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BRIEF REPORT

Eculizumab induces long-term remission in recurrent post-transplant HUS associated with C3 gene mutation

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Abstract A 15-year-old male patient developed atypical hemolytic uremic syndrome (aHUS) at 16 months of age leading to end-stage renal disease. The family history was suggestive of autosomal dominant aHUS, and he was more recently found to have a C3 heterozygous gene mutation (*1835C>T* mutation in exon 14, which determines the amino-acidic substitution *R570W*) with no other complement abnormalities. He had two renal transplants, the first at 2.5 years, and the second at 8 years of age, but allograft dysfunction developed in both transplants leading to graft failure due to recurrent HUS at 5 years and 18 months post-transplantation respectively. At 15 years of age he received a third transplant from a deceased donor with pre-emptive plasmapheresis. He had immediate graft function and nadir serum creatinine was 1.3–1.4 mg/dl. Severe allograft dysfunction and hypertension developed 2 months after transplantation following influenza infection. Renal allograft biopsy showed thrombotic microangiopathy. He received plasmapheresis followed by eculizumab therapy. Allograft function returned to baseline 3 weeks after starting therapy, and post-treatment allograft biopsies showed improvement in thrombotic microangiopathy. He continues to receive eculizumab every 2 weeks with stable graft function 13 months after transplantation.

Keywords Atypical hemolytic uremic syndrome · Renal transplantation · Eculizumab · Pediatric · Plasma exchange · Complement

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Introduction

Atypical hemolytic uremic syndrome (aHUS) is a serious life-threatening disease leading to end-stage renal disease in up to 80% of affected individuals [1–4]. Depending on the underlying defect causing aHUS, post-transplant recurrence occurs in 30–100% of patients, leading to significant graft dysfunction, and graft loss in up to 60% of patients [1, 3, 5–9]. Genetic or acquired defects in complement regulation lead to endothelial cell activation, which activates platelets, resulting in the formation of platelet and fibrin thrombi, and deposition of C3 in the glomerular capillaries and renal arterioles [10, 11]. Complement defects that have been identified in patients with aHUS include acquired autoantibodies to complement factor H, genetic mutations in complement regulatory proteins, such as complement factor H (CFH), complement factor H-related proteins (CFHR), factor I (CFI), and membrane co-factor protein (MCP) or CD46, and genetic mutations of complement activators such as complement factor B (CFB) and complement C3, and thrombomodulin gene mutations leading to decreased factor I-mediated inactivation of C3b [6, 12–20].

Plasma infusion or exchange therapy is the first-line therapy in most patients with atypical aHUS [21]. Plasma

therapy has been used both for treatment and prophylaxis with variable success rates. Combined liver–kidney transplantation for patients with complement factor H or factor I deficiency or gene mutation is currently being evaluated, but is associated with higher mortality rate compared with kidney transplantation alone [22–25]. There is currently little information on the treatment of patients with aHUS associated with C3 gene mutation. Plasma therapy in such cases may temporarily correct the "gain-of-function" status and decrease complement activation by providing normal C3 complement. Alternatively, inhibiting the generation of the pro-inflammatory terminal complement component may achieve the same effect.

Eculizumab (Soliris®, Alexion Pharmaceuticals, Cheshire, CT, USA), a humanized monoclonal antibody that blocks complement C5 activation and prevents common terminal complement pathway activation is approved for treatment of paroxysmal nocturnal hemoglobinuria [26]. We describe the successful use of eculizumab in the treatment of recurrent aHUS in the third renal transplant of a 15-year-old patient with C3 gene mutation and two previous graft losses due to recurrent aHUS.

Case report

The initial course and details of the first transplant up to 30 months post-transplantation have been previously reported [2]; however, recurrence of HUS post-transplantation occurred after that report was published. Briefly, this patient developed end-stage renal disease because of aHUS at 16 months of age. The family history was significant for a paternal uncle, a paternal aunt, and the paternal grandmother, with aHUS leading to end-stage renal disease at 42, 19, and 34 years of age respectively. In addition, his paternal great grandfather died at 68 years of age with severe hypertension, uremia, and heart failure, severe anemia, thrombocytopenia, and thrombotic microangiopathy on renal biopsy. The diagnosis of autosomal dominant aHUS was made on clinical and family history grounds.

