CASE REPORT

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Atypical hemolytic uremic syndrome treated with anti-C5 antibody agent eculizumab, without genetic complement abnormalities

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ABSTRACT

Atypical hemolytic uremic syndrome (aHUS) is a rare and life-threatening disease often complicated by end-stage renal disease. Anti-C5 antibody agents have been developed for the treatment of aHUS: these are highly effective but limited in use owing to the difficulty of diagnosing aHUS in the acute clinical phase. The pathophysiology of aHUS is a thrombotic microangiopathy (TMA) caused by complement dysregulation triggered by environmental factors in susceptible individuals with genetic factors. Although several germline variants associated with aHUS have been identified, approximately half of patients with aHUS lack known pathogenic variants. It is essential to recognize the characteristic clinical features of aHUS. These include the triad of hemolytic anemia, thrombocytopenia, and renal impairment, without the presence of Shiga toxin-producing *Escherichia coli* infection, thrombotic thrombocytopenic purpura associated with ADAMTS13 deficiency, or TMA from secondary cause. In this case, plasma exchange could not be continued owing to allergy. Early diagnosis allowed for prompt administration of eculizumab at the time of relapse, with favorable outcomes. Based on the finding of no genetic abnormalities, eculizumab was discontinued after 12 months, with no recurrence for 3 years. On day 27 of hospitalization, renal biopsy revealed endothelial damage. Since a definitive diagnosis cannot be made with genetic testing in the acute stage and approximately half of patients have no genetic abnormalities, it is suggested to diagnose the condition as per the clinical definition and commence treatment with plasma exchange. If thrombotic thrombocytopenic purpura is excluded, switching to eculizumab is another treatment option according to clinical conditions.

Keywords: atypical hemolytic uremic syndrome, eculizumab, anti-C5 antibody, thrombotic microangiopathy, complement

Abbreviations:
aHUS: atypical hemolytic uremic syndrome
TMA: thrombotic microangiopathy
AKI: acute kidney injury

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Hb: hemoglobin
PE: plasma exchange
STEC: Shiga toxin-producing *Escherichia coli*
TTP: thrombotic thrombocytopenic purpura
Plt: platelets
CFH: complement factor H

INTRODUCTION

Atypical hemolytic uremic syndrome (aHUS) is a rare and life-threatening disease complicated by vital organ damage, particularly end-stage renal disease. The pathophysiology of aHUS is considered to be as follows: patients with genetic abnormalities involving complement regulators develop persistent uncontrolled activation of the complement alternative pathway triggered by certain stressors (such as infection), leading to thrombotic microangiopathy (TMA).[1-3] As for evaluating complement dysregulation, no existing complement assay is sufficient for the diagnosis of aHUS.[4,5] Genetic testing is also still insufficient for diagnosis, as many cases do not harbor pathogenic variants.[3,6-8] Furthermore, in most cases, it is necessary to decide on a course of treatment without waiting for the results of genetic testing, because of the rapid progression of the disease. There is no gold standard for diagnosis, and it is occasionally difficult to differentiate aHUS from other TMA-causing diseases such as Shiga toxin-producing *Escherichia coli* (STEC)-associated HUS, thrombotic thrombocytopenic purpura (TTP), and secondary TMA.[1] In the same TMA condition, it is challenging to differentiate based completely on symptoms alone. However, STEC-HUS is characterized by a history of consuming raw meat, bloody stools, and edema of the right hemicolon observed on computed tomography (CT). TTP can be distinguished using the PLASMIC score, with features such as less frequent acute kidney injury (AKI) and a more severe degree of thrombocytopenia compared to aHUS.[9]

As for treatment, for many years, the only effective option was plasma exchange (PE)[3,10]; however, recently, an anti-complement recombinant humanized monoclonal antibody preparation (anti-C5 antibody agents) has been developed. Although anti-C5 antibody agents are highly effective, their high cost and side effects, which increase the risk of meningococcal infection,[10,11] require accurate diagnosis before commencing long-term administration of such agents.

