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Atypical Hemolytic Uremic Syndrome (p.Gly1110Ala) with Autoimmune Disease

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 49-year-old
Final Diagnosis: Atypical hemolytic uremic syndrome
Symptoms: Edema
Medication: —
Clinical Procedure: Plasmapheresis • immune moderating
Specialty: Nephrology

Objective: Rare disease

Background: Hemolytic uremic syndrome (HUS) can be categorized as primary (typical or atypical) or secondary (with a co-existing diseases). Typical HUS usually means shiga-toxin-medicated and thrombotic thrombocytopenic purpura. Secondary HUS is often initiated by coexisting diseases or conditions such as infections, transplantation, cancer, and autoimmune disease. Atypical HUS (aHUS) is usually induced by genetic mutations of one or several complement-regulating genes and associated with dysregulated complement activation. In the era of compliment-inhibiting therapy, early recognition of aHUS is important for patient prognosis. However, compliment-inhibiting therapy is not always beneficial in patients with secondary HUS.

Case Report: We present a case of a 49-year-old woman with aHUS, which was caused by a novel genetic point mutation of complement factor H gene (p.Gly1110Ala) mimicking secondary HUS with scleroderma. Instead of administering eculizumab treatment for C5 polymorphism, the patient was successfully treated with mycophenolate mofetil.

Conclusions: HUS has complex and mixed etiologies and requires genetic testing. Attention should be paid to new point mutations in aHUS.

MeSH Keywords: Hemolytic-Uremic Syndrome • Mutation • Scleroderma, Diffuse

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Background

Thrombotic microangiopathies (TMAs) are pathologies that result in thrombosis in capillaries and arterioles because of endothelial injuries [1]. They can be classified according to their onset – children or adults, sudden or gradual, and hereditary or acquired. Despite their different manifestations, TMA is defined by common clinical and pathological features – MAHA and thrombocytopenia with organ injury [2]. TMA syndromes are etiologically classified as thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) caused by Shiga toxin-producing *Escherichia coli* (STEC), atypical HUS (aHUS), and secondary HUS. In the era of compliment-inhibiting therapy, early recognition and concise differentiation of TMA are important for patient prognosis, especially in case of aHUS. Eculizumab is widely used for aHUS, but clinicians should be able to distinguish primary forms of the disease from secondary ones. Early and correct differential diagnosis is the key to successful eculizumab therapy.

