

# Recurrent Atypical Hemolytic Uremic Syndrome Post-Renal Transplantation: Case Report Treated with Eculizumab

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**Abstract:** *Atypical Hemolytic Uremic syndrome is disease that could results in end stage renal disease and subsequently requiring hemodialysis or renal transplant. It also could recur after renal transplant, which poses a challenge to diagnose and treat given the complexity of immunosuppressive medications. Proper preparation before the transplant and vigilant post transplant monitoring is crucial to preserve the precious graft and start the appropriate treatment promptly at recurrence. Eculizumab has been used in atypical Hemolytic Uremic syndrome. We report a case of recurrent atypical Hemolytic Uremic syndrome post renal transplant that was refractory to plasma exchange and showed excellent response to Eculizumab.*

**Keywords:** Atypical hemolytic uremic syndrome, Renal transplant, Recurrent atypical hemolytic uremic syndrome, Eculizumab

## 1. Introduction

The thrombotic thrombocytopenic purpura and Hemolytic Uremic syndrome (TTP-HUS) is a clinical syndrome associated with renal failure, hemolytic anemia and thrombocytopenia. It results in endothelial injury with thrombophilia that results in many organs failure. It could be idiopathic or secondary. Some of the secondary causes include drugs [1, 2], infections or malignancies. However, atypical hemolytic syndrome (aHUS) generally results from genetic mutations in the complement activation system that could be either sporadic or familial [3].

The syndrome could result in end stage renal disease requiring renal replacement therapy. It is estimated to be seven in one million in Europe [4]. This case report discusses a case of aHUS recurrence post renal transplantation that was refractory to the conventional treatment lines and responded with Eculizumab.

## 2. Case report

A 54-year-old Caucasian female who is known to have TTP-HUS leading to end stage renal disease (ESRD); She received plasma exchange and rituximab as part of her treatment. She achieved remission but subsequently started on hemodialysis. The genetic testing for aHUS mutation was negative.

Later on she was evaluated for living related renal transplant (brother). Her transplant profile is summarized in table 1.

**Table 1:** Transplant profile

	Recipient	Donor (Brother)
CMV*	Negative	Negative
EBV <sup>+</sup>	Positive	Positive
PRA**	0%	
Flow cross match	Negative	
DSA <sup>++</sup>	Negative	

\*CMV cytomegalovirus, <sup>+</sup>Ebstein Bar Virus, \*\* Panel reactivity antibody, <sup>++</sup>Donor specific antibodies

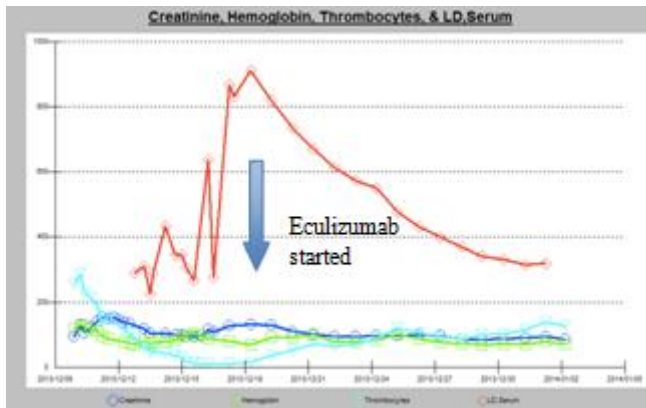
A year after starting hemodialysis, she had a living related renal transplant. For the surgery preparation, she was given two units of Solvent Detergent plasma infusion, as she was allergic to fresh frozen plasma, before and during the surgery. Although she was a low immunologic risk based on the flow cross match and donor specific antibodies, she was induced with Thymoglobulin to delay the introduction of calcineurin inhibitors that could provoke her TTP-HUS.

She was monitored postoperatively for any raising creatinine, platelets level, LDH and blood smears for schistocytes. Her postoperative course was uneventful and patient was discharged home with a creatinine of 66 mmol/l and normal values of platelets and LDH. Her discharge medication included: Advagraf 9mg once daily, Myfortic 720mg twice a day, a tapering dose of prednisone, Septra, Lansoprazole, Metoprolol and amlodipine.

A month after the transplant, she was seen in the transplant follow up clinic with a raising creatinine but normal LDH and platelets. A renal biopsy was performed which was normal.

