INTERNAL MEDICINE

□ CASE REPORT □

Long-term Eculizumab Treatment Contributes to Recovery from End-stage Renal Disease Caused by Atypical Hemolytic Uremic Syndrome

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Abstract

We experienced a favorable outcome in an adult case of atypical hemolytic uremic syndrome (aHUS) after long-term eculizumab treatment. A 38-year-old Japanese man with a history of central retinal vein occlusion was admitted to our hospital with progressive dyspnea. He was found to have non-immune hemolytic anemia, thrombocytopenia, and acute renal failure two weeks after an episode of the common cold. Plasma exchange was ineffective; therefore, we initiated eculizumab after we excluded other thrombotic microangiopathies. Although long-term peritoneal dialysis was required, we successfully discontinued dialysis 18 months after the onset of aHUS with eculizumab.

Key words: atypical hemolytic uremic syndrome, eculizumab, peritoneal dialysis, thrombotic microangiopathy

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Introduction

Atypical hemolytic uremic syndrome (aHUS) is characterized by three major components: microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and acute kidney injury. This syndrome is known to be caused by the abnormal activation of the compliment cascade (1). In Japan, the number of new patients with aHUS is estimated to be around 100 cases per year. aHUS was certified as an intractable disease by a new law in January 2015, and its medical expenses are covered by the Japanese government. This syndrome was treated previously with plasma exchange, which is a standard treatment for thromboembolic thrombocytopenic purpura (TTP), but its prognosis was poor (2). When patients with aHUS are treated with plasma exchange, a reported approximately 10% die and approximately 50% progress to end-stage renal disease 1 year after the onset of aHUS (2). Anti-complement factor 5 antibody, eculizumab, which has been used for the treatment of paroxysmal nocturnal hemoglobinuria, was recently reported effective for aHUS (3). Following that trial and US Food and Drug Administration approval, eculizumab was approved for the treatment of aHUS in Japan in 2013.

We herein report a case of aHUS, for which we successfully discontinued dialysis 18 months after initiation of eculizumab. Our case suggests that long-term treatment with eculizumab may gradually recover kidney damage and ultimately lead to discontinuation of dialysis.

Case Report

The patient was a 38-year-old man who presented with a 1-week history of dyspnea. Two weeks prior to presentation, the patient developed a cough and a fever, which resolved quickly. One week later, the patient started experiencing progressive dyspnea while walking and decided to visit our hospital. He denied having any episodes of bloody diarrhea. His medical history revealed central retinal vein occlusion at the age of 36 years. He had no family history of thrombosis

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Table. Laboratory Findings on Admission.

CBC		Chemistry		Serology	
WBC	9.53×10^3 /μL	Alb	4.2 g/dL	Direct Coomb's	(-)
Neu	81.0 %	LDH	2,470 IU/L	Indirect Coomb's	(-)
Eo	0.0 %	T-bil	2.7 mg/dL	ADAMTS13	
Baso	0.0 %	D-bil	0.6 mg/dL	activity	72.9 %
Mono	4.0 %	BUN	58 mg/dL	inhibitor	<0.5 BU/mL
Lym	14.0 %	Cre	6.8 mg/dL		
RBC	268×10^4 /μL	CRP	0.25 mg/dL	Urinalysis	
Hb	7.4 g/dL	Haptoglobin	11 mg/dL	Protein	(3+)
Ht	21.6 %			Occult blood	(3+)
MCV	80.6 fl	Coagulation			
MCH	27.6 pg	PT-INR	1.07	Stool	
MCHC	34.3 %	aPTT	27.3 sec	Occult blood	(-)
Plt	7.6×10^4 /μL	Fibrinogen	131.0 mg/dL	STEC	(-)
Ret	81.1 ‰	FDP	194.0 μg/mL		
Schistocytes (+)					

FDP: fibrin degradation product, Plt: platelet, RBC: red blood cell, Ret: reticulocyte, STEC: Shiga toxin-producing *Escherichia coli*, WBC: white blood cell

or chronic renal failure. On the day of presentation, he was alert and oriented. He was afebrile, his pulse rate was 108 beats/min, and his blood pressure was 172/90 mmHg. On a physical examination, his conjunctiva was pale and icteric. There were no other significant findings upon our examination. The laboratory data on presentation are shown in Table. Normocytic anemia, increased reticulocyte count, significant presence of schistocytes, and elevation of lactate dehydrogenase (LDH) and indirect bilirubin levels suggested MAHA.