The patient initially received 9 days of peritoneal dialysis with improvement of renal function. However, he presented 2 weeks later with relapse, and became dialysis-dependent. He received a renal transplant from a 54-year-old deceased-donor at 2.5 years of age. Bilateral native nephrectomies were performed at the time of transplantation. Immunosuppression consisted of cyclosporine, azathioprine, and prednisone. Cyclosporine was later changed to tacrolimus more than 4 years after transplantation because of cyclosporine side effects. He developed a diarrheal illness a few months later, and was found to have severe hypertension and allograft dysfunction, and required emergency dialysis because of congestive heart failure and pulmonary edema. Allograft biopsy showed advanced thrombotic microangiopathy. He continued to have severe allograft dysfunction and progressed to end-stage renal disease.

He received a second transplant from his mother at 8 years of age, and was maintained on cyclosporine, sirolimus, and prednisone regimen and anti-hypertensive therapy. He developed a viral illness 2 months post-transplantation, and biopsy showed early thrombotic microangiopathy. Cyclosporine dose was lowered, with stabilization of graft function for almost 1 year. At 14 months post-transplantation he developed proteinuria, worsening hypertension, and allograft dysfunction. Cyclosporine dose was reduced with the return of serum creatinine from 1.5 mg/dl to a baseline of 0.9–1 mg/dl. One month later he developed a viral illness, and presented with recurrent HUS confirmed by biopsy. His allograft dysfunction worsened, and he ultimately lost the second graft 18 months post-transplantation, and required chronic dialysis therapy.

At 15 years of age he received a third renal transplant from a 45-year-old, zero-HLA-mismatched deceased donor. Serum complement C3 level was decreased and was within the range of 34–44 mg/dl prior to transplantation. He received plasma exchange therapy once pre-transplant, and then received 10 sessions over 17 days immediately following transplantation. Immunosuppression consisted of induction therapy with one dose of alemtuzumab 30 mg SQ given intra-operatively and a 4-day methylprednisolone taper, and maintenance consisted of prednisone, tacrolimus, and mycophenolate mofetil. His serum creatinine reached a nadir of 1.3 mg/dl 1 week after transplantation. Serum complement C3 level peaked at 68 mg/dl by the end of plasma exchange therapy, and then started to decline slowly afterwards. He was kept on a prophylactic dose of enoxaparin. Protocol surveillance biopsy at 1 month showed mild thickening of the media of the blood vessels, but no rejection or glomerular changes, and C4d staining was negative. At 8 weeks post-transplantation he developed a persistent dry cough, and his serum creatinine was above baseline with values of 1.6–1.8 mg/dl associated with mild anemia. A repeat biopsy showed only mild mesangial expansion and vascular medial thickening. Respiratory evaluation confirmed influenza A (H1N1) infection, and he was treated with a 5-day course of oseltamivir. Over the following week his respiratory complaints improved, but he became more hypertensive than his baseline, developed facial swelling, and had a noticeable decrease in urine output with fluid retention and a 1.5-kg weight gain. During this time, his serum creatinine increased to 1.9–2.2 mg/dl, and his urinalysis showed +2 proteinuria. Platelet count trended lower, but remained within normal range, and lactate dehydrogenase (LDH) trended higher, and his peripheral blood smear did not show schistocytes. Serum

C3 complement decreased to 23 mg/dl during this time period. Allograft biopsy at this time was negative for cell-mediated rejection and C4d, but revealed thrombotic microangiopathy with narrowing of the glomerular capillary lumina and thickening of the capillary loops, mesangial expansion, and focal C3 deposition in the arterioles (Fig. 1a, b). Electron microscopic examination showed separation of the basement membrane from the endothelium with a flocculent appearance.

