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REVIEW

Thrombotic microangiopathy after kidney transplantation

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Summary

Two forms of post-transplant thrombotic microangiopathy (TMA) may be recognized: recurrent TMA and *de novo* TMA. Recurrent TMA may occur in patients who developed a nondiarrhoeal form of haemolytic uraemic syndrome (HUS) being particularly frequent in patients with autosomal recessive or dominant HUS. The recurrence is almost the rule in patients with mutation in complement *factor H* gene. Most patients eventually lose the graft. Treatment with plasma infusions or plasmapheresis is often disappointing, but few cases may be rescued. Intravenous immunoglobulins and rituximab have also been successful in anedoctic cases. *De novo* TMA is rarer. A number of factors including viral infection may be responsible of *de novo* TMA, but in most cases TMA is triggered by calcineurin inhibitors or mTOR inhibitors. The clinical presentation of *de novo* TMA may be variable with some patients showing clinical and laboratory features of HUS while others showing only a progressive renal failure. The prognosis is less severe than with recurrent TMA. Complete withdrawal of the offending drug may lead to improvement in many cases. The addition of plasma exchange may result in graft salvage in about 80% of cases.

Thrombotic microangiopathy (TMA) is a histopathological term that defines glomerular, arteriolar or interlobular artery lesions, characterized by patchy distribution, with intimal cell proliferation, thickening and necrosis of the wall, thrombi and narrowed lumens. The severity of lesions is variable ranging from endothelial swelling to complete cortical necrosis. TMA is typically found in renal biopsies of patients affected by haemolytic uraemic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP), but it is also a well-recognized complication of bone marrow [1], liver [2] and heart [3] transplantation. Of particular concern, TMA is relatively frequent in renal transplant recipients. By reviewing the United States Renal Data System (USRDS), Reynolds *et al.* [4] found that among patients transplanted because of HUS, TMA recurred in 29.2% of cases and another 0.8% of patients showed a *de novo* TMA. As the incidence, the pathogenesis, the prognosis and the treatment of the two conditions may be different, we will consider separately recurrent and *de novo* TMA after renal transplantation.

Recurrent post-transplant TMA

Haemolytic uraemic syndrome is a frequent cause of renal failure in children. Most cases are diarrhoea-associated (D+ HUS) and are usually related to exotoxins produced by *Escherichia coli* O157:H7. Other cases are not associated to diarrhoea (D− HUS). Rarely, HUS may occur in several members of the same family (familial HUS) with an autosomal dominant or recessive inheritance. In these cases, the disease may present in neonatal age or in the adulthood. About 30% to 50% of D− HUS have mutations in one of the complement control proteins: factor H, factor I or membrane cofactor protein (MCP) [5,6]. HUS may occur also in adults and is frequently classified as TTP. It may occur in pregnant women, or after exposure to drugs such as calcineurin-inhibitors (CNI), oral contraceptives, mytomycin-C, quinine, ticlopidine and clopidogrel [7]. However, many cases do not recognize any aetiological factors and are defined as idiopathic.

After renal transplantation, D+ HUS usually does not recur [8] while idiopathic D− or familial HUS may recur in 21–28% of children [9,10]. In patients with factor H or factor I, mutation recurrence occurs in about 80–100% of patients, while patients with mutation in MCP do not have recurrence after transplantation (Table 1). A high risk of recurrence ranging between 33% and 56% [11–13] has been reported in adults with an additional 16–20% of patients demonstrating TMA in the absence of clinical manifestations. Post-transplant recurrence seems to be particularly frequent in adults with autosomal recessive or dominant HUS [14].