Based on the presence of MAHA, thrombocytopenia, and renal insufficiency, thrombotic microangiopathy (TMA) was suspected. Emergency plasma exchange and steroid pulse treatment were initiated. Although we repeated plasma exchange 20 times, the patient did not respond well to the treatment, with a worsening of his renal function, persistent severe thrombocytopenia, and continuous elevation of LDH. We later found that his ADAMTS13 activity was normal while that of its inhibitor was negative, which excluded the possibility of TTP. A stool culture obtained on the day of admission was negative for Shiga-toxin-producing *Escherichia coli* (STEC); therefore, STEC-HUS was ruled out. We also excluded other diseases such as collagen disease, cancer, drug reaction, and severe infection, any of which might cause secondary TMA. Based on these results, aHUS was the working diagnosis, and eculizumab was considered as the treatment of choice. However, at that time in 2013, eculizumab had not yet been approved in Japan for the treatment of aHUS. Therefore, the validity of using eculizumab for this case was discussed by the ethics committee at our hospital. After that discussion and obtaining informed consent from the patient, we decided to import eculizumab personally from Alexion Pharma in the United States, and treatment was started on Day 29 post-admission.

To confirm activation of the complement cascade, we sent the patient's plasma to the Department of Transfusion, Nara Prefectural University, for a quantitative hemolysis assay using sheep blood cells (4). The patient's plasma revealed severe hemolysis that was 1.6 times that of the positive control, and addition of recombinant complement factor H (CFH) suppressed the hemolysis, indicating the presence of CFH-related complement amplification (data not shown). However, anti-CFH antibody in the patient's plasma was negative by Western blotting. In addition, genetic testing conducted at the National Cerebral and Cardiovascular Center in Osaka, Japan, did not reveal any abnormalities, including levels of CFH, component 3 (C3), membrane cofactor protein (MCP), complement factor I (CFI), complement factor B (CFB), and thrombomodulin. Around half of cases of aHUS do not have mutations in the complement regulatory proteins (5); therefore, we clinically diagnosed this case as aHUS.

The clinical course of our case is shown in Figure. A decrease in the LDH levels and improvement in the hemoglobin and platelet count were observed after eculizumab was initiated. However, the renal function continued to worsen, the creatinine level rose to 10 mg/dL, and hemodialysis was started shortly after the initiation of eculizumab. Hemodialysis was transitioned to peritoneal dialysis around three months after onset, based on the patient's request.

We continued eculizumab, which gradually improved his renal function, and at 18 months after onset of aHUS, we successfully discontinued dialysis. Up to 36 months after onset, the patient has had no signs of recurrence, with continuation of eculizumab.

Discussion

TMA is a syndrome of MAHA, thrombocytopenia, and organ dysfunction, which has a variety of causes (6). aHUS is one of those causes (7), and the Japanese guidelines for aHUS were first published in 2016. It is thought that genetic abnormalities of complement regulatory factors or anti-CFH