Case Report

A 49-year-old woman was referred to our hospital because of low hemoglobin level, elevated bilirubin level, and decreased kidney function. She initially presented with shortness of breath and bilateral edemas of the foot, debuted 5 days before requesting a medical examination. She had no history of hypertension or diabetes mellitus, but 5 years ago at a nearby clinic she was found to have high antinuclear antibody titer (ANA, 1: 320, speckled type). Despite lacking a diagnosis, she was administered celecoxib, pregabalin, folic acid, leflunomide, and triamcinolone due to the suspicion of rheumatoid arthritis. She discontinued the medication one month ago because she felt symptom-free. Her initial symptom was in the hands, especially finger swelling and intermittent Raynaud phenomenon. The physical examination showed no sign of arthritis, bone deformity, or skin modifications, including sclerodactyly. The laboratory findings were: hemoglobin, 8.5 g/dL; WBC, 5,390×10^9/L; platelet, 22×10^9/L; serum protein, 5.4 g/dL; serum albumin, 3.5 g/dL; total bilirubin, 4.25 mg/dL; direct bilirubin, 0.97 mg/dL; aspartate transaminase, 74 U/L; alanine transaminase, 32 U/L; blood urea nitrogen, 62.5 mg/dL; creatinine, 4.22 mg/dL; and lactate dehydrogenase, 1988 U/L. Prothrombin time was 12.2 s (ref. 10~13) and INR was 1.08 (ref. 0.85~1.3). Fibrin degradation production (FDP) was 5.7 µg/ml (ref. <5) and D-dimer was 1.85 µg/ml (ref. <0.55). Although FDP and D-dimer were slightly above the reference values, we considered this to be clinically insignificant with disseminated intravascular coagulopathy. Due to suspicion of hemolysis, additional laboratory tests were performed – peripheral blood smear, schistocyte (++); reticulocyte, 5.96%; Coombs test, negative; C3, 98.1 mg/dL (ref. 90~180); C4, 23.4 mg/dL (ref. 10~40); CH 50, 54.9 U/mL (ref. 23~46 U/ml) (Table 1). The ADAMTS13 activity test and stool exam for enterohemorrhagic *Escherichia coli* (EHEC) were immediately performed because TMA syndrome was suspected. Therapeutic plasmapheresis was performed after suspecting the TMA syndrome, and hemodialysis was performed later because of the decreased urine output (less than 100 ml per day). The clinical evolution is presented in Figure 1. The ADAMTS13 activity was 50.1% (reference, normal ≥40%) and the stool test was negative for EHEC. In evolution, neutropenic fever and erythema related antibiotics were noted (Figure 2). Autoimmune markers were determined – ANA, positive (1: 320, speckled); anti-double stranded DNA antibodies, negative; rheumatoid factor, 6.1 U/mL; anti-cyclic citrullinated peptide antibodies, below 0.5 U/mL; anti-Scl-70 antibodies, negative; anti-centromere antibodies, normal; anti-RNP antibodies, negative; anti-RNA polymerase III antibodies, weakly positive, 44.4 (reference, negative <28; weakly positive 28.0–49.9; positive ≥50). For diagnostic accuracy, gene analysis was performed, which revealed a variant, of uncertain significance, of the CFH gene (Figure 3). We eventually diagnosed the patient with atypical hemolytic uremic syndrome accompanied with an autoimmune disease, systemic sclerosis sine scleroderma. Eculizumab was not administered because the patient presented C5 polymorphism, which has been reported to have resistance to C5-inhibiting therapy; instead, the patient received mycophenolate mofetil (MMF) 1 g per day as induction and maintenance therapy, and steroid was tapered due to concern about possible renal crisis from systemic sclerosis sine scleroderma. Thrombocytopenia and hemolytic anemia were cleared after 2 months of treatment. Four months later, the MMF dosage was reduced to 500 mg per day because of the myelosuppression (Figure 4). The patient recovered successfully from MAHA and thrombocytopenia, but not from the organ damage. After 5 months of treatment, the urine output was over 1000 ml per day, but the patient still needs hemodialysis twice a week because of the other biomarkers. Informed consent for publication of the clinical data was obtained from the patient.

Discussion

Dysregulated complement activation is the main etiology of aHUS. The complement cascade consists of 3 pathways: classical, alternative, and the lectin pathway. These 3 pathways converge at component C3. C3 convertase cleaves C3 to produce more C3b to deposit on the cell membrane, where it creates C5 convertase. This leads to cell death through membrane attack complex (MAC) [3]. Unchecked C3b depositions and the destruction of normal cells are suppressed by innate regulators within the alternative pathway. For example, to prevent C3 convertase formation, complement factor H (CFH) binds to C3b and promotes the activity of complement factor I (CFI).

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Table 1. Hematologic laboratory finding of this case report at presentation.

Complete blood cell count			Metabolic panel			Blood coagulation test		
Parameter	**Result**	**Ref.**	**Parameter**	**Result**	**Ref.**	**Parameter**	**Result**	**Ref.**
Hb (g/dL)	8.5	12~16	Protein (g/dL)	5.4	6.7~8.3	PT (sec)	12	10~13
WBC (10^9/L)	5.39	4~10	Albumin (g/dL)	3.5	3.1~5.2	PT (INR)	1.08	0.85~1.3
Neutrophil (%)	92	40~80	Bilirubin, total (mg/dL)	4.25	0.2~1.1	FDP (µg/mL)	5.7	~5
Lymphocyte (%)	4	15~50	Bilirubin, direct (mg/dL)	0.97	0.0~0.6	D-dimer (µg/mL)	1.85	~0.55
Monocyte (%)	4	2~11	AST (U/L)	74	7~38			
PLT (10^9/L)	22	140~440	ALT (U/L)	32	4~43			
			BUN (mg/dL)	62.5	8~20	**Immune serology**		
			Creatinine (mg/dL)	4.22	0.6~1.2	CRP (mg/dL)	0.8	~0.3
			LDH (U/L)	1,988	130~270	C3 (mg/dL)	98.1	90~180
			Sodium (mmol/L)	140	138~148	C4 (mg/dL)	23.4	10~40
			Potassium (mmol/L)	4.2	3.5~5.3	CH50 (U/mL)	54.9	23~46
			Chloride (mmol/L)	108	98~108	Haptoglobin (mg/dL)	1.7	30~200

Hb – hemoglobin; WBC – white blood cell count; PLT – platelet; AST – aspartate transaminase; ALT – alanine transaminase; BUN – blood urea nitrogen; LDH – lactate dehydrogenase; PT – prothrombin time; FDP – fibrin degradation production.

