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【 CASE REPORT 】

Acute Kidney Injury Caused by Evans Syndrome with Systemic Lupus Erythematosus and Systemic Sclerosis

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Abstract:
A 65-year-old woman with systemic sclerosis and systemic lupus erythematosus developed acute kidney injury (AKI), Coombs-positive autoimmune hemolytic anemia and autoimmune thrombocytopenia; therefore, she was diagnosed with Evans syndrome (ES). Intravascular hemolysis was suggested as the cause of AKI based on the presence of acute tubular injury and trace hemosiderin deposits on the renal biopsy. The renal function, hemolytic anemia and thrombocytopenia were restored by an increased dose of glucocorticoids, hemodialysis, and plasma exchange. Although ES with severe hemolytic anemia is very rare, it is important to detect possible renal dysfunction when encountering patients with severe hemolysis.

Key words: acute kidney injury, Evans syndrome, autoimmune hemolytic anemia

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Introduction

Evans syndrome (ES) is characterized by the simultaneous or sequential development of autoimmune hemolytic anemia (AIHA) and immune-mediated thrombocytopenic purpura (ITP). It is classified as primary or secondary depending on its association with other diseases, such as systemic lupus erythematosus (SLE) (1). The association between AIHA and acute kidney injury (AKI) is uncommon in contrast to other hemolytic disorders, such as sickle cell disease (2), ABO-incompatible blood transfusion (3), and paroxysmal nocturnal hemoglobinuria (PNH) (4, 5). Systemic involvement, including lupus nephritis, is frequently observed in SLE patients with ES (6); however, ES presenting with AKI is extremely rare (7-9).

There is no established treatment regimen for ES. The first-line therapy is usually glucocorticoids with or without intravenous immunoglobulins; the second-line therapy for refractory ES includes immunosuppressant drugs, such as cyclosporine or mycophenolate mofetil, rituximab, and splenectomy (1). In contrast, plasma exchange (PE) has been used for life-threatening AIHA as a supportive therapy to remove autoantibodies (10, 11).

We herein report a case of ES complicated by AKI due to severe hemolytic anemia, in which the patient recovered following the administration of a glucocorticoid and blood purification therapy, including hemodialysis and PE.

Case Report

A 65-year-old Japanese woman had been diagnosed with systemic sclerosis (SSc) 10 years previously, based on Raynaud's phenomenon, interstitial pneumonia, skin sclerosis on her fingers, and anti-centromere and anti-Scl-70 antibody positivity. She had also been diagnosed with SLE seven

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Table. Laboratory Findings on Admission.

Urine test		**Chemistry**		**Immune system**	
Protein	+	TP	5.4 g/dL	IgG	995.1 mg/dL
Occult blood	3+	Alb	3.1 g/dL	IgA	186 mg/dL
RBC	<1 /HF	T-bil	3.12 mg/dL	IgM	273.7 mg/dL
TP	19.9 g/gCr	D-bil	1.11 mg/dL	C3	36.8 mg/dL
NAG	1,446.4 IU/gCr	AST	319 IU/L	C4	2.1 mg/dL
β2MG	18,765 μg/gCr	ALT	23 IU/L	CH50	<10 U/mL
		ALP	348 IU/L	ANA	×640
CBC		γGTP	41 IU/L	MPO/PR3-ANCA	<0.50
WBC	11,100 /μL	LDH	2,633 IU/L	Anti-GBM antibody	<1.4
RBC	192×10^4 /μL	BUN	64.6 mg/dL	RF	3.5 IU/mL
Hb	6.8 g/dL	Cr	2.96 mg/dL	Anti-SS-A antibody	163 U/mL
Plt	7.6×10^4 /μL	cystatin C	3.47 mg/L	Anti-SS-B antibidy	7.05 U/mL
Ret	1.1 %	UA	5.4 mg/dL	Scl-70 antibody	>240 U/mL
		CRP	11.86 mg/dL	Anti-centromere antibody	122 U/mL
Coagulation		HbA1c	4.9 %	Lupus anticoagulant	1.2
PT-INR	1.51	Fe	119 μg/dL	Anti-cardiolipin antibody	1.83
APTT	46.6 s	UIBC	154 μg/dL	Cryoglobulin	-
Fib	135 mg/dL	Ferritin	38,538 ng/mL	ds-DNA antibody	1.39
D-dimer	508.1 μg/mL	Na	140 mEq/L	ss-DNA antibody	9.8
FDP	1,081 μg/mL	K	4.6 mEq/L	Sm antibody	0.89
AT-III	60 %	Cl	109 mEq/L	RNP polymerase III antibody	1.06
haptoglobin	6 mg/dL	CK	110 U/L	Direct Coombs' test	+++
		BNP	159.7 pg/mL	ADAMTS13 activity	88 %
		sIL2-R	1,416 U/mL	ADAMTS13 inhibitor	8 U/mL
				cold agglutinin	-

