rejection may resemble the pathological features of TMA. In the renal allograft, immunohistochemical determination of C4d in interstitial capillaries may help to distinguish humoral rejection from other forms of post-transplant TMA. C4d is a fragment of the classical complement pathway component C4 and remains stable in peritubular capillaries by covalent binding to the tissue. The presence of C4d in interstitial capillaries in association with histological and serological changes is accepted as a marker of an acute [7] or chronic humoral alloimmune response [8]. The lack of C4d staining may help to exclude humoral rejection as the aetiology of post-transplant TMA. The development of acute humoral rejection with active microangiopathic changes, intervening lesions attributed to chronic organizing microangiopathy and later development of malignant hypertension and systemic TMA in our patient may suggest a common pathogenesis, a continuum of disease or a particular susceptibility of this renal allograft to endothelial damage. The outcome of positive C4d staining is not clear and has not been studied in a prospective manner. The follow-up biopsies after a year demonstrated the disappearance of C4d staining in our patient, along with negative cross-match results, consistent with a non-immunological mechanism for the second episode.
of active TMA. While it is clear that primary TMA can recur in transplant recipients, and that calcineurin inhibitor-induced TMA can recur in the allograft [3], different forms of post-transplant TMA have not been described in the same patient, and it is unusual to see an acute systemic TMA picture more than a year after renal transplantation. Following the initial endothelial injury induced by donor-specific anti-HLA antibodies, it is possible that calcineurin inhibitor therapy and hypertension contributed to the persistence of chronic microangiopathic changes. The aetiology of subsequent development of acute systemic TMA >1 year after transplantation was not clear, although calcineurin inhibitor therapy and malignant hypertension may have been contributing factors. There was no evidence of recurrent humoral rejection, with negative C4d staining and negative CDC and flow cytometry cross-match. Despite previous reports of a possible association between TMA and viral infections, including CMV and parvovirus [5], there was no evidence of active CMV disease in our patient at the time of diagnosis.

The pathogenesis of post-transplant TMA is poorly understood but is likely to be multi-factorial. Calcineurin inhibitors and infectious agents have been shown to cause direct endothelial injury and cytokine production [6]. Dysregulation of thrombotic processes has also been implicated in post-transplant TMA. Both congenital and acquired TTP have been associated with abnormalities in the clearance of von Willebrand factor, and there is at least one report of a similar association in post-transplant TMA [9]. The role of the initial endothelial injury in recurrent renal allograft TMA is unknown, as is the clinical significance of residual histological changes in this setting. The persistence of organizing microangiopathic changes following an episode of acute TMA, as in our patient, may reflect an endothelium rendered susceptible to subsequent insults.

Regardless of aetiology, the cornerstone of treatment for post-transplant TMA is removal or treatment of the inciting factor, often followed by plasmapheresis. In the case of calcineurin inhibitor-induced TMA, substitution of another calcineurin inhibitor may or may not prevent the recurrence of TMA (3). The role of calcineurin inhibitor-free sirolimus therapy is not clear. A recent large cohort study also found a significant association between sirolimus use and TMA; however, it is possible that sirolimus was being prescribed following the diagnosis of calcineurin inhibitor-induced TMA [10]. Long-term outcomes following post-transplant TMA have not been described in large populations; however, in small studies, TMA was associated with decreased allograft survival [1,2].

A recent historical cohort study including 149 cases of post-transplant TMA also found a significant decrease in patient survival [10]. Thrombotic microangiopathy is an important and incompletely understood complication of transplantation. Serial renal biopsies in our patient illustrate a spectrum of microvascular injury, with initial acute antibody-mediated microangiopathic damage, subsequent organizing microangiopathy and late development of severe systemic TMA. These findings may suggest that endothelial damage from acute humoral rejection renders the endothelium more susceptible to subsequent insults, or initiates progressive microvascular changes in the absence of persistent antibody-mediated mechanisms. Further clinical and laboratory investigation is needed to elucidate the mechanisms and long-term effects of TMA on the renal allograft.

Conflict of interest statement. None declared.

References


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