Antiphospholipid syndrome in renal transplantation: case report and review of the literature

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Abstract

Antiphospholipid syndrome (APS) may occur in isolation or in association with systemic lupus erythematosus (SLE), with the potential to cause renal failure via several distinct pathologies. Renal transplantation in
the presence of APS carries a risk of early graft loss from arterial or venous thrombosis, or thrombotic microangiopathy (TMA). Whilst perioperative anticoagulation reduces the risk of large vessel thrombosis, it may result in significant haemorrhage, and its efficacy in preventing post-transplant TMA is uncertain. Here, we report a patient with end stage kidney disease (ESKD) due to lupus nephritis and APS, in whom allograft TMA developed soon after transplantation despite anticoagulation. TMA resolved with plasmapheresis-based therapy albeit with some irreversible graft damage and renal impairment. We discuss the differential diagnosis of post-transplant TMA, and current treatment options.

**Introduction**

Antiphospholipid syndrome (APS) is an acquired disorder in which autoantibodies directed against phospholipid-binding proteins are associated with vascular thrombosis and/or pregnancy-associated morbidity\(^1\). APS may occur in isolation, or in association with systemic lupus erythematosus (SLE) or other autoimmune conditions, where it is sometimes referred to as ‘secondary’. Amongst the clinical and laboratory criteria for the diagnosis of APS\(^2, 3\) is the presence of antiphospholipid (aPL) antibodies, demonstrated through prolongation of phospholipid-dependent clotting time *in vitro* (‘lupus anticoagulant’, LA) or by specific enzyme-linked immunosorbent assay (ELISA) for high-titre anti-\(\beta_2\)-glycoprotein-1 (anti-\(\beta_2\)-GP1) or anticardiolipin (aCL) antibodies. APS-related thrombotic events may be venous, arterial or both\(^4\). Venous thrombosis most commonly results in lower limb deep venous thrombosis (DVT) and/or pulmonary embolism (PE), whereas arterial
thrombosis typically involves the cerebral circulation. APS may also cause thrombotic microangiopathy (TMA), with biopsy of affected organs revealing microvascular endothelial injury, intimal expansion and fibrin deposition culminating in microvascular thrombosis\(^5\). Occasionally TMA is the only manifestation of APS, and it remains unclear which factors in patients with APS predispose to TMA rather than macrovascular thrombosis\(^6\). In ‘catastrophic’ antiphospholipid syndrome (CAPS), TMA involving the kidneys, lungs, brain and other organs leads to acute multiorgan failure\(^7\). CAPS occurs in less than 1% of patients with APS, but in nearly half these cases it is the first manifestation of APS\(^8\). Hence awareness of CAPS is important, with one series reporting CAPS-associated mortality of 44%\(^8\). Thrombocytopenia and microangiopathic haemolytic anaemia (MAHA) are often absent\(^8\).

**Renal manifestations of APS**

APS may cause renal disease through TMA or large vessel thrombosis (Table 1)\(^9\). APS-related renal TMA affects the glomerular tuft and intrarenal vessels and may present with hypertension, haematuria, proteinuria and renal failure. It was originally described in patients with lupus nephritis\(^10\), later as a complication of pregnancy in a cohort of women, some of whom had SLE\(^11\). It may also form a part of systemic TMA as seen in CAPS\(^12, 13\). Establishing APS as the cause of renal TMA requires confirmation of persistent aPL antibody positivity and exclusion of alternative or additional causes of TMA. APS-associated nephropathy (APSN) now includes the acute lesion of TMA and/or chronic vascular changes: fibrous intimal hyperplasia, arterial or arteriolar occlusion, and focal cortical atrophy\(^14, 15\). Progression of APS-
related renal TMA to end stage kidney disease (ESKD) has been reported in a limited number of cases\textsuperscript{14, 16, 17}, while the renal prognosis of other components of APSN remains unclear\textsuperscript{14, 15, 18, 19}. Other renal lesions reported in association with APS include pre-eclampsia and glomerulonephritis (including not only lupus nephritis but also apparently non-SLE-associated glomerulonephritis\textsuperscript{20, 21}). Renal transplantation for APS patients with ESKD is associated with increased risk of systemic or allograft thrombosis or TMA\textsuperscript{22, 23}.

Here we present a transplant recipient with SLE and APS who developed acute allograft dysfunction associated with TMA, despite perioperative anticoagulation.

