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Case Report

Perioperative usage of eculizumab for prevention of recurrent thrombotic microangiopathy and graft dysfunction in a live related renal transplant recipient with atypical hemolytic uremic syndrome

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ABSTRACT

This case report describes about the graft protective role of perioperative eculizumab in a kidney transplant recipient with long standing atypical hemolytic uremic syndrome (aHUS), on 19 years of dialysis. A 30 years old male patient with history of systemic hypertension, chronic kidney disease, End stage renal disease, aHUS and Thrombotic micro- angiopathy on maintenance hemodialysis since 19 years was admitted for live related renal transplant. Eculizumab was administered perioperatively for prevention of complement mediated thrombotic microangiopathy (TMA) recurrence and graft loss. Following the surgery, the patient's kidney function improved gradually, and his serum creatinine levels remained stable. There was no evidence of recurrent TMA. The patient was discharged with preserved graft function and advised regular follow up for monitoring of renal function and complement activity.

Keywords: Atypical hemolytic uremic syndrome, Thrombotic microangiopathy, Live related renal transplant, Eculizumab, Chronic kidney disease

INTRODUCTION

Thrombotic microangiopathy (TMA) represents a group of disorders characterized by endothelial injury, platelet aggregation and microvascular thrombosis resulting in microvascular hemolytic anemia, thrombocytopenia leading to organ dysfunction. The kidneys are most frequently affected and may range from acute kidney injury to irreversible renal damage.

HUS is a form of TMA, predominantly defined by the clinical trial of hemolytic anemia, thrombocytopenia and acute kidney injury. In particular, aHUS caused by genetic mutations or by autoantibodies against complement regulatory proteins, particularly factor H leading to dysregulation alternative complement pathway, associated with a high risk of disease recurrence and progression to CKD or ESRD and the need for long-term renal replacement therapy or kidney transplantation.

aHUS is an ultra-rare complement mediated TMA with a very low global incidence and prevalence. An annual incidence in the age group of 20 years or younger ranging from 0.26 to 0.45 per million population, and for all ages, 0.23 to 1.9 per million population per year.[1] Reliable population based epidemiological data is currently not available in India.

TMA results from endothelial injury leading to microvascular platelet-rich thrombi and is caused by severe ADAMTS13 deficiency as in thrombotic thrombocytopenic purpura, complement dysregulation as

in aHUS, Shiga toxin-mediated injury, drugs, autoimmune diseases, pregnancy, malignant hypertension, malignancy, or transplantation. The primary etiology of aHUS involves genetic abnormalities in complement regulatory proteins, most commonly loss-of-function mutations in CFH, and less frequently in complement factor I (CFI), Membrane Cofactor Protein (MCP/CD46), or thrombomodulin (THBD), which normally inhibit C3 convertase activity and protect endothelial surfaces. Gain-of-function mutations in complement components such as C3 or Factor B (CFB) can also enhance complement activation. In addition to genetic causes, 5-10% of cases are due to anti-factor H autoantibodies that impair regulatory function, often associated with CFHR1/CFHR3 gene deletions. The disease typically follows a "two-hit" mechanism, where a genetic or autoimmune predisposition ultimately leading to excessive formation of the membrane attack complex (C5b-9), endothelial damage, platelet activation, and microvascular thrombosis.

The diagnostic evaluation of aHUS is made by a combination of clinical, Laboratory findings and genetic evaluation. General clinical findings include pallor, fatigue, oliguria, edema and hypertension. Haematological findings include reduced hemoglobin and platelet count, elevated lactate dehydrogenase, decreased haptoglobin, indirect hyperbilirubinemia, presence of schistocytes (>1%) on peripheral blood smear with a negative direct Coombs test, evidence of renal impairment such as elevated serum creatinine, reduced estimated glomerular filtration rate, proteinuria, and hematuria. Complement testing may show low C3 with normal C4. Genetic testing for Mutations of CFH, CFI, MCP/CD46, C3, CFB, or THBD. Additionally, testing for anti-factor H autoantibodies is recommended, particularly in pediatric and young adult patients. MLPA (Multiplex Ligation-dependent probe amplification) is used to detect gene deletions or duplications in complement regulatory genes, especially CFH and CFHR genes, which can lead to complement pathway dysregulation.

The differential diagnosis of aHUS includes ADAMTS13-deficient thrombotic thrombocytopenic purpura, Shiga toxin–associated HUS, and secondary thrombotic microangiopathies.