Plasma exchange therapy was re-instituted, and he received a total of 10 sessions in 11 days with no major adverse events. Serum creatinine peaked at 2.9 mg/dl before the fourth treatment, and declined to 2.3 mg/dl by the 10th plasma exchange treatment. Urine output and blood pressure improved immediately after starting plasma exchange therapy. Follow-up biopsy after the 8th session of plasma exchange showed more patent glomerular capillaries and less prominent features of thrombotic microangiopathy, with no evidence of cell-mediated or humoral rejection. After confirming meningococcal immunization status, eculizumab (900 mg IV) was given after the 9th plasma exchange and the dose was repeated after the final plasma exchange treatment 2 days later. He received a total of four weekly doses of eculizumab (900 mg IV) for induction. By the fourth dose serum creatinine was down to 1.6 mg/dl. Eculizumab dosing was changed to 1,200 mg IV every 2 weeks thereafter with stable allograft function and normalization of blood pressure with only one antihypertensive agent. His maintenance immunosuppression remained the same, but with lower prednisone and tacrolimus dosing as per our institutional protocol. Tacrolimus trough levels were kept within the 4–5 ng/ml range.

Allograft biopsy at 6 months post-transplantation showed mild mesangial expansion with further improvement of thrombotic microangiopathy features, and the 12-month protocol biopsy showed patent capillary loops with no evidence of thrombotic microangiopathy (Fig. 1c).

Graft function continues to be stable 13 months after transplantation, with serum creatinine of 1.2 to 1.4 mg/dl, and stable hematological parameters. The serum C3 complement level remains very low, within the range 33 to 49 mg/dl. Figure 2 shows that graft function and hematological parameters correlated with treatment, as described above.