**Case Presentation**

A 26-year old non-smoking, nulliparous female presented with three weeks of wrist and finger pain, rash involving the face and chest, mouth ulcers, fevers, weight loss and lethargy. Blood pressure was 130/70 mmHg and dipstick urinalysis revealed protein (2+) and blood (3+). Urine microscopy showed dysmorphic erythrocytes (470×10\textsuperscript{6}/L) and leukocytes (150×10\textsuperscript{6}/L), with no bacterial growth, and 24-hour urinary protein excretion was 2.1 g/day. Full blood count, serum electrolytes and liver function tests were unremarkable. Immunology studies (*Table 3*) revealed a positive antinuclear antibody (ANA 1/640 titre in a homogeneous pattern) and anti-double-stranded DNA (dsDNA). Serum complement C3 and C4 were low. LA was positive with a prolonged activated partial thromboplastin time (APTT) that failed to correct with normal serum and confirmation of phospholipid dependence through platelet neutralization. aCL antibodies were strongly
positive (anti-β2-GP1 antibodies were not tested). Treatment for SLE was commenced with oral prednisolone and hydroxychloroquine. Subsequently the patient presented with a lower limb DVT, which combined with the persistently positive LA and high-titre aCL antibodies led to a diagnosis of APS. Anticoagulation was begun with low molecular weight heparin (LMWH) followed by warfarin, later replaced by aspirin.

The patient remained well without medical review for a number of years before returning with a systemic flare of SLE and renal involvement. Renal biopsy at this time revealed diffuse proliferative lupus nephritis (WHO class IV-g/a). Administration of high-dose steroids, mycophenolate mofetil, and rituximab was followed by a fall in the dsDNA titre and normalization of serum complement levels, but LA and aCL antibodies remained positive. Anaemia (haemoglobin 95 g/L) and thrombocytopenia (platelet count 65×10⁹/L) were present without red cell fragmentation. Renal function deteriorated leading to dialysis dependence, and a further biopsy showed quiescent lupus nephritis with superimposed TMA. Glomeruli were variably haemorrhagic or ischaemic, many showing fibrin thrombi at the vascular pole and red cell fragments in capillary lumina. Electron microscopy revealed markedly swollen endothelial cells and abundant subendothelial flocculant material. Assays for reduced ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 domains number 13) activity, anti-ADAMTS13 autoantibodies, complement regulatory gene mutations and anti-factor H autoantibodies were not performed. After plasmapheresis was commenced, the platelet count normalized but the patient remained dialysis-dependent. Unprovoked PE led to reinstitution of warfarin, with the international normalized ratio (INR)
targeted at 2.0-3.0. Echocardiography showed mild, global left ventricular systolic dysfunction, no thrombus and normal valves.

The patient underwent maintenance haemodialysis whilst remaining on mycophenolate sodium 360mg twice daily and prednisolone 5mg daily. Two years later, with SLE in clinical and laboratory remission, the patient was scheduled to receive a renal transplant from her father. LA remained positive, although aCL antibodies were within the normal range. Warfarin was ceased 3 days prior to transplantation, and the INR was 1.7 the day before surgery. A single dose of unfractionated heparin 5,000 U was administered subcutaneously the night before transplantation. Basiliximab induction was accompanied by prednisolone and tacrolimus, with mycophenolate sodium increased to 720mg twice daily. An implantation biopsy of the transplant kidney was normal with the exception of mild acute tubular injury, and global sclerosis of 2 out of 16 glomeruli. Despite postoperative hypotension, a MAG-3 isotopic renal scan showed normal perfusion and graft function was immediate, the serum creatinine falling to 130 μmol/L by postoperative day 2. On day 1, subcutaneous LMWH (enoxaparin) 60 mg daily was commenced (just over 1mg/kg/day). Oliguria developed on day 4, the creatinine rising to 360 μmol/L, accompanied by a normocytic, normochromic anaemia (haemoglobin nadir 39 g/L). Red cell fragmentation was absent and the platelet count remained normal, but the serum lactate dehydrogenase (LDH) was 1,337 IU/L (reference range 210-420). 12-hour ‘trough’ plasma tacrolimus levels were between 6 and 10 ng/mL. Serial ultrasounds showed an unchanging collection adjacent to the transplant kidney thought to represent a haematoma. Repeat nuclear scanning on day 5 showed impaired transplant function.
perfusion, with multiple punctate defects (Figure 1). A presumptive diagnosis of recurrent APS and allograft TMA prompted daily plasmapheresis using fresh frozen plasma (FFP), and intravenous methylprednisolone, while tacrolimus was withheld to minimize exposure to potential endothelial toxin. A transplant biopsy on day 6 confirmed glomerular and arteriolar TMA (Figure 2) with patchy infarction and no evidence of rejection (peritubular capillary C4d staining negative). No donor-specific anti-HLA antibodies (DSAb) were detected using the Luminex™ solid phase assay, and the cytotoxic crossmatch remained negative. Mycophenolate and prednisolone were continued with intermittent intravenous immunoglobulin (IVlg) 0.5mg/kg to compensate for the withdrawal of calcineurin inhibition. The patient's SLE remained clinically and serologically quiescent, and there was no other organ dysfunction to suggest CAPS, nor any evidence of infection. LA remained positive with normal aCL titres throughout the post-transplant period (other results in Figure 3).