The pathogenesis of recurrent post-transplant TMA is still poorly defined. A key role in regulating complement activity is played by factor I, a serin protease that can downregulate the activity of both classical and alternative complement pathways. Both MCP, a transmembrane complement regulator, and factor H act as co-factors of IF. Mutation of factor H is the most frequent cause of recurrent TMA. The human plasma protein factor H, which is a multifunctional and multidomain protein, is a central regulator of the complement system. Factor H interacts with a wide selection of ligands, such as thrombospondin, bone sialoprotein, osteopontin and heparin [15]. These ligands increase the affinity of factor H for C3b and increase its inhibitory effect on the alternative pathway of complement activation [16]. In factor H-associated genetic HUS, the mutant factor H proteins can cause reduced binding to the central complement component C3b/C3d to endothelial cells, so favouring progression of endothelial cell and microvascular damage [17]. Therefore, uncontrolled complement activation and secondary endothelial injury may explain the high incidence of recurrent TMA in patients with factor H deficiency. The pathogenesis of idiopathic TTP has been linked to a deficiency of a metalloprotease referred to as ADAMTS 13 (A disintegrin and metalloprotease with thrombospondin-1-like domains). This protease cleaves the large multimers of von Willebrand factor that can trigger platelet aggregation and microvascular thrombosis. Anecdotal case reports suggest that also patients with congenital deficiency in the activity of von Willebrand factor-cleaving ADAMTS 13 or with acquired inhibition of ADAMTS 13 may be more susceptible to post-transplant recurrence [18], although the role of these abnormalities is still unclear [19,20]. Apart from the genetic predisposition, it is possible that some factors such as calcineurin inhibitors, anti-mTOR agents, viral infection and acute rejection may precipitate the recurrence of TMA after renal transplantation.

Table 1. Risk of recurrence of the different forms of thrombotic microangiopathy (TMA) after renal transplantation.

Forms of TMA in native kidneys	Risk of recurrence in transplanted kidneys
Postdiarrhoeal (D+)	Negligible
Nonpostdiarrhoeal (D−). Sporadic or familial forms	
Mutation in factor H	80%
Mutation in factor I	80–100%
Mutation in membrane cofactor protein	0%
Idiopathic	33–56%
Secondary to pregnancy, drugs, etc.	Negligible

With few exceptions [21], post-transplant TMA occurs in the early postoperative period. Many patients show microangiopathic anaemia, thrombocytopenia and renal failure. Neurologic abnormalities and fever occur rarely. However, some cases of post-transplant recurrence are characterized by rapidly progressive graft dysfunction and do not present the typical signs and symptoms of HUS. The diagnosis may be difficult in the latter cases and relies on renal biopsy.

The prognosis is poor. The USRDS data reported a patient survival rate of 50% at 3 years [4]. In a review, 24 patients had renal transplantation for HUS/TTP, the 2-year graft survival was 35%, but eventually all patients with recurrence lost their allograft [11]. In another series, the 1-year graft survival in 17 adult patients with TMA recurrence was 29%, while survival in childhood-onset HUS was comparable with matched controls [12].

Treatment is also disappointing. Plasmapheresis or generous plasma infusion may increase the serum levels of factor H/factor I and obtain recovery of thrombocytopenia and microangiopathic anaemia in some patients, but are only rarely effective [22] on preventing renal damage. However, prevention of relapses and preservation of renal function have been obtained in a renal transplant child treated with prophylactic plasmaferesis twice weekly [23]. Two transplant patients with life-threatening recurrent HUS resistant to multiple courses of plasma exchanges were rescued by the administration of i.v. immunoglobulins [24] and rituximab [25], respectively. The recent evidence that some cases of HUS may be sustained by antifactor H autoantibodies [26] may provide a rationale for these attempts. Moreover, experimental studies showed that i.v. immunoglobulins were able to inhibit the local intraglomerular complement activation and to reduce injury when given prophylactically in a model of TMA [27]. In order to restore the defective factor H, combined liver and kidney transplantation has been performed in few patients. In a child, no signs of haemolysis occurred after transplantation [28], but liver was destroyed by a humoral rejection and the child died after a second liver transplantation [5]. Liver failure and death occurred in another child [29] and in an adult [5]. In

summary, on the basis of the available data, we feel that patients at high risk of TMA recurrence should initially avoid those immunosuppressive drugs (CNI, mTOR antagonists and OKT3) that may enhance the development of TMA. A possible strategy may consist in an induction therapy with an anti-CD25 monoclonal antibody associated with mycophenolic acid and corticosteroids. In case of recurrence, plasma exchange twice a week and i.v. immunoglobulins (0.4 g/kg body weight) should be administered until remission. If there is no response, rituximab (375 mg/m^2 weekly for 2–4 administrations) may be attempted.