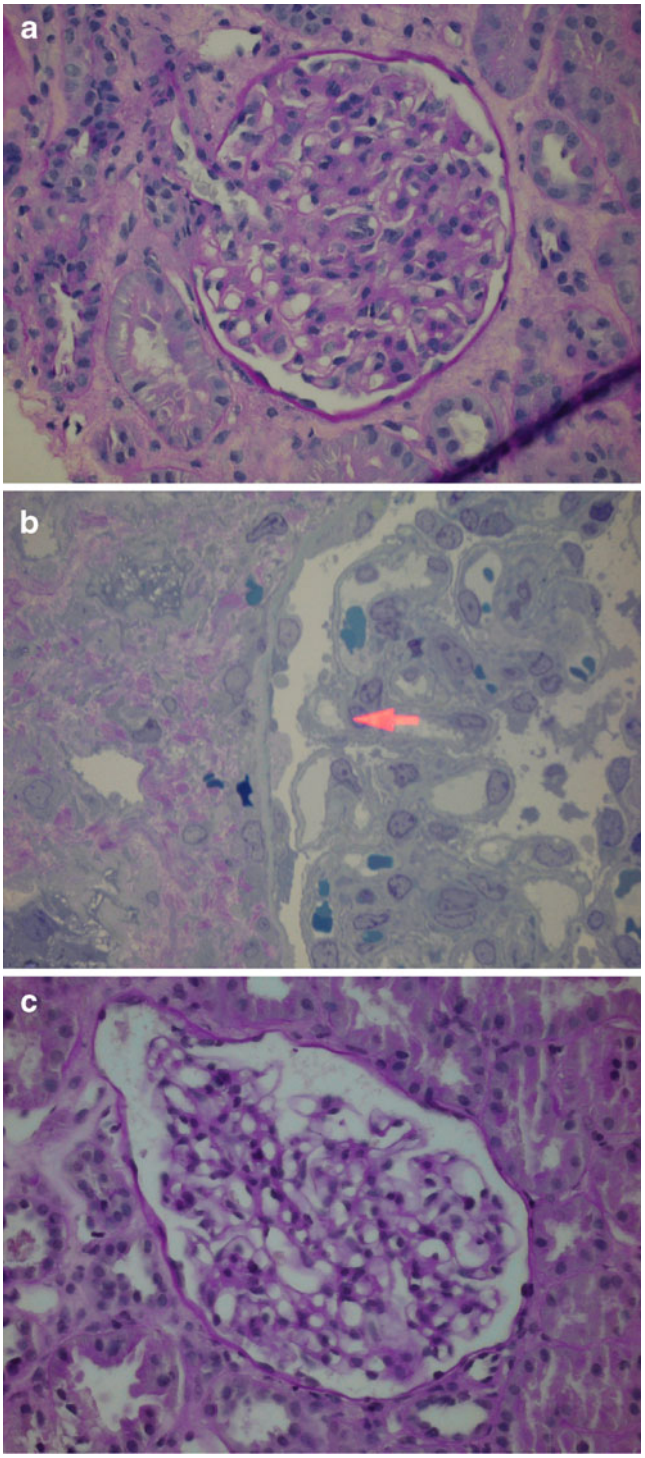

Fig. 1 Renal allograft biopsy during allograft dysfunction at **a**, **b** 2.5 months post-transplantation, and **c** while on eculizumab therapy. **a** ×400 magnification, Periodic acid Schiff (PAS)-stained section showing mesangial expansion and narrowing of the capillary lumina. **b** ×1,000 magnification of a toluidine blue-stained "thick section" with the *arrow* showing thickening of the glomerular capillaries and narrowing of the lumina due to microangiopathic changes. **c** ×400 magnification, PAS-stained section showing open capillary lumina at 12 months' post-transplantation

Discussion

Atypical HUS is a devastating disease that recurs in up to 60% of transplanted patients with a graft failure rate of about 80%. Atypical HUS associated with C3 gene mutations has been recently identified, and accounts for 5–10% of all cases of familial HUS [27]. The recurrence

