

# Successful Renal Transplantation in a Patient with Atypical Hemolytic Uremic Syndrome Treated with Eculizumab in China

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## INTRODUCTION

Hemolytic uremic syndrome (HUS) is a rare disease characterized by thrombocytopenia and acute renal failure. Atypical HUS (aHUS) accounts for approximately 10% of all HUS cases. The pathogenesis of aHUS is mainly associated with gene mutations in complement factor H, complement factor I, and membrane cofactor protein (MCP). The prognosis of aHUS is generally poor. Totally, 60% of patients develop renal failure or even die within 1 year. The efficacy of blood transfusion, dialysis, or plasmapheresis is not excellent. Kidney transplantation is an important method for treating end-stage renal diseases. Studies from other countries show that for patients with complement system function disorders caused by aHUS, the transplantation success rate is low and the postoperative aHUS recurrence rate is high.<sup>[1-3]</sup> With the introduction of the complement component 5 (C5) monoclonal antibody eculizumab (Alexion, CT, USA), the long-term survival of patients significantly improves.<sup>[1]</sup>

We reported a 45-year-old male with aHUS caused by H factor gene mutation. We performed successful kidney transplantation with the perioperative application of eculizumab. During the 6-month follow-up, the function of the transplanted kidney was stable, recurrence of aHUS did not occur, and no other complications were noted.

## MEDICAL RECORDS

In January 2012, a 42-year-old male presented with 3-week history of cough, wheezing, and edema. The laboratory examination showed the following results: hemoglobin (HGB) 65 g/L, platelet (PLT)  $79 \times 10^9/L$ ,

serum creatinine (Scr) 1089  $\mu\text{mol/L}$ , blood urea nitrogen 50.4  $\mu\text{mol/L}$ , complement C3 0.44 g/L, and complement C4 0.24 g/L. Thoracic X-ray suggested diffuse interstitial disease in both lungs. The main diagnoses were severe pneumonia and acute renal failure. After treatment with respiratory support, hormone pulse, hemodialysis, PTL transfusion, and antibiotics for 2 weeks, the respiratory symptoms of the patient disappeared, and his body temperature returned to normal. Gene detection analysis results suggested a factor H gene mutation. In addition, anti-factor H antibody was not detected in his blood. Renal biopsy showed thrombotic microangiopathy.

In January 2014, he continued to receive regular hemodialysis and symptomatic treatment in our hospital. The medication regimen with the complement C5 monoclonal antibody (eculizumab) consisted of 900 mg/week for 4 continuous weeks, and then 1200 mg every 2 weeks until the surgery. Each tube of eculizumab was diluted with an equal volume of 0.9% NaCl and intravenously infused at a speed of 150 ml/h. Then, we stopped the plasmapheresis treatment. Because the application of eculizumab might induce a serious *Neisseria meningitidis* infection, a meningitis vaccination was provided to the patient before the start of the antibody therapy. In December 2014, he was stable. PLT level had recovered

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to the normal range, and HGB level had increased to 98 g/L. After careful preparation, he received a kidney transplant from a donor in January 2015. Laboratory examination results were as follows: panel reactive antibodies I 22.5%, II 0%, total 13%; donor-specific antibody (–). The donor was a 31-year-old male with brain death. We selected basiliximab (Novartis, Basel, Switzerland) (20 mg on day 0 and day 4) for immune induction. The immunosuppressive regimen consisted of tacrolimus, mycophenolate mofetil, and prednisone. He recovered well after the operation. The perioperative eculizumab medication regimen consisted of 1200 mg 3 hours before surgery, 900 mg each on day 1, day 8, day 15, and day 22 after surgery, 1200 mg on day 29, and 1200 mg every 2 weeks afterward to maintain the long-term inhibition of complement activity. During the 6 months of postoperative follow-up, hematology examinations were regularly performed every month. The complement C3 level of the patient gradually increased to a normal level. The Scr, PLT, HGB, and complement C4 levels were within normal ranges [Table 1].

