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DE NOVO ACUTE HEMOLYTIC UREMIC SYNDROME IN A RENAL ALLOGRAFT RECIPIENT ASSOCIATED WITH SIROLIMUS ADMINISTRATION

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ABBREVIATIONS

CsA : Cyclosporine
SCr : Serum creatinine
HUS : Hemolytic uremic syndrome

KEY WORDS

renal transplantation, hemolytic uremic syndrome, sirolimus

ABSTRACT

De novo acute hemolytic uremic syndrome (HUS)/ thrombotic microangiopathy is known to occur within 1 month of renal transplantation with the use of calcineurin inhibitors like cyclosporine/ Tacrolimus/ secondary to infective episodes. However Sirolimus is a rare culprit of this event. We report here HUS in a renal allograft recipient 3.9 years post transplant associated with administration of Sirolimus.

CASE REPORT

A 45 years old man underwent renal transplantation in our institute on 21st November, 2001 with HLA mismatched wife's kidney for chronic glomerulonephritis induced end stage renal disease. He underwent short Ahmedabad tolerance induction protocol which included 1 donor derived bone marrow infusion with 1.2 x 10^8 nucleated cells /kg BW ($CD34^+$ count: 0.7 %) which was administered intra-marrow, in thymus, portal circulation and periphery.

He achieved early stable graft function and had been maintaining serum creatinine (SCr) around 1.2 mg % on immunosuppressive medication of Cyclosporine (CsA), 4 mg/ kg BW/ day, Azathioprine, 1mg/kg BW/ day and Prednisone, 10 mg/day. At 4 months post transplant, his SCr slowly increased to 1.5 mg %. Hence Azathioprine was replaced with mycofenolate mofetil (MMF), 2 gm/day. He had been maintaining stable graft function with SCr around 1.4 mg % till February 2004 on immunosuppressive medication of CsA, 2.5 mg/kg BW/ day, Prednisone, 10 mg/day and MMF, 2 gm/ day. He had rise in SCr of 2 mg % in July 2004 and biopsy although inadequate for definite diagnosis, revealed focal global sclerosis, focal tubular atrophy, periglomerular fibrosis, isometric vacuolization in tubules and segmental subintimal arteriolar hyalinosis

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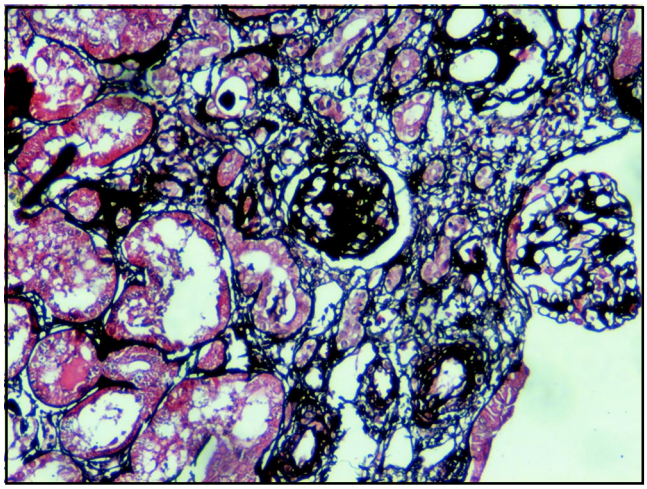

Figure 1 Low power view showing one sclerosed glomerulus and the other showing segmental mesangial prominence. Focal tubular atrophy is noted. Jone's silver methane amine stain, x 100

He presented on 1st August, 2005 with fever and cellulitis of right lower limb for which he was treated with antibiotics and he responded to the treatment clinically. However he again developed fever with right lower zone pulmonary infiltrates after 13 days (on 13th August, 2005). He did not respond to antifungal/ antibiotics/ anti-tuberculous regimes. Ultrasonography and Doppler of the graft were rather unremarkable. His SCr was raised to 6.59 mg %, urine albumin was +2, microscopy examination revealed 8-10 RBCs, 2-4 pus cells and 3-5 granular casts/ high power field. His hemoglobin had dropped to 6.9 gm/dL from 11 gm/dL, total white cell count was 3000/cmm., platelet count was 88,000/ cmm and absolute neutrophil count was 2200/cmm. No active hemolysis or parasites were noted. However serum lactic dehydrogenase was elevated to 910 units /L.

Renal biopsy performed at this time revealed focal global sclerosis in 30 % glomeruli and mesangiolysis with RBCs and platelet thrombi in ectatically dilated glomerular capillaries. Platelet thrombi were also noted in parietal cell of one glomerulus. There was focal parietal cell proliferation in one glomerulus. Tubules showed focal atrophy and isometric vacuolization as well as proteinaceous casts (figure 2A, B).

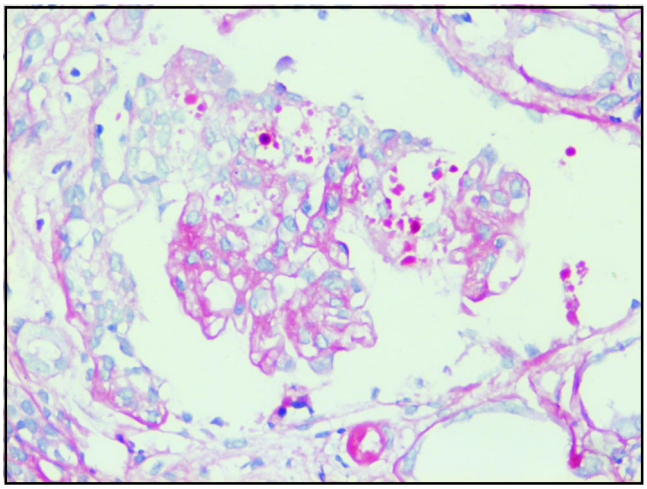

Figure 2A Glomerulus with mesangiolysis, ectatically dilated glomerular capillaries that are ruptured at places and contain RBCs and platelet thrombi, noted in parietal cell also in right lower end.Parietal cell hyperplasia at vascular pole (on left side). Small caliber artery showing segmental subintimal hyalinosis and tubule on right upper hand corner showing isometric vacuolization. Periodic acid Schiff stain, x 200

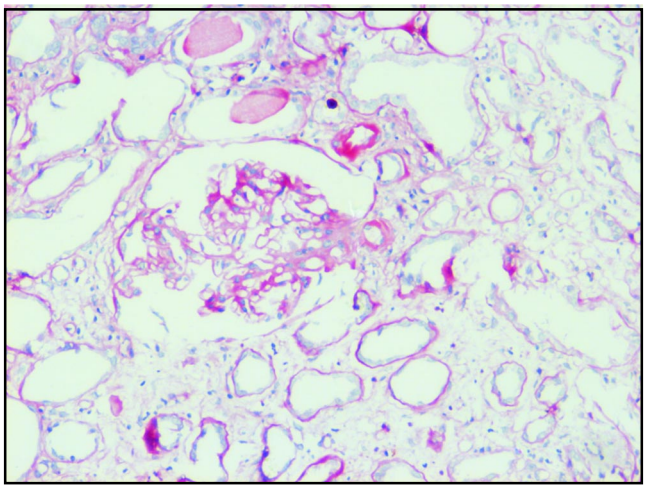

Figure 2B Low power view showing segmental subintimal hyalinosis of small caliber artery, focal tubular atrophy, interstitial edema and scant mononuclear cellular infiltration, glomerulus showing focal mesangiolysis, hyalinosis of capillary at afferent end and ectatically dilated capillaries. Periodic acid Schiff stain, x 100

Interstitium had scanty mononuclear cellular infiltrate with mild focal fibrosis. Medium caliber arteries were unremarkable. One small caliber artery showed subintimal fibrin deposition.

Acute humoral rejection was ruled out with negative C4d stain. We therefore reported it as de novo acute HUS associated with Sirolimus.

Following these findings, Sirolimus was discontinued and he was treated with plasmapheresis 3 times (with complete 2.4 liters exchange per each pheresis), Amoxycillin and levulinic acid, and immunosuppression was readjusted with MMF, 2 gm/day and Prednisone, 5 mg/ day. Now he has recovered with normal X ray chest, hematological profile and present SCr is 2.4 mg %.

DISCUSSION

HUS may occur in renal allograft recipients either as recurrence or as de novo or associated with acute humoral rejection. CsA or Tacrolimus are known to cause HUS in these patients [1,2]. As a rule, Sirolimus is the drug of choice for CsA induced HUS in renal allograft recipients [3]. We have reported CsA induced HUS in 7.7 % of our tolerance induction protocol patients and in 1.7 % of our controls with recommended CsA trough levels [4]. Although Sirolimus was not known to be nephrotoxic, recent reports have challenged this concept [5]. Sirolimus when used in early posttransplant period may cause delayed graft function by producing distal tubular injury. It may produce thrombotic microangiopathy when used with calcineurin inhibitors. However Sirolimus alone is not known to cause thrombotic microangiopathy/ HUS. Sirolimus is a potent immunosuppressant which acts by interfering with the intracellular signal transduction caused by binding of interleukin-2 to its receptor (m-TOR). It displays myelodepressive and hyperlipidemic side effects.

This patient developed acute on chronic CsA toxicity at 2 years and 7 months posttransplant and therefore had to be switched over to Sirolimus. He developed biopsy proven HUS after an infective episode and while on Sirolimus as the principal immunosuppressant. Infective episode in the form of pulmonary infiltrates could be considered as triggering factor. He had already recovered from cellulitis of lower limb hence that could not have been the contributing factor. However no management other than discontinuing of Sirolimus and plasmapheresis led to his recovery. The other interesting observation was that pulmonary lesions also recovered after discontinuing Sirolimus. Hence Sirolimus was associated with HUS although it may not be the initiating factor.

CONCLUSION

We are reporting the development of HUS associated with Sirolimus administration in renal allograft recipient, who recovered after its withdrawal.

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I feel that the greatest reward for

doing is the opportunity to do

more.

- James E. Salk