A week after the biopsy she presented to the emergency department with ischemic bowel. Her laboratory investigations showed: low platelets ( $13 \times 10^9/l$ ), high LDH (912 u/l) and hemolytic anemia. Her genetic testing for aHUS was repeated and found to be negative. A prompt diagnosis of recurrent aHUS was made and she was started on Plasma Exchange with Solvent detergent plasma (a dose of 2 blood volume using OPTRA machine) concurrently with a high dose of methyl prednisone, 100mg daily. The Advagraf was switched to Sirolimus to eliminate its potential role in the disease.

Despite treatment with higher doses of plasma Exchange, her clinical condition continued to deteriorate with no significant improvement in her platelet and LDH. A dose of Eculizumab was given to her on the fifth day of her diagnosis and this resulted in an immediate clinical response and improvement of platelets counts. Within 10 days her platelets increased from as low as  $11 \times 10^9/l$  to  $120 \times 10^9/l$  (Figure1).



**Figure 1:** Laboratory markers before and after starting Eculizumab

She received an induction dose of Eculizumab 900 mg weekly for 4 weeks then 1200mg every two weeks for life. She was put on antibiotics for two weeks and given meningococcal vaccine.

- Two years later, She continue to do well with no recurrent disease and remains on Eculizumab and Silrolimus.

### 3. Discussion

Atypical HUS is a rare disease that accounts for about 5% of the complement mediated thrombotic micro-angiopathies [5]. It is considered a serious illness that requires prompt diagnosis and treatment. It can subsequently lead to ESRD and requires renal transplant.

The recurrence rate post renal transplant is high and it depends on the underlying cause and its estimated to be between 25-50% [6, 7]. For instance, ESRD from TTP-HUS secondary to infectious etiology has a very low rate of recurrence; about 1% [6], whereas ESRD from aHUS has a high recurrence rate reaching up to 100% in some cases depending on the type of genetic mutation, the use of living related donors and the age at presentation [7]. Living related donors could increase the risk of recurrence given the genetic nature of this illness [7, 8].

The perioperative period should be planned to prevent provocation and recurrence of the illness. It is recommended to use Eculizumab preoperatively to prevent recurrence [9, 10]. However the access to the medication may not be feasible because of its cost. In our case we chose to give the patient 2 units of solvent detergent plasma and thymoglobulin for induction to delay the calcineurin inhibitor initiation associated with Basiliximab induction. The postoperative monitoring for recurrence should be extended as it may take more than 4 weeks for the disease to recur [11].

The recurrence usually presents with acute renal injury (AKI), thrombocytopenia and hemolytic anemia. Other features include fever and neurological symptoms such as: confusion or stroke. The post transplant period is complex, and that can make the diagnosis of the recurrence challenging. Furthermore, many causes resulting in thrombocytopenia and renal failure such as: rejection or immunosuppressive drugs, can mask or delay the diagnosis.

The diagnosis is usually based on the clinical features and laboratory testing showing renal failure, hemolytic anemia and thrombocytopenia. Renal biopsy usually shows features of micro-angiopathy and fibrin deposits, which is suggestive of recurrence. Genetic testing for the known mutation for aHUS can also aid in the diagnosis. However, it can be negative in 50% of cases with aHUS [3].

The treatment consists of prompt initiation of high dose corticosteroid and plasma exchange. The pathogenesis of aHUS proposes a new treatment target, the complement activation system [12, 13]. Eculizumab is a humanized monoclonal IgG antibody that binds to complement protein C5, preventing cleavage into C5a and C5b. Blocking the formation of C5b inhibits the subsequent formation of terminal complex C5b-9 or membrane activation complex. For this reason we chose to use Eculizumab. Our patient response to Eculizumab was remarkable. This makes aHUS the most likely diagnosis despite the negative genetic mutation.

The downside to using Eculizumab is its cost, which makes the access to it challenging. It is not clear whether a lifelong treatment is required or not. More studies with long-term follow-ups are needed to study its effectiveness, side effects and the appropriate treatment duration.

### 4. Conclusion

aHUS recurrence is a disease with high morbidity and mortality rates. Discussion pre transplantation for this risk is very important for the donor as well as the recipient. Appropriate preparation and monitoring is essential. Prompt diagnosis and initiation of the treatment is a life saving measure. Cases with refractory disease may respond to Eculizumab. However, the cost of the treatment could limit the access to it.

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## Author Profile

**Abdullah Kashgary** received the MB BS in 2004 from King Abdulaziz University. Then he earned the royal college of physicians of Canada certificate in internal Medicine and Nephrology from Western University, Canada in 2011 and 2013, respectively. During 2013-2015 he stayed in Western University doing a clinical fellowship in transplant nephrology. He is now with King Abdulaziz University, Saudi Arabia.