For the remainder of the first month, anticoagulation consisted of intermittent, reduced-dose LMWH targeting subtherapeutic anti-factor Xa levels. At one month, therapeutic anticoagulation was resumed with warfarin, targeting an INR of 2.0-3.0, and plasmapheresis was weaned. Tacrolimus was reintroduced targeting serum trough levels of 3 to 5 ng/mL. Renal function gradually improved, with creatinine 170 μmol/L at 2 months post-transplant, and resolution of perfusion defects on nuclear scanning. Biopsies at three and eight weeks showed focal areas of infarction affecting up to 25% of the cortex but no thrombotic features in viable glomeruli. Renal function has
remained stable over the ensuing 4½ years.

**Discussion**

Lupus nephritis remains a significant cause of ESKD accounting for approximately 1% of patients commencing renal replacement therapy each year in Australia and New Zealand. TMA in patients with SLE is usually associated with lupus nephritis and/or serologic evidence of APS. This patient, who first presented with renal and systemic involvement from SLE, was subsequently diagnosed with APS in the setting of recurrent DVT/PE, with serial testing positive for LA and high-titre aCL antibodies. It appears that both diffuse proliferative nephritis and the subsequent APS-related renal TMA contributed to this patient's rapid progression to ESKD.

Post-transplant TMA has numerous potential causes (Table 2) and sometimes occurs without thrombocytopenia or MAHA. The most common causes include antibody-mediated rejection (AbMR), calcineurin inhibitor (CNI) toxicity and recurrent or de novo atypical haemolytic uraemic syndrome (aHUS). When acute allograft dysfunction developed in this patient, a transplant biopsy revealed TMA in the absence of AbMR. LA was positive, while the unusual scintigraphic appearance suggested APS-mediated focal renal infarction, as confirmed histologically. Previous reports of APS-related allograft TMA include recipients with established APS but no pre-transplant history of TMA, LA-positive recipients in whom native APSN was the only prior manifestation of disease, and LA-positive patients with no previous APS-related clinical events. Allograft TMA with elevated aCL antibody titres...
has also been reported in the setting of untreated hepatitis C virus (HCV) infection without prior evidence of APS.\textsuperscript{35}

Testing for aHUS and thrombotic thrombocytopenic purpura (TTP) was not performed in this patient. aHUS is a rare but increasingly recognized condition causing renal-predominant TMA and ESKD.\textsuperscript{36} Acute mortality is as high as 25%, depending on the genetic or acquired abnormalities in regulation of the alternative pathway of complement (identified in ~60% of aHUS cases).\textsuperscript{37} In transplant recipients with an uncharacterized history of TMA as a cause of ESKD, it is important to consider the possibility of aHUS as it carries a high risk of post-transplant recurrence and graft loss.\textsuperscript{38} Suspicion may be raised by an unexplained rise in LDH in an otherwise stable dialysis patient. In this case, the pre-existing diagnoses of SLE and APS appear to exclude aHUS (http://rarerenal.org).\textsuperscript{37} Although low serum C3 (usually without low serum C4) is a common finding in aHUS, in this patient reduced serum levels of both C3 and C4 prior to transplantation could be a feature of SLE\textsuperscript{39} or APS\textsuperscript{6, 40}. Progressive renal disease is not typical of acquired TTP, which in patients with APS\textsuperscript{42-44} or SLE\textsuperscript{45, 46} (including lupus nephritis\textsuperscript{47}) is generally characterized by absence of renal TMA. However, post-renal transplant TMA with severely reduced (<10%) ADAMTS13 activity has been reported in non-SLE/APS recipients\textsuperscript{48-50}, including with allograft failure\textsuperscript{48}. Rare congenital TTP may present with renal failure in adulthood\textsuperscript{37}, although progressive renal disease (and recurrence post-transplantation\textsuperscript{51, 52}) mainly follow a paediatric diagnosis.
Environmental triggers are identified in around half of CAPS patients, and several factors present at the time of transplantation may contribute to the onset of APS-related allograft TMA. In this patient, TMA both in the native kidneys and post-transplantation followed cessation of warfarin, consistent with reports in CAPS. Abrupt withdrawal of warfarin in such patients can increase synthesis of fibrin and thrombin with transient rebound hypercoagulability. Endothelial activation due to surgery is another major precipitant of TMA, reported as second only to infection in triggering CAPS.