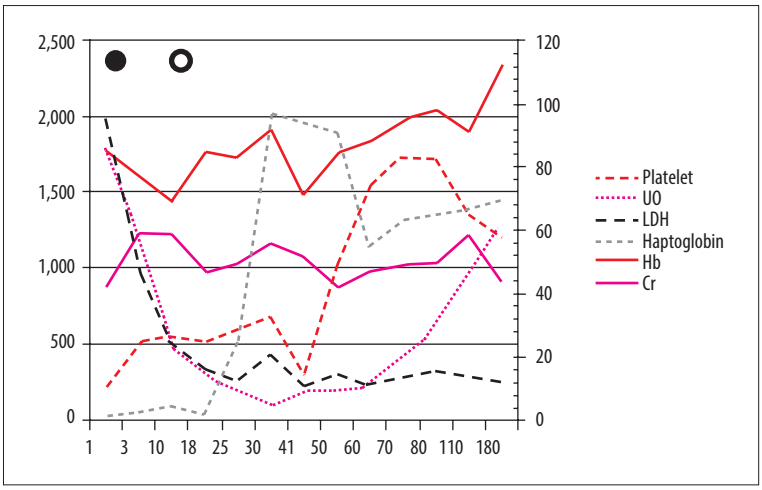

Figure 1. Clinical evolution of the patient for 180 days following presentation. This figure is summarizing the clinical evolution of the patient. TPE and hemodialysis were started after 10 days and hemodialysis is continued to the present time. The platelet levels recovered (over 100×10^9/L) after almost 30 days. Urine output has recovered (over 1,000 ml/day) after almost 150 days. X axis for hospital days. Y (left) axis for UO (mL) and LDH. Y (right) axis for platelet (10×10^8/L), haptoglobin, Hb (g/L), and Cr (10×1 mg/L). Closed circle for the first therapeutic plasmapheresis (TPE). Open circle for the first hemodialysis. UO – urine output; LDH – lactate dehydrogenase; Hb – hemoglobin; Cr – creatinine.

FI is a serine protease that downregulates C3 convertase by proteolytic inactivation of C3b [4]. In aHUS, the alternative complement pathway is over-activated through the autoantibodies of the innate regulators and/or genetic mutations affecting factors such as FI, FH, and C3 [5]. In primary aHUS, pathogenic genomic variants have been reported in 40% to 60% of cases, and 5% to 10% of cases present anti-FI antibodies [6]. The genomic variants with complement related can be divided 2 groups according to its function. Mutations of C3 and complement factor B show about 10% of aHUS as pathway activators (gain of function). CFH variants are the most frequent mutation and account for 30% of aHUS as pathway regulators

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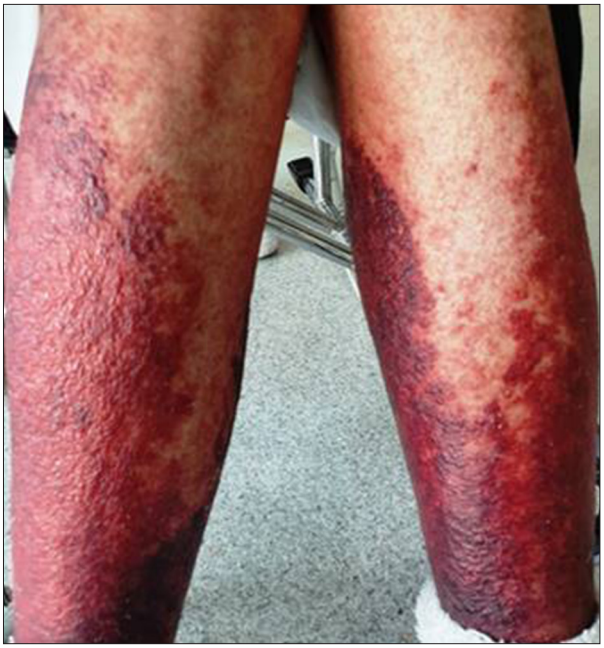

Figure 2. A photograph of the patient's legs. A photograph of the patient's legs taken during the neutropenic fever and in the presence of the erythema. Diffuse purpuric edematous patches are noted on both legs. The skin lesions look thickened and hardened.

Gene	Isoform	NT change	AA change	Zyg	ACMG class
CFH	NM_000186.3	c.3329G>C	p.(Gly1110A1a)	Het	VUS

Figure 3. Identified variant of the CFH gene. The CFH gene mutation is p.Gly1110Ala. AA – amino acid; Het – heterozygous; Hom – homozygous; NT – nucleotide; VUS – variant of uncertain significance; Zyg – zygosity.

(loss of function). CFI, membrane cofactor protein (MCP/CD46), and complement factor H-related proteins (CFHR1-5) account for 8%, 9%, and 4%, respectively, of aHUS as loss of function mutation [7]. Acquired autoantibodies against CFH have been identified in almost 20% of aHUS cases. Coagulation-related factors such as thrombomodulin (THBD), diacylglycerol kinase epsilon (DGKE), and plasminogen (PLG) are also associated with aHUS [8]. Secondary HUS may be associated with infections, transplantation (solid organ or bone marrow), autoimmune disease, cancer, pregnancy, and the use of certain cytotoxic drugs. To differentiate aHUS from secondary HUS, clearly identifiable causes are needed. However, the identifiable causes may not always be the diagnosis of the secondary HUS.

In our case, the equivocal anti-RNA polymerase III antibodies, the initial high blood pressure (190/100 mmHg), and decreased renal function raised the possibility of scleroderma renal crisis (SRC) from systemic sclerosis sine scleroderma. SRC is an uncommon but life-threatening manifestation of systemic sclerosis. SRC has been reported in up to 33% of patients with RNA polymerase III antibodies [9]. SRC is characterized by a sudden and marked increase in systemic blood pressure, and rapidly progressive acute kidney failure. MAHA is detectable in 50% of patients [10]. Because of the clinical overlap with aHUS, SRC is suggested as a cause of HUS. Autoimmune diseases can also trigger dysregulation of the alternative complement pathway, which is the main mechanism of aHUS. However, the clinical presentation and the outcome might be different between primary and secondary HUS. In the French registry, patients with secondary HUS needed dialysis therapy less frequently at presentation, progressed less frequently to end-stage renal disease, and experienced fewer relapses [11]. Also, genetic variants in complement genes were similar between secondary HUS patients and healthy controls [11]. This finding is in contrast to aHUS, which features a high incidence of mostly pathogenic complement genes variants [12]. More than 100 mutations were described as associated with aHUS, but it still accounts

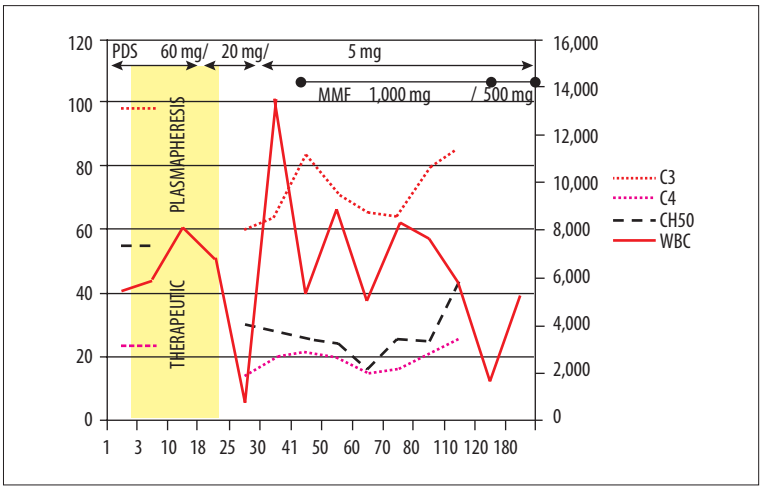

Figure 4. Complement and WBC changes with immune-modulating treatments. Following therapeutic plasmapheresis, severe neutropenia was noted. The C3 levels recovered after about 80 days. PDS – prednisolone; MMF – mycophenolate mofetil; WBC – white blood cells.

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for only 60% of the disease. New mutations will continue to be discovered in the future and we should keep looking.

