Abstract:
Thrombotic microangiopathy (TMA) is a histopathological term that is used to define glomerular, arteriolar and arterial lesions with patchy involvement. It is characterized by mesangiolysis, fibrin thrombi, splitting of capillary basement membrane and cortical necrosis. Two forms of post-transplant TMA are described namely recurrent disease and de novo TMA. TMA is a serious complication in renal transplant recipients that often leads to graft dysfunction. We present six renal transplant recipients who developed de novo TMA. Our cases were treated by interchanging the calcineurin inhibitors (CNI) and plasmapheresis in 2 cases. On follow up, 2 patients developed permanent graft dysfunction and become dialysis dependent. 
Keyword : clinical profile, de novo TMA and graft dysfunction.

RESULTS
Patients with graft dysfunction and biopsy evidence of thrombotic microangiopathy over 3 years were included in our study. A total of six cases of de novo thrombotic microangiopathy were included in our study. Clinical details of 6 cases are summarised as:
Evidence of microangiopathic haemolytic anaemia (raised serum lactate dehydrogenase, thrombocytopenia, fragmented red blood cells on peripheral smear) was present in only one patient (17%). Renal biopsy done in all patients revealed:
Fibrin thrombi – in glomerular capillaries in all 6 patients (100%). Fragmented rbc in glomeruli in 3 cases (50%). Interstitial fibrosis and tubular atrophy in 2 cases (33%).
Cytoplasmic vacuolation in 2 cases (33%). Arteriolar luminal hyaline change in 2 cases (33%). Two patients (33%) had associated hepatitis C virus infection, of them one had anticardiolipin antibodies (17%). Two patients (33%) had high trough levels of calcineurin inhibitor. Two patients had renal biopsy evidence of calcineurin inhibitor (33%). Two patients (33%) on tacrolimus were changed to cyclosporine, two patients (33%) on cyclosporine were changed to tacrolimus, for the remaining two patients (33%) the dosage of cyclosporine was reduced. Plasmapheresis and hemodialysis was given to two patients (33%) with severe graft dysfunction. On follow up, two patients (33%) became dialysis dependent.

DISCUSSION:
In the analysis of USRDS data, among the patients transplanted with TMA as an etiology, TMA recurred in 29.2% of cases and de novo TMA was reported in only 0.8% of cases (1)(2). In about 30% of cases TMA localizes only to the graft with no signs of hemolysis and thrombocytopenia. In these cases only a renal biopsy can allow a diagnosis (3).

CLASSIFICATION OF POST TRANSPLANT TMA

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Donor</th>
<th>Time of presentation</th>
<th>Peak s.creatinine</th>
<th>Immunosupression</th>
</tr>
</thead>
<tbody>
<tr>
<td>50/m</td>
<td>Live related</td>
<td>2 years</td>
<td>2.6 mg/dl</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>22/f</td>
<td>Live related</td>
<td>6 months</td>
<td>1.9 mg/dl</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>17/m</td>
<td>Live related</td>
<td>11 month</td>
<td>1.8 mg/dl</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>17/f</td>
<td>Live related</td>
<td>6 month</td>
<td>1.8 mg/dl</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>26/m</td>
<td>Deceased</td>
<td>20 days</td>
<td>6.1 mg/dl</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>38/f</td>
<td>Live related</td>
<td>8 months</td>
<td>2.1 mg/dl</td>
<td>Cyclosporine</td>
</tr>
</tbody>
</table>

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cyclosporine (CsA), the incidence of de novo TMA is 4–15% with 43% graft survival. De novo TMA has been documented in approximately 1% of patients receiving tacrolimus\(^3\). Vasoconstriction due to a reduction of both prostacyclin synthesis and prostacyclin to thromboxane A\(_2\) ratio, decreased generation of activated protein C, increased production and release of high molecular weight VWF multimer from endothelial cells, endothelial toxicity and its pro-thrombotic and antifibrinolytic activity, all enhance leukocyte adhesion to vascular endothelium, and release of thromboplastin from mononuclear cells. All these factors are proposed mechanism for CsA-induced TMA. Concomitant ischemia-reperfusion and its deleterious effect on endothelium, and higher dosage of CsA further augment the deleterious effects of CsA. Pre-glomerular constricting properties of both CsA and tacrolimus in turn result in increased vascular shear stress, which amplify the microangiopathic process\(^4\). Rarely, OKT3 has been associated with de novo post-transplant TMA, and recently, sirolimus (mammalian target of rapamycin –mTOR inhibitor) has been implicated as possibly contributing with increased complement activation, thrombin activity and increased TNF–alpha release being the proposed mechanisms. Renal ischemia by itself is an initiating event for development of TMA. Prolonged ischemia is a pro-apoptotic factor and endothelial cells acquire pro-coagulant properties upon activation of apoptosis\(^5\). After reperfusion, contact between apoptotic micro vascular endothelial cells and blood constituents, causes activation of platelets and occurrence of TMA alongside with acute tubular necrosis (ATN) during renal transplantation without significant independent association between human leukocyte antigen (HLA) mismatch significant independent association between human leukocyte antigen (HLA) mismatch and recipient sensitization\(^6\). 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\(^7\). Prognosis is more favourable when TMA occurs later in the post-transplant course or when it affects recipients of allografts from living donors\(^8\). 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\(^9\). Therapeutic guidelines for de novo TMA are not well defined. Complete withdrawal of the offending CNI is essential\(^{10}\), although not all patients respond\(^{11}\). In a few cases, reversal of TMA was obtained by switching from cyclosporin to tacrolimus\(^{12}\) or from tacrolimus to sirolimus\(^{13}\). 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\(^{14};\(^{15}\) and in other anecdotal cases.

**Figure 1:** FRAGMENTED RBCs (H&E)

**Figure 2:** FIBRIN THROMBI (TRICHOME STAIN)
REFERENCES:


