Renal Replacement Therapy

CASE REPORT Open Access

Plasma exchange for thrombotic microangiopathy secondary to dermatomyositis associated with acute kidney injury and complement activation: a case report with literature review

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Abstract

Background: Thrombotic microangiopathy (TMA) in patients with connective tissue disease is rare but life-threatening. In particular, the survival rate of patients with dermatomyositis (DM) that develop TMA is low. The effectiveness of plasma exchange (PEX) therapy is unclear for the treatment of TMA secondary to DM.

Case presentation: We describe a case of a 28-year-old woman who developed severe DM complicated by aspiration pneumonia from dysphagia and acute kidney injury. The patient was unresponsive to corticosteroids and intravenous immunoglobulin (IVIG) therapy and developed TMA. In this case, immunofluorescence of skin biopsy revealed that complement activation was involved in the pathogenesis of DM. After 6 PEX therapies, thrombocytopenia improved. She was successfully treated by intensive care and PEX therapy.

Conclusions: PEX therapy was effective to treat TMA secondary to DM associated with complement activation.

Keywords: Dermatomyositis, Thrombotic microangiopathy, Plasma exchange, Complement activation, ADAMTS13

Background

Dermatomyositis (DM) is an idiopathic inflammatory muscle disease with characteristic cutaneous manifestations such as a periorbital heliotrope rash with edema and violaceous eruption on the knuckles (Gottron's papules) [1]. Skin manifestations often accompany or precede muscle weakness, which is typically distributed symmetrically and proximally [2]. Thrombotic microangiopathy (TMA) in patients with connective tissue disease (CTD) is rare but life-threatening. In particular, the survival rate of patients with DM that develop TMA is low, only 18.8% in a small case series study [3].

For the treatment of corticosteroid-resistant DM, plasma exchange (PEX) therapy is not effective for muscle strength and functional capacity [4]. Furthermore, because the disease is rare, the effectiveness of PEX is unclear for the treatment of TMA secondary to DM.

Here, we describe a patient with DM accompanied by DM-associated TMA who survived by intensive care and PEX therapy.

Case presentation

A 28-year-old woman with no significant medical history was admitted to the dermatology department for the treatment of a rash and muscle pain. Eighteen days before admission, erythema appeared over the trunk, face, and extremities. Three days later, pain and weakness of the bilateral thigh muscles developed. The muscle weakness progressed including difficulty climbing stairs. On admission, physical examination revealed Gottron's

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papules on the metacarpophalangeal joints (Fig. 1), heliotrope rash, and muscular pain and weakness in the thighs and upper arms. Laboratory evaluation revealed elevated levels of creatine kinase (CK, 9823 U/L) and myoglobin (307.3 ng/mL). Serum anti-PL-12 antibody, an anti-aminoacyl tRNA synthetase antibody, was weakly positive and anti-factor H antibodies were negative (Table 1). Magnetic resonance imaging (MRI) revealed high intensity in the lesions of the bilateral thigh muscles in T2-weighted and STIR (short tau inversion recovery) images (Fig. 2a, b). The pathological findings from a skin biopsy showed a perivascular infiltration of inflammatory cells in the superficial dermis (Fig. 2c), whereas in muscle biopsy, muscle fiber necrosis and inflammatory infiltrates were not observed. Immunofluorescence of the skin biopsy revealed deposition of IgM, fibrinogen, C3d, C4d, and C5b-9 on dermal vessels (Fig. 2d).

According to these findings, she was diagnosed with dermatomyositis (DM), and therapy was initiated with methylprednisolone pulse (1 g/day for 3 days). However, the response to this therapy was poor, her muscle weakness progressed, and she developed severe dysphagia. Therefore, intravenous immunoglobulin (IVIG) therapy (20 g/day for 3 days) was performed. She developed acute kidney injury (AKI) and was referred to our nephrology department. On the 18th day, continuous hemodiafiltration (CHDF) was initiated because of AKI with anuria, hyperkalemia, and hypermyoglobinemia. Furthermore, respiratory failure developed because of complications with aspiration pneumonia and exhausted respiratory muscles, and mechanical ventilation was started. Laboratory evaluation revealed marked thrombocytopenia and hemolytic anemia with fragmented erythrocytes. Her kidney injury and the instability of her consciousness suggested a diagnosis of thrombotic microangiopathy (TMA), and we initiated PEX therapy using fresh frozen plasma at the dose of 1.5 times the estimated plasma volume (EPV). EPV was calculated from the equation given below [5],

$$\mathrm{EPV\ (L)} = \mathrm{body\ weight\ (kg)} \times 0.065 \times (1 - \mathrm{hematocrit})$$

In PEX therapy, we used Plasmacure PE-05 (Kuraray Medical, Tokyo, Japan) as a plasma separator. In our case, body weight was 49.0 kg and hematocrit was 0.23, respectively, as the initiation of PEX therapy.

Her clinical course is shown in Fig. 3. After 6 PEX therapies, thrombocytopenia improved. After pneumonia was resolved, azathioprine was added to oral prednisolone to control DM. On the 36th day, she was withdrawn from mechanical ventilation. Her urine volume recovered gradually, and hemodialysis therapy was discontinued on the 37th day. After long-term rehabilitation, her muscle strength gradually recovered, and she was discharged on the 200th day.

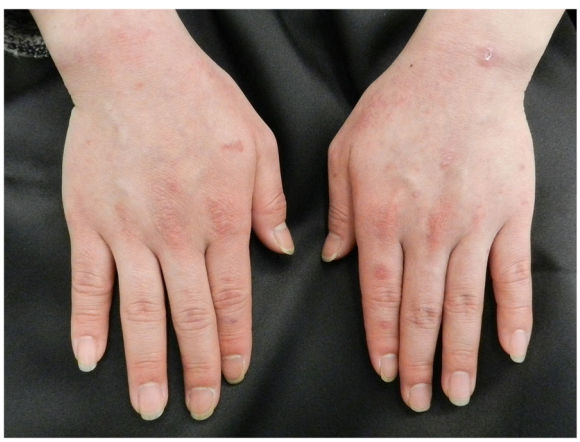

Fig. 1 A pathognomonic manifestation of dermatomyositis, Gottron's papule is seen on the metacarpophalangeal joints

Discussion and conclusions

Our patient was diagnosed with DM by characteristic cutaneous manifestations, progressive muscle weakness, muscle enzyme elevation, and MRI findings. Although muscle biopsy revealed no characteristic features of DM, we considered this result was caused by sampling error. The patient was unresponsive to corticosteroids and IVIG in the first line therapy and developed TMA. However, immunosuppressive therapy was not increased because of aspiration pneumonia from dysphagia, which is frequently observed in severe DM [6].

The pathogenic mechanism underlying the relationship between DM and TMA is unclear. In the pathogenesis of DM, however, complement C5b-9 is activated and deposited on the endothelial cell wall of endomysial capillaries, which leads to necrosis, ischemia, and muscle fiber destruction [2]. Low-serum complement level and C5b-9 deposition on dermal vessels suggest that complement-mediated microvasculopathy was involved in the pathogenesis of DM and TMA in our patient.

Our patient did not exhibit a severe deficiency of ADAMTS13 activity (i.e., < 5% of normal). For CTD-associated TMA, there are fewer patients who have a severe deficiency of ADAMTS13 activity (21%) than patients who have a mild-to-moderate deficiency of ADMATS13 activity (79%) [7]. In contrast to thrombotic thrombocytopenic purpura (TTP), most patients with CTD-associated TMA have high plasma levels of von Willebrand factor (VWF) and a mild-to-moderate deficiency of ADMATS13 activity [8].

For TTP treatment, survival rate improves markedly by PEX therapy [9]. PEX works by replenishing ADMATS13 and by removing ADAMTS13 inhibitors and UL-VWFM. The efficacy of PEX for the treatment

Table 1 Laboratory data

Hematology		
WBC	18,000	/μL
Neut	92	%
Ly	3	%
RBC	268×10^4	/μL
Hemoglobin	7.9	g/dL
Platelet	19,000	/μL
Fragmentation	+	
Haptoglobin	< 10	mg/dL
ADAMTS13		
Activity	17.8	%
Inhibitor	–	
Direct Coombs' test	–	
Indirect Coombs' test	–	
Biochemistry		
TP	6.0	g/dL
Alb	2.0	g/dL
BUN	32	mg/dL
Cre	0.6	mg/dL
Na	120	mEq/L
K	6.1	mEq/L
Cl	89	mEq/L
LDH	1942	IU/L
AST	260	IU/L
ALT	138	IU/L
CK	9823	IU/L
Myoglobin (≦ 154.9)	307.3	ng/mL
Ferritin (12–60)	876	ng/mL
Serology		
CRP	0.27	mg/dL
C3	65	mg/dL
C4	14	mg/dL
CH50	32.6	U/mL
ANA	< 40x	
Anti-DNA Ab	–	
Anti-Jo-1 Ab	–	
Anti-ARS Ab	PL-12 +	
Anti-factor H Ab	–	
Coagulation		
PT-INR	1.07	
APTT (24–40)	39.3	sec
Fibrinogen	252	mg/dL
FDP	12.4	μg/mL
D-dimer	5.74	μg/mL
Urinalysis		
pH	5.5	
Protein	1+	
Glucose	–	
Occult blood	2+	
Sediment		
RBC	10–19	/hpf
WBC	1–4	/hpf
Cast	–	
Myoglobin (≦ 10)	110	ng/mL

WBC, leukocytes; *RBC*, erythrocytes; *Neu*, neutrophil; *Ly*, lymphocyte; *TP*, total protein; *Alb*, albumin; *BUN*, blood urea nitrogen; *Cre*, creatinine; *LDH*, lactate dehydrogenase; *AST*, aspartate aminotransferase; *ALT*, alanine aminotransferase; *CK*, creatine kinase; *CRP*, C-reactive protein; *ANA*, anti-nuclear antibody; *Ab*, antibodies; *ARS*, aminoacyl-tRNA synthetase; *PT*, prothrombin time; *APTT*, activated partial thromboplastin time; *FDP*, fibrin degradation products; *hpf*, high-power field

of TMA of unclear etiology and without severe ADAMTS13 deficiency remains controversial [10–12]. For CTD-associated TMA, the efficacy of PEX is unclear because of the lack of controlled prospective studies, but PEX is usually administered to eliminate UL-VWFM and activated complement factors and to replenish complement regulatory factors. In our case, PEX was considered as effective in eliminating UL-VWFM caused by complement-mediated microvasculopathy and calming complement activation. Because an improvement of CTD is important for the treatment of CTD-associated TMA, PEX therapy combined with immunosuppressors, including glucocorticoids and cytotoxic agents, results in better outcomes [13].

In conclusion, we described a patient with severe dermatomyositis complicated by TMA who was successfully treated by intensive care and PEX therapy. Considering complement-mediated microvasculopathy as a pathogenic mechanism of DM, PEX therapy may be highly effective in treating TMA secondary to DM.

Mini review

TMA in connective tissue disease

Thrombotic microangiopathies (TMAs) are diseases characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ failure due to microvascular occlusions caused by platelet thrombi [14]. TMA is a pathological diagnostic term for pathological conditions exhibiting systemic microvascular thrombosis and vascular endothelial dysfunction. Japanese Society of Nephrology and Japan Pediatric Society developed diagnostic criteria for atypical hemolytic uremic syndrome (aHUS) [15]. In this diagnostic criterion in 2015, TMAs were classified according to their pathogenesis as follows: Shiga toxin–producing *E. coli* hemolytic uremic syndrome (STEC-HUS), TTP, atypical HUS (aHUS), and secondary TMA (Table 2).

