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A Case of Atypical Hemolytic Uremic Syndrome With a Complement Factor I Mutation Triggered by a Femoral Neck Fracture

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ABSTRACT

Atypical hemolytic uremic syndrome is a thrombotic microangiopathy caused by the abnormal activation of the alternative complement pathway. Mutations in complement-related genes and autoantibodies against complement regulators are involved in the pathogenesis of this condition; the frequency of, and prognosis of patients harbouring, each genetic mutation varies based on the region and race. Complement factor I (*CFI*) mutations have been observed in 4%–8% of cases in Europe; however, they have not yet been reported in Japan. We present the first Japanese case of atypical hemolytic uremic syndrome in a patient harbouring a *CFI* mutation. An 83-year-old female patient presented with severe acute kidney injury, thrombocytopenia, and hemolytic anaemia following a femoral neck fracture. Plasma exchange and haemodialysis were initiated, resulting in improved kidney function and platelet count. However, the platelet count decreased when plasma exchange was discontinued. Therefore, we administered ravulizumab, an anti-complement 5 monoclonal antibody, which led to the maintenance of stable kidney function and platelet count. Genetic analysis revealed a *CFI* mutation, and the patient was treated with ravulizumab for 2 years without relapse. Individuals diagnosed with atypical hemolytic uremic syndrome harbouring *CFI* mutations experience poor outcomes, including low rates of remission, high rates of mortality, and progression to end-stage kidney disease. Our case serves as a crucial example demonstrating how prompt identification and appropriate management can lead to better patient outcomes.

1 | Introduction

Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy (TMA) caused by abnormal activation of the alternative complement pathway [1]. Therapeutic intervention is urgently required for this disease, which is primarily associated with kidney failure and has a poor prognosis. Notably, the recent introduction of anti-complement (C) 5 monoclonal antibodies has dramatically improved the outcomes of aHUS [2]. However, diagnosing this condition is often difficult due to the lack of appropriate biomarkers for early diagnosis and differentiation.

The complement system is a part of the innate immune system and comprises plasma- and membrane-bound proteins that, when activated, interact to form an inflammatory cascade. The

pathogenesis of complement activity in patients with aHUS involves mutations in complement-related genes and autoantibodies against complement regulatory factors. However, approximately 40%–60% of aHUS patients do not harbour these known genetic mutations or autoantibodies; therefore, aHUS cannot be ruled out even if no mutations are identified. Regional and racial differences in the genetic variations of aHUS have also been observed [3–7]. Complement factor H (*CFH*) mutations are more prevalent in Europe, whereas *C3* mutations are more common in Japan [4–6]. Complement factor I (*CFI*) mutations are present in 4%–8% of European cases. However, only a few Asian patients with aHUS have been reported to harbour *CFI* mutations; further, to the best of our knowledge, there have been no reports of these mutations in Japan [4, 7, 8]. Therefore, here, we report the first case of aHUS occurring due to a *CFI* mutation in Japan.

2 | Case Presentation

An 83-year-old woman fell at home and visited an orthopaedic hospital, where the patient was diagnosed with a fracture of the left femoral neck and admitted. However, during the admission examination, her serum creatinine level, which had been 0.77 mg/dL a month earlier, was found to have increased to 7.23 mg/dL. The patient was subsequently referred to our department for further examination and treatment of acute kidney injury and finally transferred to our hospital 2 days later. Her vital signs were normal, except for a blood pressure of 146/80 mmHg, indicating hypertension. The laboratory results revealed a haemoglobin level of 9.2 g/dL, a platelet count of 7000/μL, a creatinine level of 8.20 mg/dL, and a lactate dehydrogenase level of 2838 IU/L. A peripheral blood smear revealed the presence of occasional schistocytes, with a reduced platelet count at admission, consistent with HUS. Urinalysis revealed an elevated urine protein level (6.55 g/gCre; Table 1). The patient had a history of hypertension, postoperative uterine fibroids, and a right femoral neck fracture at age 82, with no significant family history. Computed tomography revealed no pleural or ascitic effusions, left–right kidney differences, atrophy, or hydronephrosis.

Kidney function continued to decline on hospitalisation day 2. Haemodialysis was initiated owing to the blood urea nitrogen and creatinine levels reaching 142 and 8.90 mg/dL, respectively. Moreover, the hemolytic anaemia and thrombocytopenia were not alleviated, and plasma exchange was initiated (Figure 1).

The ADAMTS13 activity was normal, and the patient had no history of diarrhoea. Additional rheumatologic/immunologic workups, including the analyses of anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, and anti-DNA antibodies, yielded negative results. Thus, collagen disease, anti-neutrophil cytoplasmic antibody-related vasculitis, and systemic lupus erythematosus were ruled out. A kidney biopsy was not possible due to the post-femoral neck fracture.