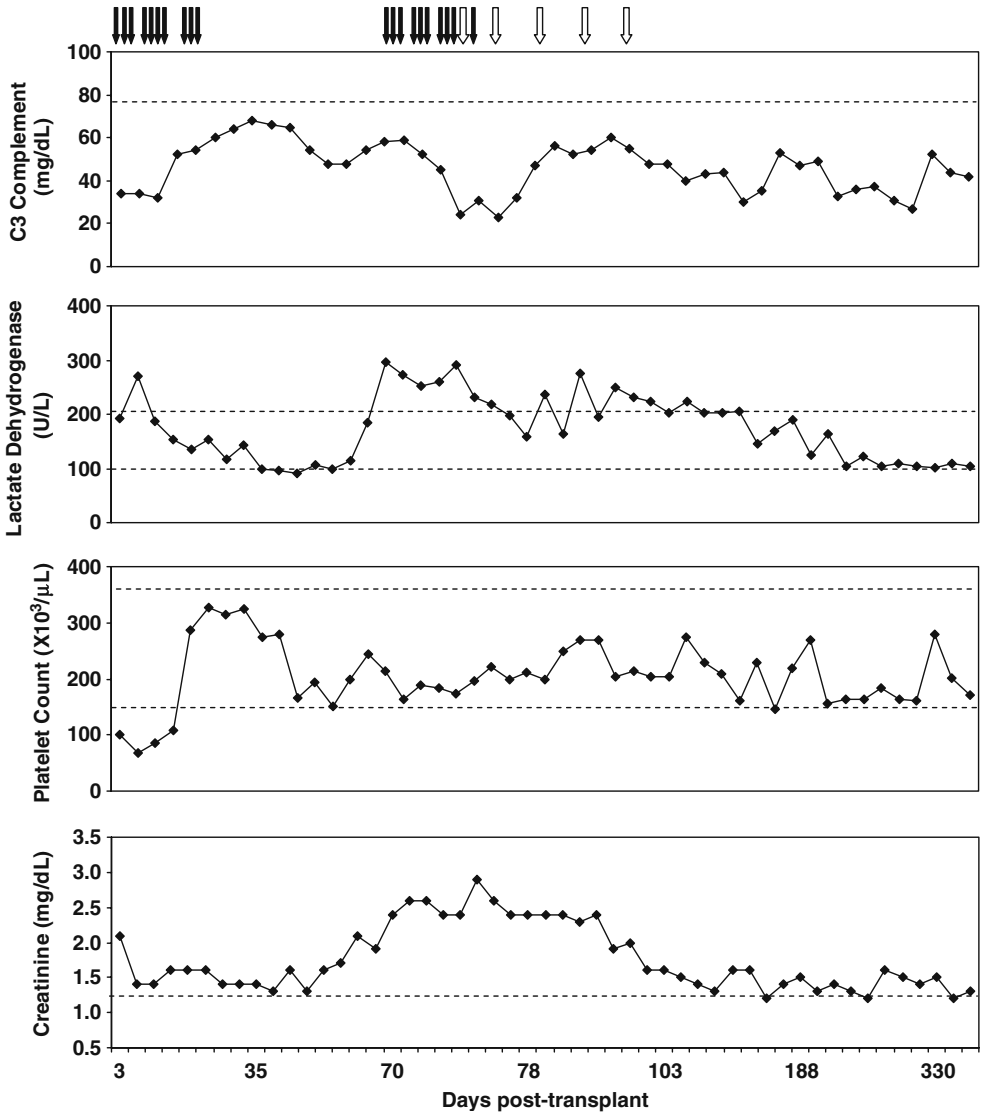

Fig. 2 Clinical parameters throughout the follow-up period. *Black arrows* represent plasma exchange therapy, and *open arrows* represent eculizumab induction therapy

rate varies with the underlying genetic defect, with a recurrence rate of up to 80% reported for patients with complement factor H mutation. The recurrence of aHUS associated with C3 gene mutation has been reported to be at 40–50% [16]. However, the recurrence rate may be under-reported as most reported patients were reported prior to identification of the C3 gene mutation in association with aHUS, and the follow-up of reported patients has been relatively short, including that of our patient. Prior to his most recent transplant, our patient and his uncle lost four transplants due to recurrent disease, while an aunt has a functioning graft more than 30 years after transplantation. This constitutes a recurrence rate of almost 70% in the first transplant, and 100% with subsequent transplants within this family. Most recurrences have been reported to occur within the first year after transplantation for most forms of aHUS, which highlights the importance of early therapy, or prophylactic therapy in the early phase after transplantation [28–30]. Our patient had two graft losses due to recurrence, and the recurrence after the second transplant occurred much earlier than that following the first transplant; therefore, we felt that he was at very high risk of recurrence and planned prophylactic plasma exchange therapy peri-operatively.

Plasma therapy has been used successfully to treat aHUS in the pre- and post-transplant setting [7, 21, 31–34]. Plasma exchange therapy is preferred over plasma infusion for initial treatment to allow removal of non-functional proteins and replacement with normal functional proteins that are present in sufficient amounts in fresh frozen plasma from healthy donors, and once the exact underlying defect is determined, tailored therapy can be planned more accurately. However, long-term use of plasma therapy is often required, which may be associated with significant side effects, requires vascular access, and may not be effective long term, in spite of initial response, possibly because of the development of autoantibodies to the various complement proteins [33].

Table 1 Summary of recent reports of eculizumab in patients with atypical hemolytic uremic syndrome (aHUS)

Reference	Age	Native or transplant	PE, number of sessions	Genetic defect	Peak serum creatinine before eculizumab (mg/dl)	Serum creatinine (mg/dl) and length of FU	Response
[39]	18 months	Native, 4th relapse	32	None identified	3	0.6 60 days	CR, sustained
[36]	37 years	Recurrence in second Tx	4	CFH mutation	1.5	1.1 12 months	CR, sustained
[35]	18 years	Native	21	None reported	3.5	6	PR, hematological recovery
[38]	42 years	Recurrence in 2nd Tx	60	C3 gene mutation	5	3.6 182 days	PR, hematological recovery
[41]	17 years	Native	27	None identified	7.8	9.2 200 days	PR, hematological recovery
[37]	17 years	Recurrence in 3rd Tx	Daily×1 week, then 1–2×/week for 10 months	CFH mutation	1.48	1.36 6 months	CR
[40]	34 years	Recurrence after 1st Tx	Every other day×5 months	Not reported	3.65	2.7	PR

Tx, transplant; PE, plasma exchange; CFH, complement factor H; FU, follow-up; CR, complete recovery; PR, partial recovery