During the follow-up, he did not show obvious signs of graft rejection, aHUS recurrence, or infection.

## DISCUSSION

The typical symptoms, laboratory test results, clear factor H gene mutation, and renal biopsy evidence prompted us to confirm the diagnosis of aHUS. Literature from other countries reported that eculizumab was the most effective way to treat aHUS.<sup>[4]</sup>

As we know, there are three pathways to activate complement system in human body, including classic pathway, alternative pathway, and mannose-binding lectin pathway. Under normal physiological conditions, C3 interacts with factor B and factor D to produce a very small amount of C3b and C3bBb (i.e., the C3 convertase in the alternative pathway). However, factor H, factor I, and MCP can mediate the conversion of C3b into the inactive form C3bi, to block the complement reaction activated by the alternative pathway and to prevent the body from being attacked by the complement system. If a patient has a genetic defect in factor H, factor I, or MCP,

or if a patient has autoantibodies against factor H, factor I, and MCP, C3b cannot be inactivated, and the excessively activated complement system in the alternative pathway will attack PTLs and endothelial cells to cause the typical clinical manifestation of aHUS. Eculizumab can specifically block the pyrolysis of complement C5 and inhibit the formation of C5a and C5b, to prevent the release of the inflammatory factor C5a and to stop the formation of C5b-9.<sup>[4]</sup>

A study by Cugno *et al.* shows that the half-life of eculizumab is approximately 11 days and the complement activity is significantly inhibited after 2–3 weeks of application. However, starting at week 4, the inhibitory effect gradually decreases. Therefore, the factor H-deficient patient in this case requires long-term maintenance treatment at least for 6 months.<sup>[1,5]</sup>

In this case, two issues captured our attention:

1. Mutation of the factor H gene produce a congenital disease. Most patients exhibited disease onset in childhood or adolescence. However, this patient had disease onset at the age of 42
2. Eculizumab is a complement C5 monoclonal antibody. It exerts a regulatory function on the complement system by blocking the final pathway. However, it does not affect the formation of C3 convertase in the alternative pathway. C3b can still label red blood cells, which are cleared by the reticuloendothelial system, thus causing the persistent destruction of HGB. However, in this case, we found that after eculizumab application and kidney transplantation, the levels of HGB and complement C3 in the patient gradually increased to normal range. The underlying mechanism still requires further clinical and basic research as well as drug exploration.<sup>[6]</sup>

According to a literature review and a summary of our experiences, kidney transplantation is an important measure for treating kidney failure caused by aHUS. Perioperative eculizumab treatment is a safeguard for successful kidney transplantation, and long-term maintenance treatment is crucial for the prevention of aHUS recurrence. However, our conclusion is obtained from one single case. The detailed mechanisms of immunological and genetic pathogenesis require further investigation. It is still unclear whether all patients with factor H mutations require lifelong medication. In particular, further clinical research is required to determine the efficacy and safety of perioperative and long-term preventive applications of eculizumab in China for the treatment of aHUS.<sup>[7]</sup>

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## Conflicts of interest

There are no conflicts of interest.

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**Table 1: Laboratory test results during the 6-month follow-up**

Time since transplantation (months)	Serum creatinine (μmol/L)	Platelet (×10 <sup>9</sup> /L)	Complement C3 (g/L)	Complement C4 (g/L)
–12	860.10	33.00	0.44	0.24
–1	726.30	132.00	0.59	0.25
0	233.70	142.00	0.59	0.25
1	69.10	156.00	0.60	0.25
2	57.80	151.00	0.61	0.25
3	72.20	146.00	0.72	0.25
4	70.30	160.00	0.72	0.24
5	75.60	178.00	0.77	0.25
6	66.10	173.00	0.79	0.25

Minus represent preoperation and zero represents the day of surgery. C3: Component 3; C4: Component 4.

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