After initiating haemodialysis and plasma exchange, the serum creatinine level decreased to approximately 2.0 mg/dL, and the platelet count increased to 144,000/μL. Eight plasma exchange and nine haemodialysis sessions were performed, with

TABLE 1 | Laboratory characteristics of the patient at admission and after 1 and 6 weeks.

Investigation	At admission	After 1 week	After 6 weeks
Total leukocyte count (cells/μL)	5800	7900	4300
Haemoglobin (g/dL)	9.2	9.2	9.8
Haptoglobin (mg/dL)	< 10		
Platelets ($\times 10^4$ cells/μL)	0.7	11.3	17.3
Total protein (g/dL)	5.9	5.9	5.7
Albumin (g/dL)	2.8	3.3	2.9
BUN (mg/dL)	132	81	38
Creatinine (mg/dL)	8.20	6.47	1.55
AST (IU/L)	63	33	22
ALT (IU/L)	45	16	11
LDH (IU/L)	2838	521	250
γ-GTP (IU/L)	8	16	8
CK (IU/L)	883	54	9
Glucose (mg/dL)	125	105	83
UA (mg/dL)	7.8	7.2	6.3
Sodium (mmol/L)	133	140	134
Potassium (mmol/L)	5.2	4.4	4.4
Chlorine (mmol/L)	81	104	99
Calcium (mg/dL)	7.5	8.0	7.9
Phosphorus (mg/dL)	4.4	4.2	3.0
CRP (mg/dL)	5.87	0.83	1.44
LDL-C (mg/dL)	66		
HbA1c (%)	5.2		
C3 (mg/dL)	82		63
C4 (mg/dL)	35		34
CH50 (U/mL)	53.2		15.8
ANA	Negative		
PR3-ANCA	Negative		
MPO-ANCA	Negative		

(Continues)

TABLE 1 | (Continued)

Investigation	At admission	After 1 week	After 6 weeks
Anti-GBM antibody	Negative		
Urine routine microscopy	pH 6.7	pH 7.0	pH 6.8
Urine RBC (/HPF)	20–29	20–29	1–4
Urine protein (g/gCre)	6.55	3.30	2.52

Abbreviations: ALT, alanine aminotransferase; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; AST, aspartate aminotransaminase; BUN, blood urine nitrogen; C3, C4, complement 3, 4; CH50, 50% hemolytic complement activity; CK, creatinine kinase; CRP, C-reactive protein; GBM, glomerular basement membrane; HbA1c, haemoglobin A1c; HPF, high-power field; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; RBC, red blood cell; UA, uric acid; γ-GTP, γ-glutamyl transpeptidase.

the patient being weaned off on days 14 and 18, respectively. However, the platelet count did not return to its previous level after plasma exchange. Therefore, a clinical diagnosis of aHUS was made; the patient received the first dose of ravulizumab (1200 mg) on hospitalisation day 35. The patient also received an initial meningococcal vaccine before the administration of the anti-C5 antibody. After the initial induction dose of ravulizumab, the patient's platelet count peaked at 170000/μL, with no further decrease in the platelet count. The genome sequences of *CFH*, *CFI*, *CD46*, *C3*, complement factor B (*CFB*), *THBD*, *DGKE*, and complement factor H-related (*CFHR*) 5 protein-coding region exons and their intron boundary regions were analysed using targeted next-generation sequencing with the hybrid capture method. The results confirmed that the patient had a novel heterozygous frameshift mutation in *CFI* (NM_000204.4: c.95_96del). This gene candidate was classified as a likely pathogenic variant (PVS1, PM2_Supporting), based on ACMG's criteria. In the protein encoded by this gene, amino acid 32 was changed from lysine to methionine, and amino acid 13 was changed, leading to the formation of a termination codon (p.Lys32MetfsTer13). Genetic analysis revealed a frameshift *CFI* mutation, and the test results and clinical course led to the diagnosis of aHUS.

On hospitalisation day 49, the patient received a second dose of ravulizumab at 2700 mg per standard weight-based dose, given that her weight was 38 kg. The patient was unable to stand before the left femoral neck fracture, in part due to the right femoral neck fracture the previous year. Therefore, surgery was not expected to improve her ability to perform daily living activities. Consequently, we decided not to perform the surgery. On hospitalisation day 71, the patient was transferred to a rehabilitation hospital.