We experienced a case in which early diagnosis based on clinical criteria, even in the absence of genetic abnormalities, led to prompt treatment with the anti-C5 antibody, eculizumab. Eculizumab administration was discontinued after 12 months based on evidence that relapse was less likely in the absence of genetic abnormalities. Herein, we report the essential diagnostic features of aHUS along with a literature review. These features include the triad of hemolytic anemia, thrombocytopenia, and renal failure, along with the exclusion of other conditions: proof of STEC infection, TTP by high ADAMTS13 activity, and secondary conditions which can cause TMA. Additionally, we discuss the indications for eculizumab therapy.

CASE

A previously healthy 40-year-old woman presented to the emergency department late at night with fever and nausea. She reported having eaten raw fish prior to the onset of symptoms but denied hematochezia or diarrhea. Her medical history was unremarkable except for nutcracker syndrome, and she was not taking any medications. There was no family history of TMA or

renal disease. On examination, her blood pressure was 176/95 mmHg, and her body temperature was 38.1 °C. She was alert and had no notable findings on physical examination, including neurological examination. Blood tests revealed renal failure (creatinine [Cre], 3.0 mg/dL) with anuria, thrombocytopenia (platelets [Plt], 16,000/μL), and hemolysis (hemoglobin [Hb], 12.6 g/dL; lactate dehydrogenase [LDH], 3,070 IU/L; total-bilirubin, 3.6 mg/dL). The patient was admitted to the hospital. The morning after admission, the patient had progressive thrombocytopenia, anemia, and renal failure (Plt, 10,000/μL; Hb, 11.6 mg/dL; Cre, 4.0 mg/dL), and haptoglobin was below the limit of detection. Table shows additional laboratory data. By the evening of the same day, her Hb levels had further decreased (Hb, 9.2 mg/dL) and schistocytes were observed. Direct and indirect Coombs' test were negative. TMA was diagnosed with thrombocytopenia, microangiopathic hemolytic anemia and renal failure. Complement factors were normal (C3, 72 mg/dL; C4, 15 mg/dL). PE was performed because of suspected aHUS or TTP. Hemodialysis (HD) was also commenced for AKI. Methylprednisolone (60 mg/day) was administered for possible acquired TTP. After the start of PE, her platelet count was increased and LDH levels were decreased. On the 7th day of hospitalization, ADAMTS13 activity was found to be normal (101%), and anti-ADAMTS 13 antibodies were not detected. Other tests for excluding STEC-HUS, autoimmune disease and viral infection were negative, as shown in Table. On the 17th day of hospitalization, upper and lower endoscopy and chest and abdominal CT were negative for cancer.

PE was conducted seven times over the first 10 days of hospitalization, and PE was discontinued due to allergic reactions. Plt increased to 191,000/μL and LDH decreased to 317 IU/L 10 days after PE interruption. However, on the 20th day of hospitalization, platelet levels began to decrease again.

Resumption of PE was adjudged to pose a risk of allergic flare-up. The patient was transferred to a university hospital for more specialized treatment including eculizumab. The patient was diagnosed with definite aHUS because she met the diagnostic criteria of hemolytic anemia (Hb < 10 g/dL), thrombocytopenia (Plt < 150,000/μL), and AKI, and secondary TMA was excluded.[12] The following conditions were excluded: STEC-HUS, TTP, secondary TMA due to autoimmune activity, cancer, and drug. Eculizumab (900 mg) was administered once weekly for one month, followed by 1,200 mg every two weeks in accordance with standard dosage and scheduling. The patient received a meningococcal vaccine prior to eculizumab because of the increased risk of meningococcal infection. Ceftriaxone was given until the vaccine was effective to prevent meningococcal infection. Figure 1 illustrates the treatment course.