The management of aHUS involves prompt initiation of complement inhibition with Eculizumab, a monoclonal antibody targeting C5. Supportive therapy includes blood pressure control, dialysis if required, and avoidance of unnecessary platelet transfusion. Meningococcal vaccination is mandatory prior to treatment. Early initiation significantly improves renal outcomes and reduces recurrence, particularly in transplant recipients.[2]

With orphan drug status in 2003 and approval by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) in 2007, eculizumab is the first drug targeting the complement system. Eculizumab is a humanized monoclonal antibody acts in aHUS by binding to complement protein C5 and prevents its cleavage into C5a and C5b, thereby inhibiting formation of the membrane attack complex (C5b-9) and reducing complement mediated endothelial injury and progression to end-stage renal disease.

As kidney transplantation does not correct the underlying complement dysregulation, patients with aHUS have a high risk of disease recurrence and graft loss after transplant. Before the availability of eculizumab, recurrence rates of aHUS after transplantation were as high as 50-80%. Eculizumab has two major roles in the transplant setting such as Prophylactic perioperative administration in high-risk patients reduces the risk of post-transplant TMA recurrence and for treatment of post-transplant TMA where early initiation of eculizumab can preserve graft function.

Eculizumab is administered intravenously and exhibits linear pharmacokinetics with a half-life of approximately 11 days, achieving steady state concentration after repeated dosing and maintaining sustained serum levels sufficient for complete C5 blockade. The eculizumab dose depends on the indication and weight of the patient. Dose adjustment needed for patients with a body weight <40 kg.[3] The recommended dosage for the treatment of aHUS in patients 18 years or older is as 900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter.

Purpose

This case report presents a 30 years old male with end stage chronic kidney disease secondary to aHUS associated TMA, with a dialysis vintage of 19 years. The patient underwent live related renal transplant (LRRT) and received perioperative eculizumab to prevent recurrence of TMA and graft dysfunction. The report emphasizes the importance of early complement inhibition to improve post-transplant graft outcomes in high risk aHUS patients, providing insights on managing such patients.

CASE REPORT

A 30-year-old male was initially diagnosed with complement mediated aHUS following presentation with microangiopathic hemolytic anemia, thrombocytopenia, and rapidly progressive renal failure consistent with TMA.

Complement evaluation at the time of diagnosis demonstrated normal C3 and C4 levels; however, CFH antibody titers were markedly elevated (58.78 AU/ml; reference range 0-20 AU/ml), suggestive of autoimmune complement dysregulation. Further genetic evaluation using multiplex ligation-dependent probe amplification (MLPA) identified homozygous deletions of the CFHR1 and CFHR3 genes, confirmed the diagnosis of complement-mediated aHUS.

Despite supportive therapy, the patient progressed to end-stage renal disease and he remained on thrice-weekly dialysis for 19 years before being evaluated for renal transplantation. Given the known high risk of post-transplant recurrence of complement mediated Ahus and graft dysfunction, complement inhibition with Eculizumab was initiated. An intravenous dose of 900 mg Eculizumab was administered at the time of surgery, no dose adjustment was required as the patient weighed 74 kg.

The postoperative course was uneventful. The patient achieved immediate graft function with gradual decline in serum creatinine and lowest S. creatinine attained was 0.79 mg/dl. Ultrasound Doppler of the transplant kidney was normal. Foleys removed on POD 6 and he voided clear urine. Second dose eculizumab was administered on POD7. Patient was monitored regularly with hemogram and lactate dehydrogenase (LDH) levels. Complement levels were within normal limits. Tacrolimus trough level was 9 ng/mL and dose modified accordingly. There was no laboratory or clinical evidence of recurrent TMA or graft dysfunction. The patient was prescribed triple immunosuppressive therapy comprising tacrolimus, mycophenolate mofetil, and corticosteroids, along with continued prophylactic Eculizumab On follow-up, the patient demonstrated sustained graft survival with preserved renal function. This case underscores the importance of perioperative complement blockade in ensuring graft survival in high-risk aHUS patients (Table 1).

Table 1: Clinical summary of a patient with complement-mediated aHUS receiving perioperative eculizumab prophylaxis during renal transplantation.

Parameter	Details
Initial diagnosis	Complement-mediated aHUS
Presenting features	Microangiopathic hemolytic anemia, thrombocytopenia, and rapidly progressive renal failure consistent with TMA
Complement evaluation	C3 and C4-normal; anti-CFH antibody titer-58.78 AU/mL (reference range: 0-20 AU/mL)
Genetic evaluation (MLPA)	Homozygous deletion of CFHR1 and CFHR3 genes
Disease course before transplant	Progressed to end-stage renal disease; maintained on thrice-weekly hemodialysis for 19 years
Pre-transplant risk assessment	High risk of post-transplant aHUS recurrence and graft dysfunction
Perioperative prophylaxis	Eculizumab initiated at the time of renal transplantation
Eculizumab-dose 1	900 mg IV administered intraoperatively (body weight 74 kg; no dose adjustment required)
Postoperative course	Uneventful; immediate graft function achieved
Lowest serum creatinine	0.79 mg/dl
Doppler ultrasound of graft	Normal
Foley catheter removal	Postoperative day (POD) 6; patient voided clear urine
Eculizumab-dose 2	Administered on POD 7
Monitoring parameters	Hemogram, LDH, and complement levels - all within normal limits
Tacrolimus trough level	9 ng/ml (dose modified accordingly)
Evidence of TMA recurrence	None-clinical or laboratory
Maintenance immunosuppression	Tacrolimus + mycophenolate mofetil + corticosteroids, with continued prophylactic eculizumab
Outcome on follow-up	Sustained graft survival with preserved renal function