Subsequently, her platelet count normalised, her anaemia remained stable, and her creatinine level decreased to 1.29 mg/dL. The standard weight-based maintenance dose of ravulizumab (2700 mg) every 8 weeks was continued. The patient experienced no recurrence of aHUS over the next 2 years.

3 | Discussion

We report the first Japanese case of aHUS that developed after a femoral neck fracture in a patient harbouring a *CFI* mutation. Previous reports indicated that aHUS is a hereditary orphan disease with a yearly incidence of 0.4–2 cases per million adults [1]. The most typical organ manifestation of aHUS is kidney failure, accounting for approximately 50%–70% of cases, with progression to end-stage kidney disease being reported in 50% of cases [4].

Microangiopathic hemolytic anaemia with organ dysfunction, such as acute kidney injury and decreased platelet count, is a suspected sign of TMA. Additionally, clinical aHUS is diagnosed following normal ADAMTS13 activity in the absence of Shiga toxin-related *Escherichia coli* infection after ruling out secondary TMA [5, 9].

aHUS is an inherited disease characterised by a defect in the complement system that activates an alternative pathway, causing endothelial damage and TMA [10]. Mutations in the complement system associated with aHUS include loss-of-function *CFH*, *CFHR*, *CD46*, and *CFI* mutations, as well as gain-of-function mutations in *CFB* and *C3* [11].

In this case, the genetic analysis revealed a *CFI* mutation. The *CFI* pathological variant was reported in 2004 in a family with familial HUS; no *CFH* variant has been reported [12, 13]. CFI is a serine protease; membrane cofactor protein (MCP) and CFH act as CFI cofactors for inactivating C3b and C4b. Exons encoding serine protease domains are the most common mutation sites. In predisposing mutants, CFI secretion is inhibited, resulting in reduced proteolytic activity in the fluid phase or at the cell surface [14, 15].

The pathogenesis of TMA in patients with aHUS is possibly attributed to a combination of genetic and acquired predispositions to abnormal complement activation by complement-related factors and other triggers, such as pregnancy and infection [16]. In this case, the femoral fracture may have induced aHUS by causing endothelial dysfunction and stimulating complement-activated tissue injury. Complement activation may be enhanced in patients with congenital defects in complement regulation.

Racial and regional differences in the frequency of genetic variation in patients with aHUS have been reported. For instance, among the 118 aHUS cases assessed from 1998 to 2016 in Japan, the *C3* complement-activating factor mutation was the most prevalent (30.8%). However, the *CFH* mutation, which is common in Europe and the USA (20%–30%), is less common in Japan (10%). The prognosis of *C3* mutation- and anti-CFH antibody-positive cases is also better in Japan than that in other countries, a characteristic trend among patients with aHUS in Japan. With regard to the *CFI* mutation identified in this patient, while *CFI* mutations have been reported in 4%–10% of patients in Italy, France, and the USA, there have been no reported cases in Japan thus far [3–6, 17]. The lack of reports on *CFI* mutations in Japan may be attributed to regional or racial differences. There are only a few papers discussing the genetic mutations of patients with aHUS in Asia. According to a 2016 report from China, the CFI mutation was only found in 1 out of 26 patients with aHUS