Table Laboratory data before plasma exchange

WBC	10.5×10^3	/μL		C3	72	mg/dL	(62–129)
RBC	3.81×10^4	/μL		C4	15	mg/dL	(14–36)
Hb	11.6	g/dL		Coombs	(–)		
MCV	86.4			Haptoglobin	<10	mg/dL	(<10)
Plt	11×10^3	/μL		ADAMTS13 activity	101%		(>10%)
Schistocyte	0	%	(<3%)	ADAMTS13 inhibitor	<0.5		(<0.5)
				LPS antibody	(–)		
TP	4.9	g/dL					
Alb	2.7	g/dL		ANA	<1:40		(<1:40)
T-Bil	2.8	mg/dL		DNA antibody	<2	IU/mL	(0–6)
AST	164	U/L		MPO-ANCA	<0.5	IU/mL	(<3.5)
ALT	31	U/L		PR3-ANCA	0.5	IU/mL	(<2.0)
LDH	3396	U/L		GBM antibody	0.5	IU/mL	(<7.0)
ALP	124	U/L		Cryoglobulin	(–)		
BUN	80.3	mg/dL		SS-A	<1.0	IU/mL	(<10)
Cre	4.07	mg/dL		HBs Ag	(–)		
Na	139	mEq/L		HBs Ab	(–)		
K	4.3	mEq/L		HCV Ab	(–)		
Cl	110	mEq/L		HIV Ag/Ab	(–)		
CRP	2.78	mg/dL		CMV IgG	170	AU/mL	(<6.0)
				CMV IgM	(–)		
PT	84	%		EBV CA IgG	8.7		(<0.5)
APTT	26.2	sec		EBV CA IgM	(–)		
Fib	304	mg/dL	(190–406)	EBV EA-DR-IgG	(–)		
FDP	18.7	μg/mL	(<5)	EBV-EBNA	3.3	AU/mL	(<0.5)
				EBV-DNA	<100	LogIU/mL	(<100)

WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; MCV, mean corpuscular volume; Plt, platelets; TP, total protein; Alb, albumin; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine minotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Cre, creatinine; CRP, C reactive protein; PT, prothrombin time; APTT, activated partial prothrombin time; Fib, fibrinogen; FDP, fibrinogen/fibrin degradation products; LPS, lipopolysaccharide; ANA, auto nuclear antibody; Ag, antigen; Ab, antibody; MPO, myeloperoxidase anti-neutrophil cytoplasmic antibody; ANCA, anti-neutrophil cytoplasmic antibody; PR3, proteinase-3-anti-neutrophil cytoplasmic; GBM, glomerular basement membrane; HB, hepatitis B; HCV, hepatitis C virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; CA, capsid antigen; EA-DR, early antigen/diffuse type and restricted type; EBNA, EBV nuclear antigen.

