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Case Report

Successful outcome of tacrolimus-associated thrombotic microangiopathy in renal transplant recipient with plasmapharesis

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ABSTRACT

We report a case of a renal transplant recipient treated with tacrolimus, who developed Thrombotic microangiopathy (TMA). TMA is a well-documented, severe and acute adverse effect of tacrolimus that occurs after solid-organ transplant. He was managed with complete withdrawal of tacrolimus, increasing the dose of mycophenolate mofetil and plasmapharesis with fresh-frozen plasma as replacement fluid. This was resulted in normalization of renal functions. The remission was sustained during follow-up of 12 months.

1. Introduction

Thrombotic microangiopathy (TMA) is a syndrome of microangiopathic hemolytic anemia, thrombocytopenia, fever, neurologic deficits, renal dysfunction, and associated organ impairments.[1] Two forms of post-transplant TMA may be recognized viz recurrent TMA and de novo TMA.[2] Recurrent TMA may occur in patients with underlying cause of renal failure as atypical hemolytic uremic syndrome (HUS). Occurrence of de Novo TMA is rarer. Other factors including viral infections may be responsible of de novo TMA, but in most cases TMA is caused by drugs such as calcineurin inhibitors or mTOR inhibitors.[2,3] It is a well-recognized complication in renal transplant recipients, affecting 3–14% of patients treated with calcineurin inhibitors.[3] Development of TMA has also been documented in other solid organ transplantation, the majority of which is presumably associated with calcineurin inhibitors (CNI). The risk of TMA is probably higher with cyclosporine than tacrolimus.[3] The clinical manifestation of post-transplant TMA can be variable. Some patients may show the clinical and laboratory features of HUS/TTP, although milder than seen in non transplant patients.[4] Other patients may only manifest as progressive graft dysfunction.[5] Therapy of post transplants CNI induced TMA is quite variable and include reduction or discontinuation of CNI. There are a few case reports in which plasmapheresis along with fresh frozen plasma was used successfully in these patients.[6,7]

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Table 1 – Laboratory investigations of patient.

Parameters	Patient's values at baseline (normal values)	Patient's values at day 7
Hemoglobin (g/dl)	10.2 (12–18)	10.9
Platelets	154,000 (150,000–450,000/cumm)	112,000
Peripheral smear	Normocytic, normochromic and no schistocytes	Normocytic and normochromic
Urea (mg/dl)	76 (15–45)	22
Serum creatinine	3.3 (0.6–1.6)	1.2
Urine pH	5.5 (<5)	5.5
Sp. Gravity	1.030	1.030
Urine protein	+	+
Urine RBC	Nil	nil
Urine WBC	Nil	nil
24 h urinary protein (g/day)	0.18 g/day	0.16
Stool examination for 3 days	Negative for occult blood	
Tacrolimus trough level C0 (ng/ml)	15.1	8.2

We report a case of renal allograft recipient, who presented with only elevated serum creatinine. On renal biopsy he was found to have TMA. Patient was successfully treated with plasmapheresis and discontinuation of tacrolimus. Patient is doing well on follow up with normal renal function.

2. Case report

A 44 year male patient underwent live related renal transplantation one year back with mother as donor. He was admitted for evaluation of elevated serum creatinine, which was rising since past 6 weeks. At admission he had no history of fever, cough, sore throat, vomiting, diarrhea, edema, flank pain, gross hematuria, oliguria etc. Patient was diagnosed with CKD-ESRD about 2 years ago, with chronic interstitial nephritis as underlying etiology. He was on regular thrice weekly hemodialysis prior to the transplantation. There was no prior history suggestive of aHUS/TMA in the patient. He did not receive any induction therapy at transplantation and he was on triple immunosupression including tacrolimus, mycophenoate and prednisolone.

His serum creatinine came to normal (0.9 mg/dl) on third post operative day. His trough level of tacrolimus (T0) was 12.2 ng/ml on fourth post op day. He was discharged on seventh day and advised for regular follow up. First year following transplantation was uneventful. His serum creatinine was around 1.0–1.2 mg/dl during follow up. There was no major change in immunosuppressive medication during these periods except for usual change in doses according to T0 level of tacrolimus.

At admission, his physical examination revealed fine tremors were present in both hands, blood pressure was 160/100 mm Hg in supine position, and pallor was present. There was no rash, edema, icterus or lymphadenopathy. Fundoscopy showed early changes of hypertensive retinopathy. His systemic examination was otherwise unremarkable.

Laboratory investigations revealed serum creatinine of 3.3 mg/dl which had risen from a value of 1.2 mg/dl, 6 weeks ago. Hemoglobin was 10.2 g/dl and peripheral blood smear showed normocytic normochromic with no evidence of schistocytes. Total leukocytes count (TLC) was 8800/cumm, platelet count was 154,000/cumm, serum urea was elevated (76 mg/dl), random blood sugar was 152 mg/dl, liver function tests were normal. His tacrolimus trough level was 15.1 ng/ml. Urine examination was unremarkable. Ultrasonography of the abdomen was normal, renal doppler showed mild elevation of resistive index (RI) (Table 1).

Presuming an episode of acute rejection, patient was given three doses of pulse methyl prednisolone (500 mg each), however the serum creatinine did not improve. In view of persistently elevated serum creatinine, renal biopsy was done. His renal biopsy revealed isolated thrombotic microangiopathy, with no evidence of either cellular or humoral rejection. Stain for SV40 was negative. (Figs. 1 and 2). He was further evaluated to determine the cause of TMA. Plasma DNA PCR for cytomegalovirus, BK virus was negative. His C3/C4 levels were normal, other investigations like ANA, lupus anticoagulant and anticardiolipin antibodies were negative. There was no other explanation for his TMA, except for the elevated tacrolimus levels.

His tacrolimus was discontinued along with an increase in the dose of mycophenolate and steroids. Despite these

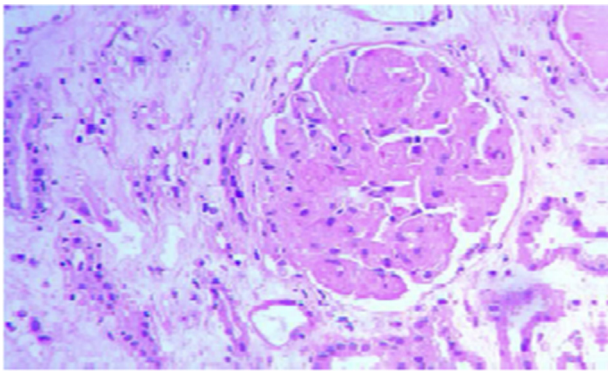

Fig. 1 – Glomerulus show mild/moderate increase in mesangial matrix and there is a prominent mesangiolysis with fluffy mesangial areas containing fragmented RBC's, and "bloodless" appearing capillaries, occluded by fibrin thrombi. There is no evidence of crescent formation or tuft necrosis and stain SV40 (aimed at detecting BK Polyoma virus) are negative in the visualized tubular epithelial cell nuclei.