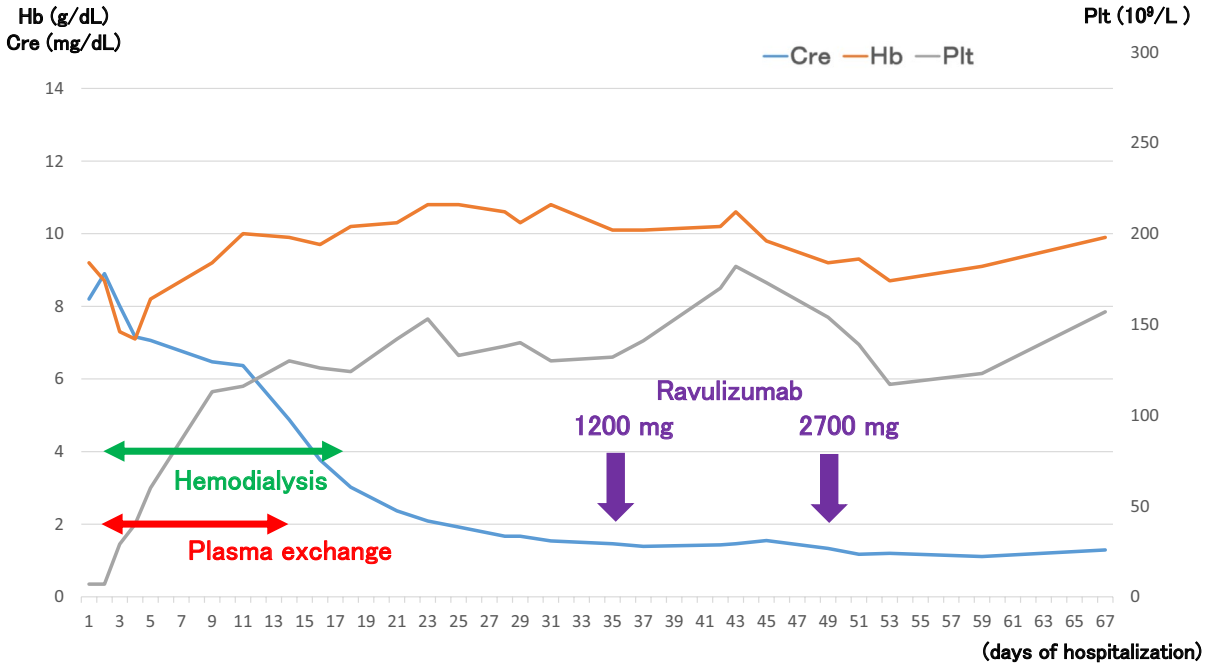

FIGURE 1 | Summary of clinical values. The data are presented chronologically with days of hospitalisation on the y-axis. Ravulizumab dosing was initiated on hospitalisation day 35. Cre, Creatinine; Hb, haemoglobin; Plt, Platelet.

(4.3%) [8]. Furthermore, according to a 2020 report from South Korea, no CFI mutations were reported in 66 adult patients with aHUS [7]. These facts suggest that the proportion of CFI mutations is lower in Asian patients with aHUS than in Western patients. Notably, the *CFI* remission rate is as low as 30%–40%, with high rates of mortality and conversion to end-stage kidney failure and notably high recurrence rates of 80%–90% after kidney transplantation [18].

There is insufficient evidence and a lack of consensus regarding the duration for which anti-C5 antibody drugs should be administered as maintenance therapy once TMA remission has been achieved. A recent systematic review of 40 observational studies, case series, and case reports, including 280 patients who discontinued eculizumab, found that 29.6% (83 patients) had recurrent TMA, with a median follow-up period of 23 months. The multivariate analysis of this review also demonstrated that younger age at onset, kidney transplant cases, and pathological variants of complement-related genes, including *CFH*, *MCP*, and *C3*, are associated with recurrence [19]. In the group with *CFI* mutations, 5 of 15 (33.3%) patients showed relapse, and one patient for whom eculizumab treatment was resumed after a relapse reportedly had decreased kidney function [19]. Notably, the continued use of anti-C5 antibodies as a maintenance therapy for aHUS reduces the risk of recurrence. However, it does not completely prevent the risk of infection, particularly meningococcal meningitis. Thus, meningococcal vaccination is necessary before the administration of the anti-C5 antibody, and if an anti-C5 antibody needs to be used urgently, appropriate antibiotic coverage for at least 14 days is necessary. In addition, it reduces the quality of life, given the increased requirement for hospital visits for intravenous administration and increases medical costs. For our patient, ravulizumab was continued on an outpatient basis, and to date, there has been no recurrence or progression of kidney dysfunction. The most important thing is to carefully discuss the risks and benefits of discontinuing anti-C5 antibody treatment with the patient based on the available data to make a decision accordingly. However, given its cost and side effects, discontinuation of ravulizumab should be fully considered.

This case report has some limitations. First, the detailed mechanism underlying the kidney failure in the patient is unknown because a kidney biopsy could not be performed. Based on previous reports, the pathology of this patient could indicate acute tubular necrosis with TMA [1]. Second, the molecular mechanism of the complement system due to the *CFI* mutation in this case is unknown as detailed complement studies were not performed. Third, it is unclear why this patient developed aHUS from the stress of this fracture, given that the patient did not develop aHUS from the stress associated with postoperative uterine fibroids or another fracture the patient sustained in the past.

In conclusion, we identified the first Japanese patient with aHUS associated with a *CFI* mutation. Notably, patients with aHUS harbouring *CFI* mutations show a low remission rate and a high rate of mortality and progression to end-stage kidney disease. However, early treatment with plasma exchange and ravulizumab resulted in successful treatment in this case. Early treatment is associated with better outcomes; therefore, it is essential to suspect aHUS and initiate treatment early when thrombocytopenia with haemolytic anaemia, high serum lactate dehydrogenase levels, or organ dysfunction is present, such as in cases of acute kidney injury.

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Ethics Statement

All procedures in the studies involving human participants were performed in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent for publication of this report was obtained from the patient.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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