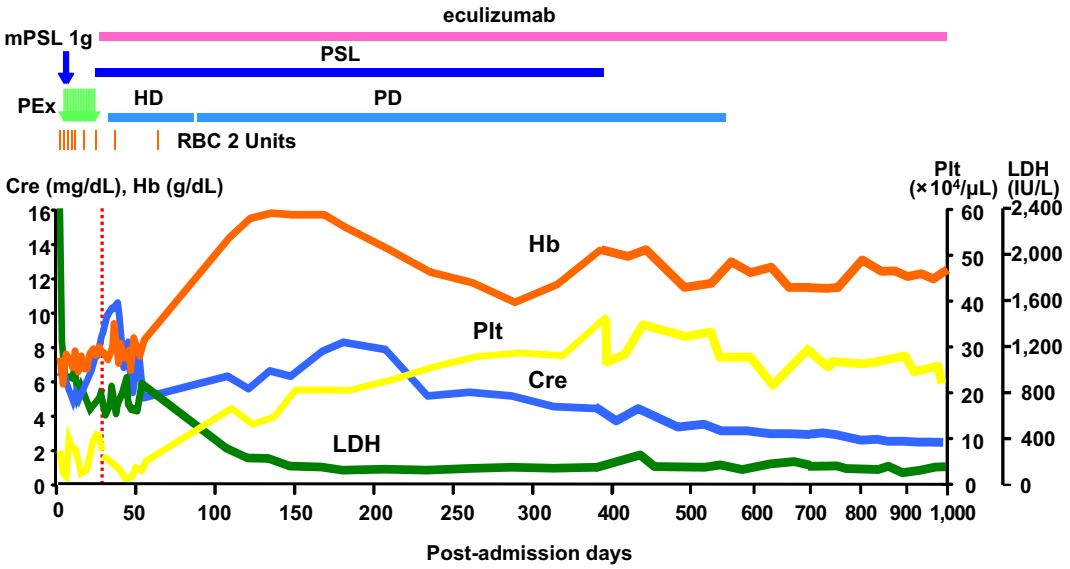

Figure. **Clinical course of aHUS. aHUS: atypical hemolytic uremic syndrome, HD: hemodialysis, mPSL: methylprednisolone, PD: peritoneal dialysis, PEx: plasma exchange, PSL: prednisolone, RBC: red blood cell transfusion**

antibody lead to uncontrollable activation of complement, which results in endothelial damage, intravascular microthrombosis, and eventually organ dysfunction (1, 8). Approximately 25% of cases of aHUS have resulted in death from thrombosis or acute renal failure (9). Even if death in the acute phase can be avoided by plasmapheresis, around half of the surviving cases eventually develop end-stage renal disease that requires dialysis (9). Kidney transplantation has been performed in such cases, but the recurrence rate was around 50%, and the rate of post-transplant kidney loss was 30% (10). Simultaneous liver and kidney transplantation has also been attempted (11), but the number of applicable cases is limited, and it is still a controversial treatment. About 40% of cases of aHUS are in young patients, including pediatric cases (12); therefore, lifelong dialysis can markedly reduce the quality of life. However, based on previous reports, eculizumab is expected to improve chronic kidney disease by more than 1 stage and meaningfully improve the health-related quality of life in more than half of all aHUS cases (3).

Based on the three major components of TMA—normal activity of ADAMTS13 and exclusion of STEC infection and other clear causes of TMA—our case met the diagnostic criteria of aHUS under the current guidelines (13), and these findings led us to the clinical diagnosis. A hemolytic analysis using sheep blood cells suggested a CFH-related abnormality, which also supported the diagnosis of aHUS. Subsequently, further genetic tests were conducted, but we did not detect any abnormalities of complement genes. To date, genetic abnormalities of C3, CFB, CFH, CFI, MCP, and thrombomodulin are reported to be related to aHUS (14-17). In Japan, several cases of abnormal C3 have also been reported (18). However, previous reports have shown that genetic abnormalities can be detected in around half of cases (5), as with the present case, which suggests that there are still several unknown genetic abnormalities causing aHUS. Considering his history of retinal vein thrombosis, we suspect that our patient might have an underlying genetic abnormality. Other experimental tests, such as measurements of C5a and C5b-9 complex in serum and urine samples by enzyme-linked immunosorbent assay (ELISA) (19), observation of deposits of C5b-9 protein on the endothelial cells *in vitro* using immunofluorescence microscopy (20), a modified Ham test using a genetically modified complement-sensitive cell line (21), and a skin biopsy (22), have been reported as possible diagnostic tools. However, further investigations are necessary to apply the findings from those tests in a clinical setting.

Eculizumab was not approved in Japan in 2013; thus, we initially treated the patient only with plasma exchange, which was insufficient to control disease progression. We started eculizumab 29 days after onset, following thorough discussion regarding the benefits and risks of off-label use of self-imported eculizumab. It has been reported that delayed initiation of eculizumab is associated with a worse outcome of the renal function (3, 23). Eventually, our case required long-term dialysis. However, long-term treatment with eculizumab resulted in our patient discontinuing dialysis 18 months after onset. This case suggests that it is worth considering long-term eculizumab, even for cases with delayed admission requiring dialysis, as the renal function can still be recovered and slowly improved by eculizumab.

Eculizumab is estimated to cost in the range of US $600,000 per year (24); thus, we need to avoid the overuse of eculizumab by performing careful diagnosis and treatment decision-making. An observational study revealed that around 70% of cases in other countries were able to successfully discontinue eculizumab without recurrence (25).

However, there are no prospective studies on the discontinuation of eculizumab in Japan. Therefore, in the present case, we are continuing treatment with eculizumab in the expectation of further, gradual improvement of the renal function.

Author's disclosure of potential Conflicts of Interest (COI).
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