De novo post-transplant TMA

The reported incidence of *de novo* TMA in kidney transplants varies considerably. In the analysis of USRDS data, a *de novo* TMA was reported in only 0.8% of cases [4]. However, this rate may be underestimated as single-centre studies reported an incidence ranging between 4% and 14% [30,31]. A number of factors may increase the risk of developing a TMA in transplanted kidneys. They include marginal kidneys [32], cytomegalovirus infection [33], parvovirus B 19 infection [34], BK polyoma virus nephritis [35], antiphospholipid antibodies [36], anticardiolipin antibodies in HCV-positive patients [37] or malignancy [38]. Rarely, drugs such as valacyclovir [39] or clopidogrel [40] may also cause TMA. However, the most important risk factors are by far represented by cyclosporin [31] and tacrolimus [41], as well as by anti-mTOR drugs [42,43]. The risk of *de novo* TMA is particularly increased when these agents are used together [44,45].

The pathogenesis of *de novo* post-transplant TMA is still poorly understood. It is possible to speculate that the endothelial lesions caused by ischaemia-reperfusion injury [46], viral infection [47,48] and/or rejection may be amplified by the endothelial injury caused by immunosuppressive drugs. CNI activate renin-angiotensin system, increase the synthesis of vasoconstrictor agents such as endothelin and thromboxane A2, and have a direct effect on renal vessels while decreasing the vasodilator nitric oxide and prostacyclin [49]. As a consequence, arteriolar lesions characterized by mucinoid thickening of the intima or nodular hyalinosis [50] may develop. The concomitant increased platelet aggregation caused by the above-mentioned abnormalities, the pro-necrotic activity of cyclosporin in endothelial cells [51] and antifibrinolysis caused by cyclosporin-induced increase in plasminogen-activator inhibitor [52] may eventually lead to TMA. The combination of CNI with mTOR may concomitantly display pro-necrotic and antiangiogenic effects on endothelial cells [53]. In fact, mTOR inhibitors may act as a subsequent aggressor, as it has been demonstrated that sirolimus may induce downregulation of vascular endothelial growth factor [43], which is required for repairing CNI nephrotoxicity and TMA [54].

Usually, *de novo* TMA occurs in the early post-transplant days, but it may also develop 2–6 years after transplantation [30,31,55]. The clinical presentation of *de novo* post-transplant TMA may be variable. Some patients may show the clinical and laboratory features of HUS/TTP, although milder than seen in nontransplant patients. Other patients show only a progressive graft dysfunction, often associated with arterial hypertension. In the latter cases, the differential diagnosis between TMA and vascular rejection may be difficult even with graft biopsy [13]. Although glomerular thrombosis is a common feature of both, irregular intimal proliferation with mononuclear cells and neutrophilic infiltration of the subendothelial layer are features of vascular rejection [56]. The positive staining of peritubular capillaries with C4d is another feature of humoral rejection [57]. However, the overlap of these features has been reported [57]. It is likely that in such cases vascular rejection could have a causative or contributory role in the development of TMA.

The prognosis is less severe than with recurrent TMA. It may depend on the severity of histological lesions and clinical features. Patients with isolated glomerular TMA usually have a good outcome [58]. Prognosis is more favourable when TMA occurs later in the post-transplant course or when it affects recipients of allografts from living donors [59]. Graft loss is rare in patients with TMA localized only to the kidney, while patients with systemic signs and symptoms of HUS are more likely to need dialysis and to lose the allograft function [60].

Therapeutic guidelines for *de novo* TMA are not well defined. Complete withdrawal of the offending CNI is essential [61], although not all patients respond [62]. In a few cases, reversal of TMA was obtained by switching from cyclosporin to tacrolimus [63] or from tacrolimus to sirolimus [64]. However, it should be kept in mind that all CNI and mTOR inhibitors may potentially lead to TMA. Therefore, these changes of therapy should be made with great caution. Plasma exchange in addition to CNI withdrawal resulted in a graft salvage rate of 80% in two series [30,56] and in other anecdotal cases [18,65]. The addition of i.v. immunoglobulins resulted in a stable remission in a patient with plasmapheresis-resistant HUS after a double liver and kidney transplantation [66]. In cases with cytomegalovirus infection, ganciclovir may resolve TMA in cases resistant to plasmapheresis and CNI withdrawal [67]. Reinstitution of the offending CNI has been successfully made in a number of patients after recovery of graft function [56,60,68]. It is possible, however, that the aetiological role of CNI in the latter cases was secondary or even questionable. As we have today a

number of possible options for different immunosuppressive drugs in renal transplantation [69], we recommend not to restart with a drug potentially involved in the aetiology of a previous TMA.

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