In the present case, we identified a novel heterozygous CFH genetic mutation on chromosome 1q32, classified as a variant of uncertain significance based on the American College of Medical Genetics criteria. A missense mutation, Gly1110Ala, was found in the CFH gene. Factor H is a single-polypeptide chain glycoprotein composed of 20 repetitive units of 60 amino acids, named short consensus repeats (SCR), arranged in a continuous fashion [13]. Among the SCRs, SCR 19-20 is the most important site and is a "hot spot" for preventing the alternative pathway activation in host cells [14]. The point mutation we found is in exon 21, encoding the SCR 19 domain. Although Gly1110Ala has not yet been reported as a pathogenic variant in aHUS [15], this missense is expected to have a pathogenic nature. The incidence of this mutation is lower than 0.01% in a multi-ethnicity pool and is lower than 0.3% in the Korean Reference Genome Database. Despite its rarity, this mutation is probably closely related with aHUS presentation as a rare pathogenic variant. Another important point is that this patient's disease manifested at the age of 49 years and it might be related with intermediate penetration of mutation. According to a familial and sporadic aHUS study, only 50% penetration is observed in atypical HUS germline mutations, which usually manifest in early life [16], and the rest of them have intermediate penetrance. This suggests the "2-hit" hypothesis with genetic mutation and aHUS. The mutation itself may not be sufficient for disease development in half of the cases with intermediate penetrance, as they need a second trigger. For example, renal crisis from systemic sclerosis sine scleroderma may be a "second hit" in this patient.

Conclusions

As illustrated by this case report, the pathogenesis of aHUS is complex, and various etiologies can coexist in a single patient. When dealing with HUS, it is recommended to check the complement gene mutations, despite pre-existing complement-amplifying conditions like systemic sclerosis sine scleroderma, in the era of compliment-inhibiting therapy, which can improve the outcome and survival of patients. This case is very unique and interesting because we were able to avoid eculizumab therapy by identifying C5 polymorphisms and identifying new factor H mutation with intermediate penetrance, which was related to the "second hit" theory from systemic sclerosis sine scleroderma.

Conflicts of interest

None.

References:

1. Benz K, Amann K: Thrombotic microangiopathy: New insights. Curr Opin Nephrol Hypertens, 2010; 19: 242–47
2. Moake JL: Thrombotic microangiopathies. N Engl J Med, 2002 ;347: 589–600
3. Haapasalo K, Meri S: Regulation of the complement system by pentraxins. Front Immunol, 2019; 10: 1750
4. Oppermann M, Manuelian T, Józsi M et al: The C-terminus of complement regulator Factor H mediates target recognition: Evidence for a compact conformation of the native protein. Clin Exp Immunol, 2006; 144: 342–52
5. Esparza-Gordillo J, Jorge EGd, Buil A et al: Predisposition to atypical hemolytic uremic syndrome involves the concurrence of different susceptibility alleles in the regulators of complement activation gene cluster in 1q32. Hum Mol Genet, 2005; 14: 703–12
6. Brocklebank V, Wood KM, Kavanagh D: Thrombotic microangiopathy and the kidney. Clin J Am Soc Nephrol, 2018; 13: 300–17
7. De Jorge EG, Pickering MC: Atypical hemolytic uremic syndrome: telling the difference between H and Y. Kidney Int, 2010; 78: 721–23
8. Yoshida Y, Kato H, Ikeda Y, Nangaku M: Pathogenesis of atypical hemolytic uremic syndrome. J Atheroscler Thromb, 2019; 26(2): 99–110
9. Steen VD: Autoantibodies in systemic sclerosis. Semin Arthritis Rheum, 2005; 35(1): 35–42
10. Steen VD: Kidney involvement in systemic sclerosis. Presse Med, 2014; 43: e305–14
11. Le Clech A, Simon-Tillaux N, Provôt F et al: Atypical and secondary hemolytic uremic syndromes have a distinct presentation and no common genetic risk factors. Kidney Int, 2019; 95: 1443–52
12. Fremeaux-Bacchi V, Fakhouri F, Garnier A et al: Genetics and outcome of atypical hemolytic uremic syndrome: A nationwide French series comparing children and adults. Clin J Am Soc Nephrol, 2013; 8: 554–62
13. Ripoche J, Day A, Harris TJ, Sim R: The complete amino acid sequence of human complement factor H. Biochemical J, 1988; 249: 593–602
14. Rodríguez de Córdoba S, Esparza-Gordillo J, Goicoechea de Jorge E et al: The human complement factor H: Functional roles, genetic variations and disease associations. Mol Immunol, 2004; 41: 355–67
15. Osborne AJ, Breno M, Borsa NG et al: Statistical validation of rare complement variants provides insights into the molecular basis of atypical hemolytic uremic syndrome and C3 glomerulopathy. J Immunol, 2018; 200: 2464–78
16. Noris M, Caprioli J, Bresin E et al: Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. Clin J Am Soc Nephrol, 2010; 5: 1844–59

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