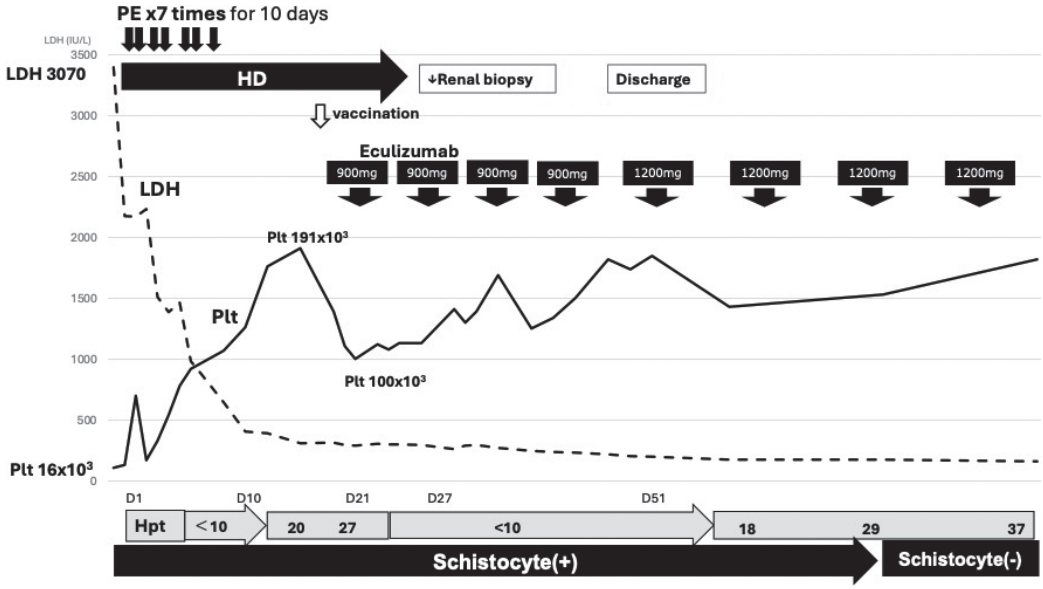

Fig. 1 Course of treatment

Plt: platelet count (/μL)
LDH: lactate dehydrogenase (IU/L)
PE: plasma exchange
HD: hemodialysis
Hpt: haptoglobin (mg/dL)

Soon after commencing eculizumab, the progressive thrombocytopenia was halted. In two weeks, Plt increased to 169,000/μL. On day 25 of hospitalization, renal function was restored and HD was ceased. The patient displayed the effects of eculizumab at an early stage. Normocytic normochromic anemia persisted without signs of hemolysis; haptoglobin levels returned to normal, and there was no elevation of LDH or bilirubin levels. Serum erythropoietin level was low (5.9 mIU/mL). On day 27 of hospitalization, a renal biopsy was performed to determine whether renal impairment was sufficient to predict renal prognosis. Renal pathology revealed extensive interstitial fibrosis, fibroblast proliferation, and tubular atrophy. Focal glomerular collapse and endothelial injury with a double contour to the glomerular basement membrane were observed (Fig. 2). Based on the extensive interstitial fibrosis observed and low erythropoietin levels, the patient was diagnosed with renal anemia and treated with erythropoietin supplementation.

Complement abnormalities were investigated using preserved plasma/serum before starting PE. Anti-complement factor H (CFH) antibody test was performed with a commercially available kit (Human CFH IgG ELISA Kit; Abnova, Taipei, Taiwan) which produced negative results. A hemolytic test with sheep red blood cells was also performed according to past a report, and observed no evidence of increased hemolysis. Genetic testing did not reveal pathogenic variants involving *CFH, CFI, CD46, C3, CFB, THBD, DGKE,* or *CFHR5*. Eculizumab was discontinued at 12 months after disease remission, with no TMA recurrence for three years.

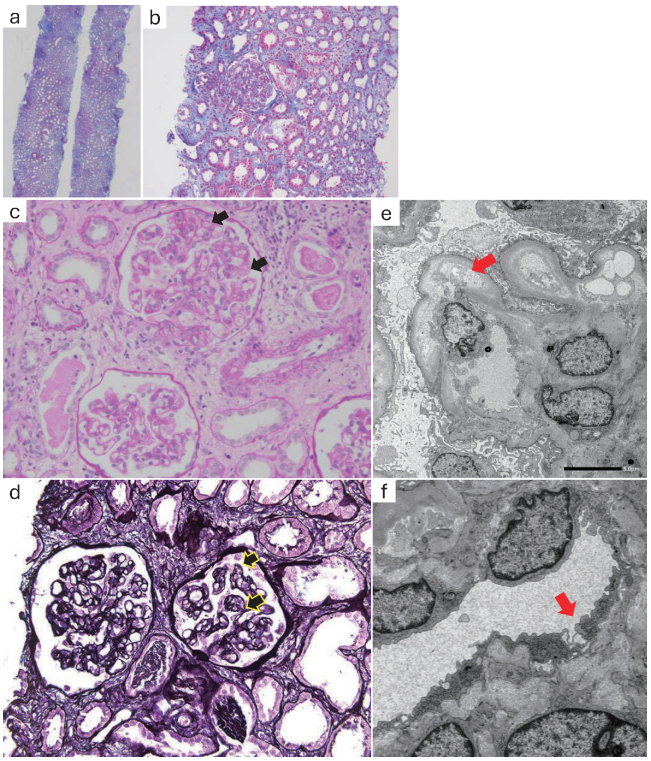

Fig. 2 Renal pathology

Fig. 2a, b: Extensive interstitial fibrosis (Masson's Trichrome stain, a, ×40; b, ×100).