Thus the combination of surgery, transplant ischaemia-reperfusion injury, alloimmunity and exposure to CNI may all have contributed to endothelial activation and concomitant activation of complement and coagulation, culminating in TMA.

Therapeutic anticoagulation is recommended in all APS patients with a history of DVT/PE or arterial thrombosis. Whilst this includes perioperative anticoagulation, the risks of postoperative haemorrhage must be evaluated in each case. In renal transplantation, reduced rates of graft thrombosis have been reported in APS recipients receiving perioperative heparin or (less commonly) warfarin. However, these studies also show a corresponding increase in major bleeding. In some cases this led to haemorrhagic graft loss, while in others anticoagulation had to be ceased with subsequent graft thrombosis. In one recent transplant series in which anticoagulation was variably used, both haemorrhagic and thrombotic complications were reported, including fatalities due to haemorrhage or CAPS. Importantly, perioperative anticoagulation does not appear to
eliminate the risk of allograft TMA\textsuperscript{30, 31, 33, 66, 67} and associated graft loss\textsuperscript{17}. In the current case, LMWH was started 24 hours post-operatively at a reduced dose. After renal failure developed, LMWH was continued at subtherapeutic levels to minimize bleeding risk, particularly given concurrent plasmapheresis and the potential requirement for allograft biopsies. The perinephric haematoma seen on ultrasound underscores the risk of anticoagulation in the early post-transplant period.

Evidence for treatment of APS-related renal TMA is limited to case reports and retrospective series\textsuperscript{8, 68}. In APS-related allograft TMA (Table 4) plasmapheresis has been associated with a good response in two cases\textsuperscript{31, 69}, and may have contributed to partial renal recovery in a further two cases\textsuperscript{30, 67}. However, a patient in the HCV/aCL transplant series died of multiorgan infarction despite plasmapheresis\textsuperscript{35}. In the current case, TMA resolved following prompt intervention with daily plasmapheresis, IVIg and high dose steroids, before eventual reinstitution of warfarin. In CAPS, it is postulated that plasmapheresis removes pathogenic aPL antibodies and other prothrombotic factors\textsuperscript{70}. FFP is generally recommended as replacement fluid\textsuperscript{71}, although the potential for procoagulant factors in FFP to exacerbate CAPS has led some to suggest albumin as the replacement fluid\textsuperscript{68, 72}. FFP was used in this case to minimize the risk of bleeding from concomitant anticoagulation. In a previous case report, perioperative unfractionated heparin and plasmapheresis (with unspecified replacement fluid) was associated with supratherapeutic anticoagulation and retroperitoneal haemorrhage\textsuperscript{73}.
Evidence from animal models suggests a role for complement inhibition at the C5 level in the treatment of APS. Eculizumab is a monoclonal antibody blocking C5 activation approved for use in aHUS (including in transplantation). Eculizumab has been associated with successful prevention and treatment of AbMR and post-transplant APS-related TMA; the latter includes cases where APS-related allograft TMA was unresponsive to anticoagulation and plasmapheresis, but resolved after the addition of eculizumab. A phase 2 clinical trial is investigating whether eculizumab administered in the course of renal transplantation is beneficial in recipients with a pre-transplant history of CAPS (NCT01029587). Finally, use of rituximab has been reported in conjunction with other therapies in patients with APS and renal-limited TMA, CAPS with renal involvement, and previous CAPS undergoing renal transplantation.