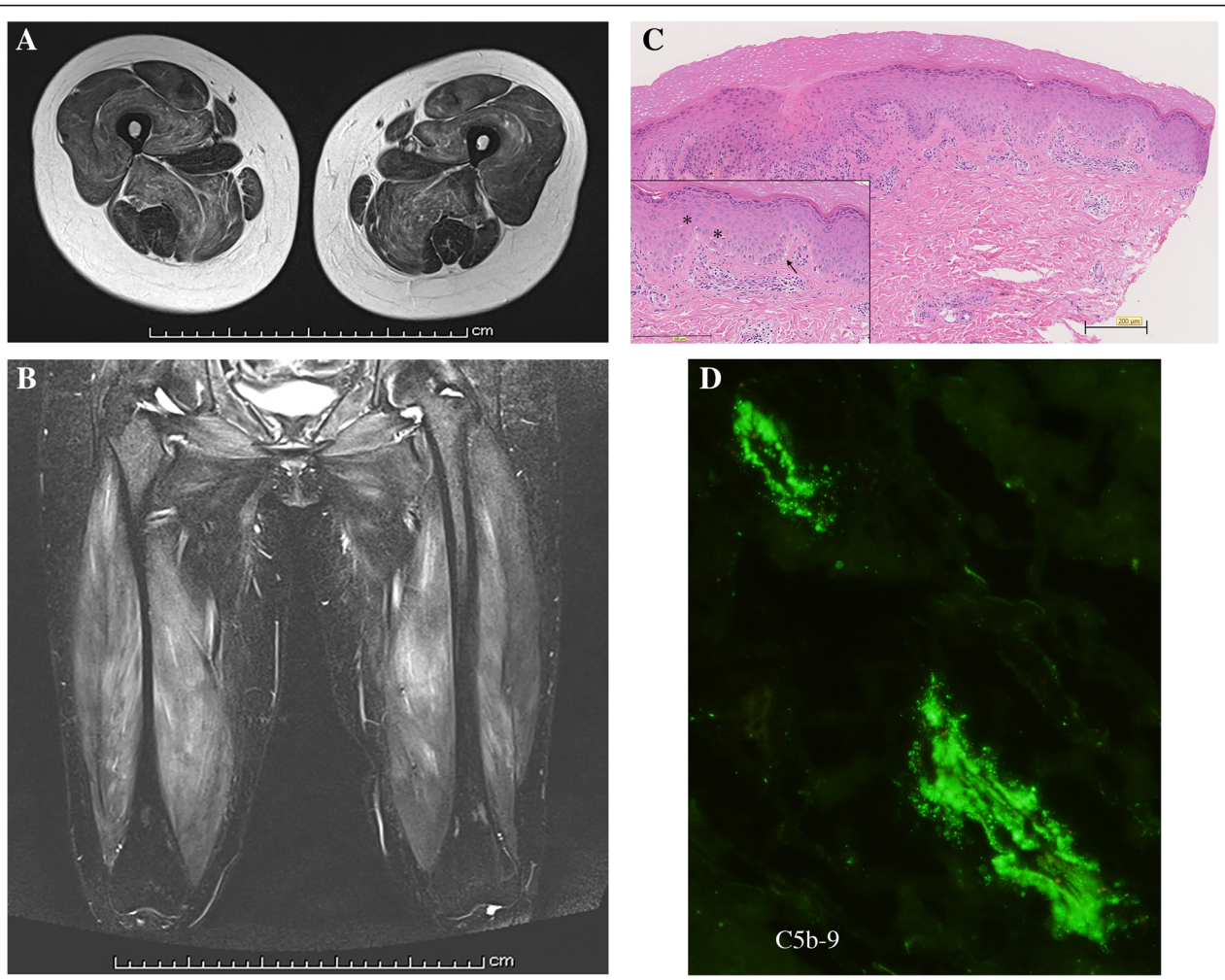

Fig. 2 MRI and histological findings of the dermal biopsy. MRI showed high intensity in the lesions of the bilateral thigh muscles in T2-weighted (**a**) and short tau inversion recovery (**b**) imaging. In a skin biopsy, a perivascular infiltration of inflammatory cells in the superficial dermis, slight basal liquefaction degeneration (arrow), and some apoptotic cells (asterisk) in the epidermis were observed (**c**). C5b-9 deposits on the endothelial cell wall of the dermal vasculature (**d**)

In a Japanese registry of 919 TMA patients [7], CTD-associated TMA is the most common cause of secondary TMA (221 out of 382 patients, 57.8%). In CTD-associated TMA, TMA complicated by systemic lupus erythematosus (SLE) is the most frequent (41.6%) followed by systemic sclerosis (23.0%) and polymyositis/dermatomyositis (6.3%).

TMA occurs in 3 to 9% cases of SLE patients [16]. The differential diagnosis of TMA with SLE patients includes malignant hypertension, antiphospholipid syndrome (APS)/catastrophic APS, TTP, and drug-induced TMA. Careful evaluation of peripheral blood smear is useful for the diagnosis of these clinical syndromes. The patients with SLE accompanied by malignant hypertension and TTP show fragmented red blood cells in peripheral blood smear [17].

In the management of CTD-associated TMA, treating underlying autoimmune disorders is important. Furthermore, in suspected cases, anticoagulation, corticosteroids, PEX therapy, and IVIG have been used. In some cases showing resistance for these conventional therapies, the efficacy of anti-C5 monoclonal antibody eculizumab has been reported [16, 18]. Eculizumab binds to the C5 complement with high affinity and blocks the assembly of C5b-9. Eculizumab has shown the effectiveness and been approved for the treatment of patients with aHUS [19]. However, the effectiveness of eculizumab for the treatment of TMA secondary to SLE is still controversial.