Fig. 2c, d: A double contour to the glomerular basement membrane demonstrates endothelial injury (black arrows). (c, Periodic acid Schiff (PAS) stain, ×200; d, Periodic acid silver-methenamin (PAM) stain, ×200).

Fig. 2e, f: Endothelial cell swelling (e, red arrow), loss of fenestra (f, red arrow). (e, f: electron microscopy)

DISCUSSION

In this case of aHUS, serum C3 and C4 protein concentrations were within the normal range and no related gene mutations were detected by genetic testing, but eculizumab still exhibited a favorable therapeutic action. This is a useful report for considering the indication of administration of anti-C5 monoclonal antibody in patients with aHUS.

aHUS is a rare disease that damages vital organs and exhibits a high mortality rate. It requires prompt diagnosis but is nevertheless difficult to diagnose in its early stages. Its pathogenesis is persistent and invokes uncontrolled complement activation, but there is no test that can absolutely diagnose complement dysregulation in aHUS. aHUS occurs in individuals with genetic abnormalities involving complement regulation. However, in approximately half of all patients, no known pathogenic variants can be detected. In addition, early genetic testing results are generally not rapidly available.

Complement dysregulation in aHUS is subject to the alternative pathway, so patients sometimes exhibit low serum C3 levels and normal serum C4 levels.[1,4,13] However, it has been reported that only half of patients with aHUS have low C3 and normal C4 levels.[4] In the present case, both C3 and C4 levels were normal. As a functional test for the complement system, a hemolysis test using sheep erythrocytes was conducted.[14] This test can predominantly detect CFH deficiency due

to genetic abnormalities or acquired autoantibodies against CFH. Genetic abnormalities involving *CFH* are the most common of the various genetic abnormalities associated with aHUS in most countries, but account for only approximately 30% of all patients with aHUS.[3,6-8,15] This test was negative in this case.

aHUS occurs in individuals with genetic abnormalities involving complement regulation. Known pathogenic variants include loss-of-function in complement regulatory genes (*CFH, CFI, CD46* and *THBD*) or gain-of-function in effector genes (*CFB* or *C3*).[2,16] However, many patients do not harbor these known pathogenic variants. As mentioned previously, *CFH* defect accounts for around 30% of aHUS cases, while other genetic abnormalities account for only a few percent.[17] Although no genetic abnormalities were identified in this case, aHUS cannot be excluded. aHUS is a disease with very low genetic penetrance, and the presence of pathogenic gene variants is merely a background factor for this disease.

According to Japanese clinical guidelines, the definitive diagnostic criteria for aHUS are the presence of (1) congenital genetic abnormalities or (2) acquired auto-anti-CFH antibodies.[12] However, these criteria can be used to diagnose a limited number of patients. Therefore, aHUS is also defined as presenting clinical features of (1) anemia (Hb < 10g/dL) due to hemolysis, (2) thrombocytopenia (Plt < 150,000/μL), and (3) AKI. Clinical aHUS is defined as TMA with AKI, excluding STEC-HUS, TTP, and secondary TMA (metabolic disorders, infectious diseases, drug-induced states, autoimmune diseases, malignancy, hemolysis, elevated liver-enzyme levels, and a low platelet count [HELLP] syndrome, and post-transplant TMA).[12] STEC-HUS is diagnosed with STEC strains isolation from cultured stool specimens with demonstrable Shiga toxin production. Serum anti-pathogenic *E. coli* O157 lipopolysaccharide-IgM antibodies are also helpful in diagnosis.[18] TTP is diagnosed by decreased ADAMTS13 activity. Tests to exclude STEC-HUS and TTP take time, so associated symptoms can help to infer aHUS. STEC-HUS is usually accompanied by hematochezia. TTP often presents with central nervous system symptoms, whereas aHUS is often complicated by renal dysrunction.[9,19] In this case, hematochezia and neurologic deficiency were not observed. To rule out secondary TMA, a systemic imaging test for cancer and an assay to detect autoantibodies were performed in addition to a medical history of no underlying disease. Based on the above, a clinical diagnosis of aHUS was made.

