Interesting Case

Resolution of thrombotic microangiopathy following renal transplant

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Keywords: immunosuppresion; renal transplant; systemic lupus erythematosus; thrombotic microangiopathy; thrombotic thrombocytopenic purpura

Introduction

Thrombotic microangiopathy (TMA) is characterized by aggregation of platelets in the renal and/or systemic circulation, thrombocytopenia and intravascular haemolysis. TMA is well recognized in the setting of renal transplantation and has been attributed to a variety of aetiologies such as recurrence of original disease, use of calcineurin inhibitors, acute rejection and viral infections [1,2]. Thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS) represent the two most frequently encountered clinical presentations of TMA. There is considerable overlap in the clinical features of HUS and TTP and it is often difficult to distinguish between these entities. Moreover, in the setting of renal transplantation, both entities have been described, suggesting that the same underlying mechanism may result in TTP in some individuals and HUS in others [1]. The commonality between these syndromes makes it tempting to lump them together into the single entity of TMA. There are, however, important differences in the underlying disease mechanisms that may have prognostic and therapeutic implications, particularly in the setting of renal transplantation [3].

Case

The subject of this report, a female of East Indian origin, initially presented at age 14 with a malar rash, arthralgias and pericarditis. Laboratory studies at this time revealed a positive antinuclear antibody (ANA), positive anti-DNA antibody and low C3 and C4 complement levels consistent with the diagnosis of systemic lupus erythematosus (SLE). She was treated initially with hydroxychloroquine and prednisone in addition to having a pericardial window created. One year later, she was noted to have an elevated serum creatinine, active urine sediment and hypertension. Renal biopsy appearance was consistent with WHO class IV lupus nephritis with severe glomerular sclerosis and crescent formation. Renal disease was treated with intravenous (i.v.) cyclophosphamide and oral prednisone. Despite maintenance immunosuppresion with oral cyclophosphamide, her renal disease progressed. In September 2001, she started haemodialysis while her mother completed her evaluation as a living-related kidney donor. At this time, she was clinically and serologically in remission and all immunosuppresion had been discontinued 4 months earlier.

One week after starting dialysis, she presented with purpura of her tongue and buccal mucosa. No neurological symptoms or fever were noted. She had thrombocytopenia (platelet count $54 \times 10^9/l$; normal $150–400 \times 10^9/l$) and anaemia (haemoglobin $8.4 \text{ g/dl}$; normal $13–17 \text{ g/dl}$) with an elevated level of lactate dehydrogenase (LDH) of $587 \text{ IU/l}$ (normal $100–225 \text{ IU/l}$), reduced haptoglobin, negative Coomb's test, schistocytes on a peripheral blood smear and normal coagulation tests including fibrinogen level. The clinical and laboratory findings were felt to be consistent with TMA. Further investigation revealed a negative anti-DNA antibody, normal levels of C3 and C4, negative anticardiolipin antibody test, negative heparin-induced thrombocytopenia assay and negative cytomegalovirus immediate early antigen test. There was no preceding diarrhoeal illness and no family history of TMA or history of exposure to drugs associated with the development of TMA, including oestrogens. The clinical diagnosis was felt to be acquired idiopathic TTP variant of TMA. She was started on prednisone at 1 mg/kg/day, which resulted in rapid resolution of purpura. Platelet count and haemoglobin improved but remained below the normal range. LDH also remained elevated in the range of $400–500 \text{ IU/l}$ consistent with ongoing TMA. Three months after developing TMA, azathioprine was started and, despite some improvement in platelet...
The pathogenesis of TMA involves increased expression of unusually large von Willebrand factor (ULvWF) multimers on endothelial cells, decreased breakdown of these multimers and/or increased secretion of these multimers into the circulation [3]. In TTP, this situation arises either as a result of an inherited deficiency of the metalloprotease ADAMTS13 that normally cleaves the ULvWF multimers, or as a result of circulating IgG directed against ADAMTS13 [3]. These mechanisms explain the reduced ADAMTS13 activity in the familial and acquired idiopathic variants of TTP, respectively. In both cases, ULvWF multimers can persist on the surface of endothelial cells and in the systemic circulation and cause platelet aggregation by binding to the platelet glycoprotein Ib/IX/V receptor much more efficiently than ‘normalized’ multimers. This results in systemic platelet thrombi. In contrast, ADAMTS13 activity is normal in HUS, another variant of TMA, and the mechanism of TMA in this setting is thought to be due to locally increased expression and/or release of ULvWF multimers by endothelial cells in response to endothelial cell injury [3]. Shiga toxin may cause endothelial cell injury in diarrhoea-associated HUS, in which case endothelial cells expressing the receptor for this toxin, primarily in the renal and cerebral circulations, are the sites of injury. Endothelial cell injury in this case may also cause local activation of the coagulation cascade and initiate a local inflammatory reaction involving tissue invasion by neutrophils and monocytes. Consequently this mechanism results in platelet-fibrin thrombi and an inflammatory reaction that is usually localized to the renal circulation. A similar clinical picture may be seen in the familial variants of HUS in which the endothelial cell injury may be due to a deficiency in factor H. Factor H regulates the activity of the alternative complement pathway, and deficiency may lead to increased C3 convertase activity that potentiates auto-antibody- and/or immune complex-mediated glomerular injury [3]. In the autosomal recessive form of HUS, factor H levels and serum C3 levels are both reduced. The autosomal dominant form of HUS is due to a defective factor H protein, and the levels of both factor H and serum C3 are typically normal. The mechanisms of TMA in association with transplantation are multifactorial. Although one case of TMA post-renal transplant associated with reduced ADAMTS13 has been described, it appears that most transplant-related TMA is unrelated to reduced ADAMTS13 activity [4,5].