**Conclusions**

Renal transplantation in patients with APS may be associated with macrovascular thrombosis or TMA. Consideration should be given to the range of available therapies to address both the large vessel occlusive and microangiopathic manifestations. Based on current evidence, this includes anticoagulation in conjunction with plasmapheresis (with or without IVIg) and/or eculizumab. Results of ongoing studies are awaited with interest.
Table 1. Renal manifestations of APS

<table>
<thead>
<tr>
<th>Renal manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renovascular hypertension</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
</tr>
<tr>
<td>Renal infarct</td>
</tr>
<tr>
<td>Renal vein thrombosis</td>
</tr>
<tr>
<td>Renal TMA/APSN</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Preeclampsia</td>
</tr>
<tr>
<td>ESKD</td>
</tr>
<tr>
<td>Renal allograft thrombosis/TMA</td>
</tr>
</tbody>
</table>
Table 2. Causes of allograft TMA following renal transplantation

<table>
<thead>
<tr>
<th>Cause</th>
<th>Diagnostic findings</th>
<th>Options for treatment/prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbMR</td>
<td>Peritubular capillary C4d positivity on graft biopsy</td>
<td>Plasmapheresis and/or IVlg, immunoadsorption, eculizumab&lt;sup&gt;77,78&lt;/sup&gt;</td>
</tr>
<tr>
<td>CNI toxicity</td>
<td>High CNI plasma levels</td>
<td>Dose reduction during acute episode&lt;sup&gt;56&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
| aHUS (recurrent or de novo) | Low serum/plasma C3 levels
Complement regulatory gene mutations
Anti-factor H autoantibodies | Eculizumab<sup>79,75</sup> otherwise plasmapheresis ± steroids/rituximab/immunosuppressives<sup>56</sup> |
| APS (or CAPS)       | Positive LA, high titre aCL and anti-β2GPI IgM/IgG                                   | Anticoagulation, plasmapheresis ± IVlg, rituximab, eculizumab<sup>56,67</sup>                   |
| TTP                 | Severely low ADAMTS13 levels
Anti-ADAMTS13 autoantibodies
ADAMTS13 gene mutation | Plasmapheresis, steroids, rituximab/immunosuppressives (plasma infusion for congenital TTP)<sup>37</sup> |
| Infection           | Clinical features and appropriate bacterial/viral studies                             | Surveillance/prophylaxis/treatment as per local protocols                                        |
| De novo carcinoma   | Clinical features and appropriate investigations                                     | Surveillance and treatment as per local protocols                                               |
| Recurrent scleroderma renal crisis | Clinical features                                                        | Antihypertensives (esp. angiotensin blockade)                                                   |
**Table 3.** Case presentation: results of immunological studies in the diagnosis of SLE

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear antibodies (ANA)</td>
<td>640</td>
<td>&lt;40</td>
<td>titre</td>
</tr>
<tr>
<td>Double stranded DNA (dsDNA)</td>
<td>440</td>
<td>&lt;4</td>
<td>IU/mL</td>
</tr>
<tr>
<td>Extractable nuclear antigens (ENA)</td>
<td>negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complement C3</td>
<td>0.7</td>
<td>0.9-2.0</td>
<td>mg/mL</td>
</tr>
<tr>
<td>Complement C4</td>
<td>0.12</td>
<td>0.15-0.45</td>
<td>mg/mL</td>
</tr>
<tr>
<td>Lupus anticoagulant (LA) panel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRVVT</td>
<td>2.02</td>
<td>0.50-1.29</td>
<td>ratio</td>
</tr>
<tr>
<td>DTPIT</td>
<td>2.22</td>
<td>0.50-1.29</td>
<td>ratio</td>
</tr>
<tr>
<td>APTT (patient)</td>
<td>68.8</td>
<td>25.0-37.0</td>
<td>seconds</td>
</tr>
<tr>
<td>APTT (control)</td>
<td>30.8</td>
<td>25.0-37.0</td>
<td>seconds</td>
</tr>
<tr>
<td>APTT (mixing)</td>
<td>47.8</td>
<td>25.0-37.0</td>
<td>seconds</td>
</tr>
<tr>
<td>Anticardiolipin (aCL) antibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM</td>
<td>16.1</td>
<td>0-5.0</td>
<td>units/mL</td>
</tr>
<tr>
<td>IgG</td>
<td>225.6</td>
<td>0-5.0</td>
<td>units/mL</td>
</tr>
</tbody>
</table>