The roles of complements in TMA

Dysregulation of complement cascade plays a major role in the pathogenesis of TMAs. Complement is part of the

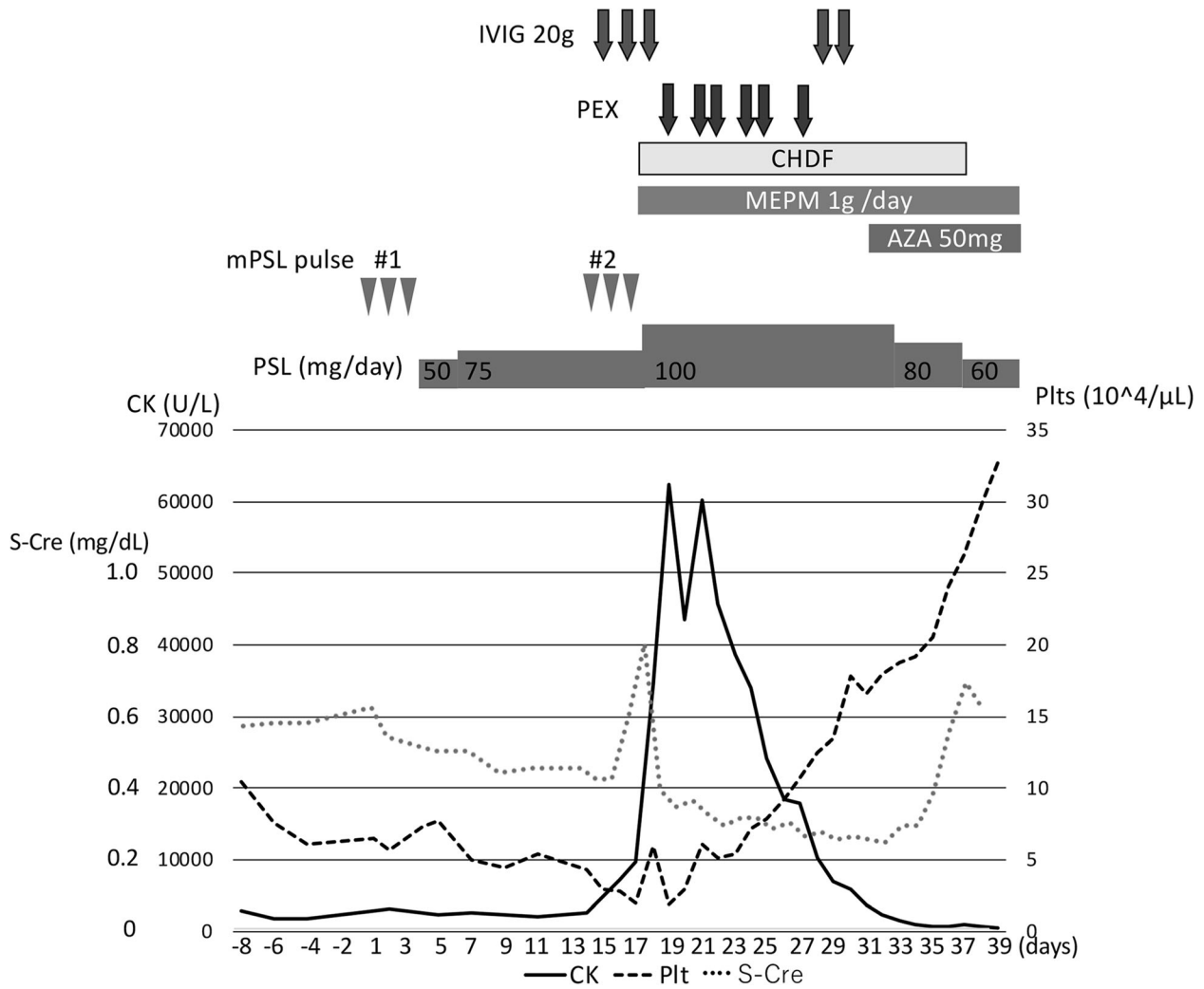

Fig. 3 Clinical course. CK, creatine kinase; Plt, platelet; IVIG, intravenous immunoglobulin; PEX, plasma exchange; CHDF, continuous hemodiafiltration; MEPM, meropenem; AZA, azathioprine; mPSL, methylprednisolone; PSL, prednisolone; S-Cre, serum creatinine

innate immune system and has three main physiologic activities, that is, defending against pyogenic bacterial infection, interfacing innate and adaptive immunity, and disposing of immune complexes and the products of inflammatory injury. Under normal circumstances, the regulatory mechanisms of complement are well balanced. For instance, complement attacks against invading pathogens, on the one hand, complement activation on normal cells and tissues are limited on the other hand [20]. Insufficient or excessive complement activity disturbs homeostasis and causes some diseases. These delicate balances are usually maintained by specific complement regulators.

Complement regulatory proteins inhibit complement activation both in the fluid phase and on membrane surface. Dysfunction or deficiency of some complement regulatory protein is associated with TMAs. aHUS is caused by genetic mutations in factor H, factor I, membrane cofactor protein (MCP), C3, factor B, and thrombomodulin [21]. Furthermore, in 6 to 10% of patients with aHUS have anti-Factor H autoantibodies (Table 3) [22, 23]. Factor H is a soluble complement regulator of the alternative pathway by competing with factor B in binding to C3b, by acting as a cofactor for factor I in inactivation of C3b, and by enhancing dissociation of C3 convertase [24, 25]. On endothelial cell surface, inactivation of deposited C3b to iC3b by concerted action of factor H, factor I, and MCP prevents the progression of the C3b-amplification loop [25]. Dysfunction of Factor H by genetic mutation or anti-Factor H antibodies decreases the avidity of factor H to C3b. These results in the progression of the C3b-amplification loop and finally

Table 2 Classification of TMA

STEC-HUS
Infection with Shiga toxin–producing *Escherichia coli* or less frequently with *Shigella dysenteriae*. The most common cause of HUS in children.
TTP
Deficiency of ADAMTS13 hereditary (Upshaw-Shulman syndrome) or acquired that causes by ADAMTS13 inhibitor.
aHUS, complement regulation abnormality
Congenital
Genetic mutations of complement proteins
Acquired
Autoantibodies against complement proteins, such as anti-factor H antibody
Secondary TMA
Cobalamin metabolism disorder
Drug-induced
Chemotherapeutic agents (e.g., gemcitabine, mitomycin)
Immunosuppressive agents (e.g., cyclosporine, tacrolimus)
Antiplatelet agents (e.g., ticlopidine)
Infection
Pneumococcus, human immunodeficiency virus, pertussis, influenza, *varicella*
Pregnancy-related
Preeclampsia/eclampsia, hemolysis, elevated liver HELLP
Auto-immune disease, collagen disease
Systemic lupus erythematosus, systemic sclerosis, polymyositis/ dermatomyositis
Bone marrow transplant, organ transplant-related

Table 3 Complement abnormalities in aHUS

Form of aHUS	Complement abnormalities
Familial	Mutations in factor H, 40–45%
	In factor I, 5–10%
	In C3, 8–10%
	In membrane cofactor protein, 7–15%
	In thrombomodulin, 9%
	In factor B, 1–2%
Sporadic	Mutations in factor H, 15–20%
	In factor I, 3–6%
	In C3, 4–6%
	In membrane cofactor protein, 6–10%
	In thrombomodulin, 2%
	In factor B, 2 cases
	Anti-Factor H antibodies, 6–10%

leads to C5b-9 formation. C5b-9 formation on endothelial cells induces pore formation and leads to calcium-influx into the cells, metabolic activation, and membrane alterations. As a result, endothelial cells become swollen and detach from the vessel walls [21]. Combined with similar changes in platelets and leukocytes, an increase in procoagulant activity causes thrombosis [26].

Abbreviations

aHUS: Atypical hemolytic uremic syndrome; AKI: Acute kidney injury; APS: Antiphospholipid syndrome; CHDF: Continuous hemodiafiltration; CTD: Connective tissue disease; DM: Dermatomyositis; EPV: Estimated plasma volume; IVIG: Intravenous immunoglobulin; MCP: Membrane cofactor protein; MRI: Magnetic resonance imaging; PEX: Plasma exchange; SLE: Systemic lupus erythematosus; STEC-HUS: Shiga-toxin-producing *E. coli* hemolytic uremic syndrome; TMA: Thrombotic microangiopathy; TTP: Thrombocytopenic purpura; UL-VWFM: Unusually large VWF multimers; VWF: von Willebrand factor

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Authors' contributions

NH, KO, YT, YK, SK, and YI took care of this patient. KT and MN evaluated the findings of skin biopsy. NH, KF, HA, and HY analyzed and interpreted the patient data. NH and HY prepared this manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data and materials were all included in the manuscript.

Ethics approval and consent to participate

The case report was written in compliance with the Declaration of Helsinki.

Consent for publication

Agreement was obtained from the patient for publication of this case report.

Competing interests

The authors declare that they have no competing interests.

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