DISCUSSION

aHUS is a rare, life threatening genetic or autoimmune disease causing chronic, uncontrolled complement system activation, resulting in blood clots, hemolytic anemia, thrombocytopenia and kidney failure. It predisposes patients to recurrent TMA even after renal transplantation, because the underlying systemic alternative complement pathway dysregulation persists despite renal replacement. The introduction of eculizumab has significantly altered the therapeutic approach to aHUS, by selectively inhibiting complement component C5 and preventing membrane attack complex formation, initially used as rescue therapy for active TMA. Its role has expanded to peri-transplant prophylaxis which significantly reduced recurrence rates and graft survival even in high risk patients.

Munch et al described a 53 years old female with post-transplant aHUS based on a homozygous deletion of

CFHR1 and CFHR3 and concomitant development of CFH autoantibodies, who was effectively treated with eculizumab and belatacept.[4]

Similarly, our patient had homozygous CFHR1 and CFHR3 deletions with anti-complement factor H antibodies, representing a high-risk autoimmune complement mediated aHUS. Early recognition of genetic and immunologic predisposition and peri-transplant prophylactic eculizumab prevented recurrence of aHUS in our case in contrast to post-transplant management after recurrence. Both cases highlight the critical role of eculizumab to improve transplant outcomes in CFHR1 and CFHR3 deletion associated anti CFH antibody associated aHUS.

In a multicenter cohort study, Zuber et al evaluated 22 renal transplant recipients with aHUS who received eculizumab. Nine patients, all carrying a complement genetic abnormality associated with a high risk of aHUS recurrence, received prophylactic anti-C5 therapy to prevent post-transplant recurrence. Eight of them had a successful recurrence-free post-transplant course and achieved a satisfactory graft function. Thirteen renal transplant recipients were given anti-C5 for post-transplant aHUS recurrence, a complete reversal of aHUS activity was obtained in all of them.[5] This study highlighted the efficacy of early complement blockade in preventing irreversible graft injury shifted thinking from reactive treatment to preventive strategy.

Similarly, outcomes were clearly more favorable when eculizumab was administered prophylactically according to a systematic literature review of EMBASE. MEDLINE and Cochrane databases was performed by Maria L. Gonzalez Suarez et al including eighteen studies consisting of 380 kidney transplant patients with aHUS who received eculizumab for the prevention and treatment of post-transplant aHUS recurrence, reported lower recurrence (6.3%) and graft loss (5.5%) with prophylactic eculizumab, compared to 22.5% graft loss rate when used for treatment after recurrence.[6]

In our genetically predisposed patient with a dialysis vintage of 19 years, initiating eculizumab intraoperatively and continuing with scheduled maintenance therapy was associated with stable graft function and absence of TMA recurrence. Interpretation of these findings is limited by several important factors. The findings are based on a single patient without a comparator, limiting generalizability and making it difficult to determine the optimal duration of ongoing therapy and long-term outcomes such as graft survival and recurrence. Additionally, the high cost of Eculizumab and the increased risk of serious infections may limit its wider clinical applicability.

This case strengthens the existing international cohorts and clinical experience highlighting the critical role of timely complement blockade in preventing recurrence of aHUS in high-risk settings. Going forward, large scale prospective studies and registries to better establish efficacy, safety and cost effectiveness in the long term will be essential to guide evidence based clinical practice.

CONCLUSION

In conclusion, this case highlights the successful perioperative use of eculizumab in preventing recurrence of TMA and preserving graft function in a living-related renal transplant recipient with aHUS. The patient had several high-risk features for recurrence, including genetic susceptibility involving CFHR1 and CFHR3 gene deletions, circulating anti-CFH antibodies, prolonged dialysis vintage of 19 years and end stage renal disease. Prophylactic initiation of eculizumab intraoperatively followed by continuation as maintenance therapy, along with standard immunosuppression using Mycophenolate mofetil, Tacrolimus and Prednisolone, resulted in stable graft function without recurrence of TMA on follow-up. This case adds to the emerging evidence supporting prophylactic complement inhibition in high-risk transplant recipients with aHUS, however further studies and longer follow-up are required to better define the optimal treatment strategies and long-term outcomes.

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