TMA has been associated with autoimmune disease, most notably SLE. A review of the literature includes >40 cases of TMA related to SLE [6]. Diagnosis of TMA in the setting of active SLE may be difficult, as there is considerable overlap in disease symptoms, including the haematological, renal and neurological abnormalities. Although TMA in the setting of active SLE is well documented, most cases of TMA in patients with SLE occur when the disease appears to be quiescent [6]. The overall incidence of TTP
in SLE patients is unclear, although it has been reported to be as low as 0.5% [6]. There are several potential mechanisms linking SLE and TMA, such as immune-mediated endothelial cell injury in association with antiphospholipid antibody and/or acquired ADAMTS13 deficiency [7]. Reduced ADAMTS13 activity may be seen in 50% of patients with SLE [8]. Antiphospholipid antibodies and reduced ADAMTS13 activity may co-exist in patients with SLE and TMA, in which case the risk of thrombotic episodes appears to be increased [2].

In the case presented here, the lack of a family history, lack of a history of exposure to infectious agents or drugs known to be associated with TMA, normal C3 levels and negative antiphospholipid antibody at the onset of TMA were consistent with the clinical diagnosis of acquired idiopathic TTP. A review of the literature did not reveal any cases of TMA associated with dialysis. We did not formally measure the ADAMTS13 level as this assay is not available locally. It was also felt that this result would not alter the therapeutic plan, which was a trial of immunosuppression using the haematological indices to gauge success. Therapeutic plasma exchange was not performed in this case as the disease was mild and initially improved with corticosteroids alone. Cognisant of the likely underlying pathogenesis of TMA in this case (IgG antibody to ADAMTS13), we attempted to treat TMA with immunosuppression that would reduce both T- and B-cell activity. Having observed some success with this strategy, particularly when using MMF, it was felt that TMA was more likely to improve with increased immunosuppression following transplantation rather than be exacerbated by transplantation and the use of a calcineurin inhibitor. This indeed turned out to be the case.

In the setting of renal transplantation, TMA has been reported to occur in between 3 and 14% of patients and is associated with an increased risk of early graft loss [9]. A recent cohort study determined that patients transplanted secondarily to HUS had a 29% incidence of recurrent TMA, while the incidence of TMA in patients transplanted secondarily to other causes was only 0.8% [10]. Therefore, TMA in the setting of renal transplantation may present a therapeutic dilemma. Some causes of TMA may be induced by immunosuppressive agents, either directly in the case of calcineurin inhibitor-induced TMA, or indirectly in the case of TMA associated with viral infections, e.g. cytomegalovirus infection [1]. On the other hand TMA in which the mechanism is immunological, e.g. acute rejection or, as was the case here, acquired idiopathic TTP, may improve with increased doses of immunosuppression [11].

This case serves to highlight the importance of understanding and addressing the underlying mechanism in patients with TMA, particularly in the setting of renal transplantation. While the development of TMA represents a risk to allograft survival when it occurs following renal transplantation, some cases of TMA, particularly those associated with reduced levels of ADAMTS13, such as acquired idiopathic TTP, may improve following renal transplantation.

Conflict of interest statement. None declared.

References


Received for publication: 15.4.04
Accepted in revised form: 18.10.04