If the clinical criteria indicate aHUS, treatment with anti-C5 antibody agents should be considered as an option. It has been reported that patients whose platelet count normalizes within 2 weeks of treatment with ravulizumab, a long acting anti-C5 antibody with the same target epitope as eculizumab, exhibit good renal prognosis.[20] In this case, as an initial treatment, PE was performed but discontinued due to allergy. Ten days after cessation of PE, Plts were decreased again. Eculizumab administration was commenced soon after relapse. The response to eculizumab was good, as the progressive thrombocytopenia was halted rapidly after starting eculizumab and returned to normal within 2 weeks. The patient was able to discontinue HD.

The next question arises as to how long eculizumab use should be continued. It has also been reported that patients with pathogenic variants of *CFH* have a high relapse rate.[3] In the absence of known genetic abnormalities, the relapse rate is considered to be low. A retrospective study of a small population from France reported that eculizumab can be discontinued after six months of remission. In this case, genetic testing did not reveal any known genetic abnormalities, so eculizumab was discontinued after 12 months.[21] It is impossible to predict when and what will trigger persistent uncontrolled complement activation in patients with or without known genetic abnormalities, therefore, discontinuation of eculizumab requires a shared decision-making process with the patient. A trigger for complement activation could be a common event such as influenza or vaccination. Patient self-monitoring for urine occult blood may help to detect relapses at an early stage, as intravascular hemolysis may cause positive urine occult blood results.

In conclusion, aHUS should be diagnosed clinically according to its typical features, which are hemolytic anemia, thrombocytopenia, and renal impairment, in the early phase. Although a complete differential diagnosis of TMA is difficult, the following clinical features would be helpful. aHUS shows acute onset with a possible trigger event, severe AKI, and sometimes accompanied by a family history. In STEC-HUS, there is a history of consuming raw meat, bloody stools, and edema involving the right semicolon. TTP shows less frequent AKI involvement and a more severe degree of thrombocytopenia compared to aHUS. In secondary TMA, there exist underlying conditions such as auto-immune disease, active cancer, and drugs that possibly cause TMA. Definitive diagnoses are based on confirming the existence of pathogenic variants in associated genes; however, less than half of patients have known genetic abnormalities. In this case, even though genetic testing was negative, early diagnosis based on clinical features allowed prompt treatment with eculizumab and may have contributed to renal recovery.

The patient has consented to the submission of this case report to the journal. Approval was obtained from the Ethics Committee of Nagoya University Hospital to report the case (Approval No. 2024-0368).

AUTHOR CONTRIBUTIONS

Y Sato and NK contributed equally. Y Sato was in charge of medical treatment, writing the original draft and creating figures. NK was in charge of medical treatment, collecting and summarized data, creating figures, and supervising draft. MA, HS, Y Shimamura were in charge of medical treatment. YT was collecting medical information and assisting diagnosis. AH was performing complement testing. SK was submitting the application for the Ethics Committee. KM, TK, SM were supervising manuscript drafting.

CONFLICTS OF INTEREST

NK, YT, and SM receive lecture and advisory fees from Alexion Pharmaceuticals, Inc. Y Sato, MA, HS, Y Shimamura, AH, KM, TK, and SK have no conflicts of interest to disclose concerning the study.

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