**DRVVT** dilute Russell’s viper venom time; **DTPIT** dilute thromboplastin inhibition test; **IgM** and **IgG** immunoglobulins
<table>
<thead>
<tr>
<th>Report (year)</th>
<th>Anticoagulation</th>
<th>CNIs</th>
<th>Plasmapheresis</th>
<th>Eculizumab</th>
<th>Other</th>
<th>Outcome [creatinine μmol/L]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mondragón-Ramírez</td>
<td>✓†</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td></td>
<td>Graft loss, nephrectomy day 7</td>
</tr>
<tr>
<td>(1994)17</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Died at 4 months</td>
</tr>
<tr>
<td>Baid (1998)20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td></td>
<td>Allograft and multiorgan failure; died at 3 weeks</td>
</tr>
<tr>
<td>Patient 2</td>
<td>×</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td></td>
<td>Died at 3 months</td>
</tr>
<tr>
<td>Patient 3</td>
<td>×</td>
<td>✓</td>
<td>briefly withdrawn</td>
<td>×</td>
<td></td>
<td>Allograft failure; died at 21 months</td>
</tr>
<tr>
<td>Patient 4</td>
<td>×</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td></td>
<td>Died at 5 years</td>
</tr>
<tr>
<td>Patient 5</td>
<td>×</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td></td>
<td>[~160 at 5 years]</td>
</tr>
<tr>
<td>Chew (1999)20</td>
<td>✓†</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>CS, aspirin, PC</td>
<td>[440 at 4½ months]</td>
</tr>
<tr>
<td>Erkan (2002)29</td>
<td>✓†</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>CS, IVIg</td>
<td>[~88]</td>
</tr>
<tr>
<td>Ruffatti (2007)31</td>
<td>✓†</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>IVIg</td>
<td>[160 at 4 years]</td>
</tr>
<tr>
<td>Hadaya (2011)38</td>
<td>✓†</td>
<td>×§</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>[120 at 6 months]</td>
</tr>
<tr>
<td>Canaud (2013)33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>✓†</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>[~240 at 18 months]</td>
</tr>
<tr>
<td>Patient 2</td>
<td>✓†</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>[~150 at 12 months]</td>
</tr>
<tr>
<td>Patient 3</td>
<td>✓†</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>[~140 at 12 months]</td>
</tr>
<tr>
<td>Lonze (2014)37</td>
<td>✓†</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td></td>
<td>[~350 at discharge]; dialysis after 7 years; successful retransplantation</td>
</tr>
<tr>
<td>(Patient 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This report</td>
<td>✓†</td>
<td>briefly withdrawn</td>
<td>✓ (FFP)</td>
<td>×</td>
<td>CS, IVIg</td>
<td>[156 at 4½ years]</td>
</tr>
</tbody>
</table>
Notes to Table 4.

Where anticoagulation was started perioperatively (†), this was invariably continued after diagnosis of TMA.

Preoperative plasmapheresis (‡) or rituximab ($) were used in one case each.

CNIs formed a part of transplant immunosuppression in all cases except ($) and were withdrawn after TMA diagnosis in some cases as shown.

Other treatments were high dose corticosteroids (CS), IVIg, and in one case aspirin and prostacyclin (PC).

All transplant recipients in Baid (1998) had untreated HCV infection.
Figure 1. MAG-3 nuclear scan of transplant kidney in left iliac fossa, on postoperative day 5. Anterior image at 30 minutes shows normal renal pelvis facing outwards with minimal tracer uptake. Surrounding distribution of tracer should be uniform and smooth, but punctate defects are seen (arrows) at the outer surface of the kidney and in the upper pole. These represent focal areas of infarction.
**Figure 2.** Transplant renal biopsy on postoperative day 6 (magnification ×40). Silver Masson trichrome stain shows heterogeneity of glomerular lesions due to recurrent APS.

A: Unaffected glomerulus with patent arterioles.

B: Microthrombi within capillary loops.

C: Ischaemia resulting from afferent arteriolar thrombosis, with wrinkling and retraction of capillary loops.

D: Congestion resulting from efferent arteriolar thrombosis (seen at vascular pole).
Figure 3. Parameters of allograft TMA and response to treatment. Serum creatinine (μmol/L) and LDH (IU/L) are shown on the left x axis. Serum 12-hour trough tacrolimus levels are shown on the right x axis (the cutoff for detection is 1.2 ng/mL). Response to treatment, which included plasmapheresis and IVlg, is shown over an 8-week period along the y axis (commencing at renal transplantation on Day 0).
References


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47. Muscal E, Edwards RM, Kearney DL, Hicks JM, Myones BL, Teruya J. Thrombotic microangiopathic hemolytic anemia with reduction of ADAMTS13 activity:


