TRANSPLANT INTERNATIONAL

LETTER TO THE EDITORS

Eculizumab for the treatment of two recurrences of atypical hemolytic uremic syndrome in a kidney allograft

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Dear Sirs,

Atypical hemolytic uremic syndrome (aHUS) is a disorder of complement (C) dysregulation. In more than 50% of patients, mutations in complement factors H (CFH), membrane cofactor protein (MCP) and CFI are the underlying causes. Less likely, mutations in CFB, C3 [1] and Thrombomodulin (THBD) [2] are detected. Complements antibodies such as anti-CFH autoantibodies are found in 8–10% of patients [3]. Infection and drug-induced aHUS have been documented. Histologic changes are [4], manifested in the kidney as thrombotic microangiopathy (TMA). Recurrent aHUS after kidney transplantation (KT) is associated with high rate of allograft failure [5]. Eculizumab was found recently to be an effective therapy of aHUS. Here, we present a case of two recurrences of unclassified aHUS in a live donor kidney transplant (LDKT).

In 2004, a previously healthy 27-year-old woman developed acute renal failure and hypertension. Laboratory data showed platelets (plts) of 30 k/dl, serum creatinine (SCr) of 3.7 mg/dl, and haptoglobulin of <5.8 mg/dl. Two days later, SCr rose to 4.2 mg/dl, hemoglobin (Hg) fell to 9.2 g/dl, lactate dehydrogenase (LDH) 1665 μ/l, and a peripheral blood smear showed schistocytes. A diagnosis of thrombotic thrombocytopenic purpura (TTP)/HUS was initially made. No kidney biopsy was performed. The Plasma Exchanges (PE) and a high dose of corticosteroids were initiated along with hemodialysis (HD). She stabilized clinically and hematologic parameters improved, however, she continued on HD.

Two years later, she received a LDKT from her sister. Initial immunosuppression consisted of tacrolimus, mycophenolate mofetil (MMF), and prednisone. The kidney had prompt excellent function. Two months later, she developed thrombocytopenia, rising LDH, and schistocytes in a peripheral smear. Recurrent TTP/HUS was suspected, and treatment with PE was initiated along with switching FK (tacrolimus) to rapamycin. After 2 months SCr rose and renal biopsy showed focal segmental glomerlusclerosis (FSGS) and TMA. Several weeks later allograft function deteriorated further with worsening of thrombocytopenia; she started again on PE. Unfortunately her allograft failed shortly after that and restarted HD.

The patient was referred to our institution for second LDKT. After an extensive review of her medical history and work up included Factor H level, factor I level, von Willebrand factor and ADAMTS13 which were all normal, we concluded that the patient had unclassified aHUS; however, TTP was still a possible diagnosis. Genetic testing included CFI, CFH, CD46 (MCP), C3, THBD were obtained later and were normal.

Three years later, she underwent a second LDKT in our institution. Induction immunosuppression was with basiliximab, and maintenance consisted of cyclosporine, MMF, and prednisone. After 28 days of excellent allograft function, she developed proteinuria of 4–5 g/day; a renal biopsy showed mild nonspecific findings. Ten weeks later, SCr rose to 1.5 mg/dl, biopsy then showed TMA and FSGS (Fig. 1). A diagnosis of recurrent aHUS was confirmed at that point and patient started on PE; cyclosporine was discontinued and a dose of basiliximab was given for maintenance. Despite 8 PEs, renal function deteriorated; proteinuria increased to 11 g/day, SCr rose to 5.1 mg/dl, plts dropped to 29 k/dl, Hg fell to 6–7 g/dl, C3 was 61 mg/dl (normal 79–152), and total complement was 22 μ/ml (normal 31–66). Renal doppler showed no renal cortical blood flow. She developed oliguria with fluid overload and HD was initiated. At that point, the decision was made to start eculizumab and PE continued every other day for two more weeks. An induction dose of 900 mg Eculizumab was given followed by 600 mg after each PE and a maintenance bimonthly dose of 1200 mg. The patient made a steady progress, separated from HD and SCr stabilized at 1.8–2.0 mg/dl (Fig. 1). She continued to receive eculizumab bimonthly for 8 more months with SCr of 1.8 mg/dl and all of aHUS laboratory and clinical parameters were normal. During the 5 months after the discontinuation of eculizumab her laboratory values continued to be stable.

Five months after the discontinuation of eculizumab the patient acquired a pneumonia that resulted in a second recurrence of aHUS; SCr rose to 5 mg/dl, plts fell to

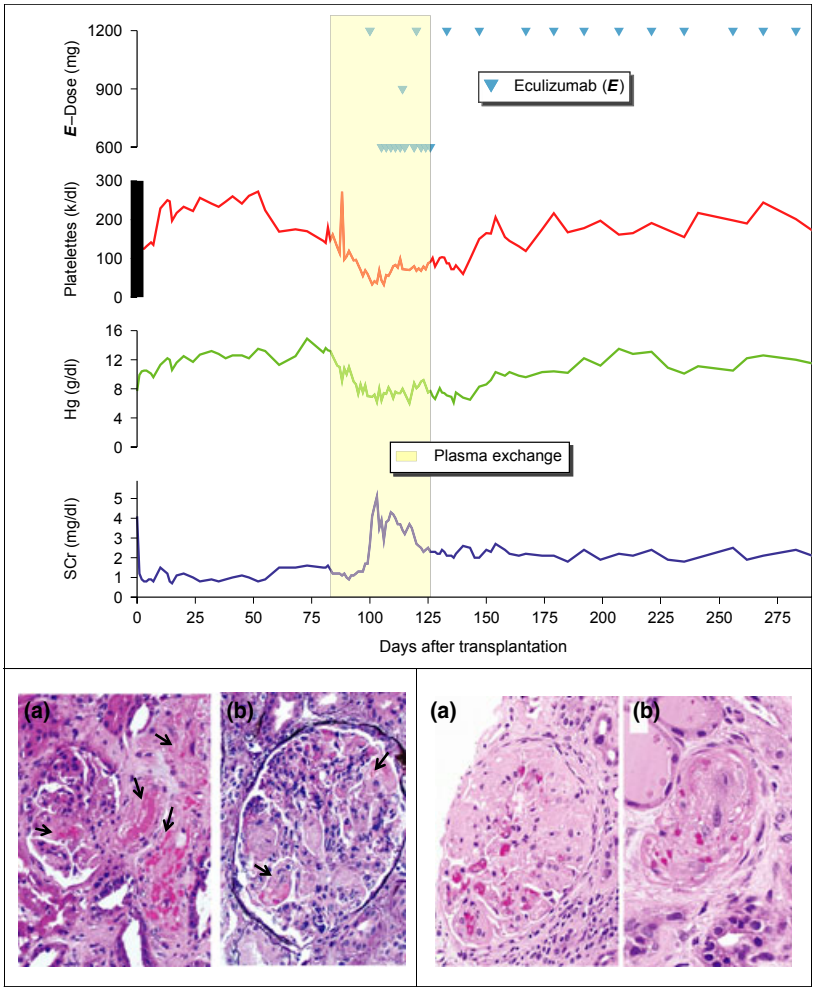

Figure 1 Trends in serum creatinine (SCr), hemoglobin (Hg), and platelets are shown in relation to the time of transplantation and treatment with plasma exchange and eculizumab during the first year after transplant. Biopsy taken after initiation of treatment shows evidence of thombotic microangiopathy, with arteriolar, and glomerular fibrin thrombi (a, arrows) and segmental double contours (b, arrows). Biopsy at 16 months post transplant, documenting recurrence of thrombotic microangiopathy. (a) Glomerular fragmented red blood cells and disruption of glomerular structure. (b) arteriolar occlusion with endothelial swelling and fragmented red blood cells in the vascular wall.

63 k/ml, and allograft biopsy showed acute and chronic TMA. Eculizumab was initiated promptly on the day of admission in a weekly dose of 900 mg, for 4 weeks; on week 5 was increased to 1200 mg to continue bimonthly; without PE. The SCr decreased to 3.2 mg/dl, plts and Hg improved. Unfortunately, after 2 weeks of stabilization, she developed severe acute tubular necrosis because of complications of an endovascular procedure resulted in rising in SCr although other aHUS laboratory parameters remained normal. The SCr increased to 4–5 mg/dl for the following 6 months and at 2 years mark after second LDKT, she placed back on HD and eculizumab was stopped.

We present a case of a patient with a very aggressive aHUS primary disease and rapid early recurrence resulted in first allograft loss within 6 months. A rapid aHUS recurrence developed after second LDKT and was recalcitrant to PE but responded to eculizumab that continued bimonthly until 1 year with full aHUS remission. Unfortunately, a second recurrence of aHUS developed in the setting of pneumonia but responded to eculizumab alone.

Eculizumab is a long acting humanized monoclonal antibody against C5 blocks the cleavage of C5 and inhibits its activation of the terminal complement system including the formation of membrane attack complex. Nürnberger *et al.* [6] reported a patient with aHUS secondary to CFHR1 gene mutation, which recurred after KT and failed to respond to PE. In a case report by Zimmerhackl *et al.* [7], a patient with CFH mutation aHUS received prophylactic therapy starting 2 days post KT with daily PE for 1 week, then ongoing treatment with eculizumab 600 mg every 2 weeks with no recurrence for 1 year. Davin *et al.* [8] reported using eculizumab successfully in a patient with a recurrence in third KT secondary to CFH mutation that failed to respond to PE. Growing data showed eculizumab to be effective in preventing aHUS recurrence [9].

In summary, our finding is consistent with several previous reports in which remission of aHUS occurred after eculizumab therapy.

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Conflicts of interest

The authors have no conflicts of interest to disclose. RAM has received a research grant from Alexion for a small clinical trial to study the efficacy of eculizumab in preventing catastrophic antiphospholipid antibody syndrome.

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