Blocking complement activation provides an attractive alternative to plasma therapy for patients with aHUS associated with complement abnormalities. Eculizumab is a humanized monoclonal antibody that binds complement C5 and prevents generation of pro-thrombotic C5a and the formation of the terminal complement component C5b-9. It is approved for treatment of paroxysmal nocturnal hemoglobinuria [26], and has recently been successfully used for treatment of aHUS in native kidneys and for post-transplant recurrent aHUS. Hematological recovery with normalization of platelet count, LDH, and haptoglobin occurred in all reported patients within a short time, but renal recovery has been variable [35–41]. Published data suggest that renal recovery was best achieved when eculizumab therapy was instituted before significant renal dysfunction occurred and permanent renal damage set in [35, 38, 40, 41]. Furthermore, eculizumab seems to be effective in patients who were refractory to plasma therapy. Table 1 summarizes recently published reports of eculizumab therapy for native kidney and recurrent aHUS post-transplant.

In our patient, we believe recurrence was triggered by influenza A (H1N1) infection, which is a similar pattern to that seen with his previous two transplants, where recurrence was preceded by a viral illness. In addition, influenza A (H1N1) infection was recently reported to cause de novo aHUS in a 5-year-old patient [42]. Rapid deterioration in allograft function was only associated with modest elevation in LDH and mild depression in platelet count. Hematological abnormalities of thrombotic microangiopathy in renal allograft recipients have been reported to occur in only 23–54% of patients with post-transplant HUS [43]; therefore, we performed serial allograft biopsies to confirm the diagnosis and measure response to therapy more accurately in the absence of significant hemolysis or thrombocytopenia. Owing to this observation, we feel that early biopsy is crucial, especially in a patient with a known risk of recurrent HUS, in making an accurate and early diagnosis and starting therapy in a timely manner to prevent permanent renal damage. Intensive plasma exchange therapy resulted in improvement in allograft function, blood pressure, LDH, and C3 levels. Eculizumab therapy resulted in further improvement in graft function and return of serum creatinine to baseline with marked improvement in blood pressure, resolution of proteinuria, and a sustained remission 13 months following transplantation. Pharmacokinetic and pharmacodynamic studies obtained after the induction regimen of eculizumab confirmed appropriate drug levels (>35 μg/ml 24 h after the first dose and just before the second dose) and sufficient blockade of the C5a-9 component. Serum complement C3 levels continued to be low afterwards, which indicates ongoing activation of alternative complement pathway, and indirectly indicates effective complement blockade downstream from C3. Furthermore, stabilization of graft function and the avoidance of long-term use of plasma therapy allowed our patient to pursue education and physical activities, including competitive sports, with minimal disruption, and a reasonable quality of life.

Chatelet et al. recently reported recurrence of aHUS after the second transplant in a 42-year-old patient with C3 gene mutation, and the efficacy of eculizumab in halting hemolysis and thrombocytopenia and stabilization of renal

function [38]. Owing to the loss of two previous allografts to recurrent aHUS we elected to continue eculizumab therapy in our patient.

In summary, eculizumab is an effective and safe alternative treatment to plasma therapy in the treatment of recurrent aHUS. Although data from clinical trials are lacking, the overall success rate with eculizumab based on individual case reports, including our patient, is more than 50%, with no mortality reported thus far. Failure to respond seems to be associated with late initiation of therapy after significant renal damage has already occurred; therefore, early use of eculizumab may be critical to achieving a successful outcome. Zimmerhackl et al. have recently reported successful prophylactic therapy in a patient with a CFH mutation up to 1 year post-transplantation without the need for plasma therapy beyond the immediate peri-operative period [44]. Therefore, eculizumab therapy should be considered for patients with native or recurrent aHUS post-transplantation, and as a rescue therapy in patients in whom plasma therapy failed. The optimal regimen, length of treatment, and whether long-term treatment with eculizumab for prophylaxis compared with treatment for relapses need further study. Results from ongoing clinical trials should allow us to better evaluate the efficacy and safety of eculizumab in aHUS patients.

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