RBC: red blood cell, TP: total protein, NAG: N-acetyl-beta-glucosaminidase, β2MG: beta 2-microglobulin, WBC: white blood cell, Hb: hemoglobin, Plt: platelet, Ret: reticulocyte, PT-INR: prothrombin time-international normalizedratio, APTT: activated partial thromboplastin time, Fib: fibrinogen, FDP: fibrin degradation product, AT-III: antithrombin III, Alb: albumin, T-bil: total bilirubin, D-bil: direct bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γGTP: γ-glutamyl transpeptidase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, Cr: creatinine, UA: uric acid, HbA1c: glycated hemoglobin, Fe: iron, UIBC: unsaturated iron binding capacity, Na: sodium, K: potassium, Cl: chlorine, CK: creatine phosphokinase, BNP: brain natriuretic peptides, sIL2-R: soluble interleukin-2 receptor, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, C3: complement 3, C4: complement 4, CH50: 50% hemolytic unit of complement, ANA: antinuclear antibody, MPO: myeloperoxidase, PR3: proteinasen3, ANCA: antineutrophil cytoplasmic antibody, GBM: glomerular basement membrane, RF: rheumatoid factor, SS: Sjögren's syndrome, Scl-70: topoisomerase 1, Sm: Smith, RNP: ribonucleoprotein, ADAMTS13: a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13

years previously, based on pancytopenia, anti-nuclear antibody (ANA), anti-double stranded DNA (dsDNA) antibody and lupus anticoagulant positivity. Her condition had been maintained with prednisolone (PSL, 2 mg/day) for seven years. She had also taken trimethoprim/sulfamethoxazole, lansoprazole**,** alendronate, magnesium oxide, tocopherol acetate, sarpogrelate hydrochloride, and beraprost sodium. Two weeks prior to her admission, she visited a community hospital complaining of a cough and runny nose, and hypocomplementemia, urinary occult blood and urinary protein were pointed out, although her renal function was normal (serum creatinine, 0.69 mg/dL). She was referred to our hospital and urgently hospitalized due to severe anemia (hemoglobin, 6.8 g/dL) and renal impairment (serum creatinine, 2.96 mg/dL).

On admission, a physical examination revealed the following: height, 153.8 cm; weight, 51.2 kg; blood pressure, 95/65 mmHg; pulse, 111 beats per minute; body temperature, 36.8°C. Her conjunctivae were anemic with jaundice, and fine crackles were found in her bilateral lower lungs. She also showed Raynaud's phenomenon and skin sclerosis on her fingers. A blood examination showed thrombocytopenia and hemolytic anemia (hemoglobin, 6.8 g/dL; platelets, 76,000/μL; total bilirubin, 3.12 mg/dL; lactate dehydrogenase, 2,633 IU/L; haptoglobin, 6 mg/dL) with 0.5% schistocytes in a peripheral smear, while her white blood cell count was 11,100/μL (segmented cells, 69%; stab cells, 23%; lymphocytes, 7%; monocytes, 1%). Her liver enzymes were stable, and her C-reactive protein level was 11.86 mg/dL (Table). Her prothrombin time-international normalized ratio was 1.51, and her fibrin degradation product (FDP) and D-dimer levels were elevated. She was positive for ANA (discrete-speckled type), anti-SS-A, anti-SS-B, anti-Scl-70, anti-centromere and anti-phosphatidylserine/prothrombin complex antibodies and negative for anti-dsDNA and anti-Sm antibodies. A direct Coombs test was positive; however,

Figure 1. Black-colored urine.

there was no CD55 or CD59 deficiency of red blood cells, and a cold agglutinin test was negative. Her serum complement C3 and C4 levels and CH50 were decreased to 36.8 mg/dL, 2.1 mg/dL and <10 U/mL, respectively, but there were no genetic abnormalities related to atypical hemolytic uremic syndrome (HUS) (e.g., *CFH*, *CFHR1-5*, *C3*, *CFI*, *CFB* and *MCP*). A stool test for verotoxin was also negative. Although a test for *Helicobacter pylori* antibodies was negative and her ferritin level was 38,538 ng/mL, bone marrow aspirate showed an increase in nucleated cells and megakaryocytes (84/μL) with only slight hemophagocytosis, and the platelet-associated IgG level was high (458 ng/10^7 cells), which suggested accompanying AIHA and ITP. Eventually, she was diagnosed with ES and disseminated intravascular coagulation (DIC) according to the diagnostic criteria by Japanese Society on Thrombosis and Hemostasis (12).

Her renal dysfunction met the diagnostic criteria for stage 3 AKI, according to the KDIGO Clinical Practice Guideline (13). Her urine was black-colored (Fig. 1) with occult blood (3+) and <1 red blood cell per high-power field (hpf), indicating hemoglobinuria. Urine sediments revealed granular casts (>100/hpf), but hemosiderin staining was negative. The urinary protein level was 19.9 g/gCr with a peak in the α2 and β area (65.6%) and low albumin area (14.9%) with protein fractionation. This indicated the massive presence of hemoglobin protein in the urine.

The fractional excretion sodium (FENa) was 3.79%, and the urinary levels of N-acetyl-β-D-glucosaminidase (NAG, 1,446.4 U/gCr), β2 microglobulin (18,765 μg/gCr) and neutrophil gelatinase-associated lipocalin (NGAL, 13,910 ng/mL) were elevated. Computed tomography (CT) revealed hepatosplenomegaly without signs of hydronephrosis in the kidneys. We therefore suspected intrinsic renal AKI.

Fig. 2 summarizes her clinical course. At night on the admission day, a high fever appeared, followed by worsened anemia (hemoglobin, from 6.8 g/dL to 5.1 g/dL) and undetectable haptoglobin the following day. Salvage therapy with PE with 4,320 mL (1.2 times the plasma volume) of fresh-frozen plasma (FFP) in each session was performed for 3 consecutive days. Continuous hemodiafiltration had been started on the day after admission due oliguria and was changed to intermittent hemodialysis (IHD) on hospital day 5. PSL was increased to 60 mg/day with angiotensin-converting-enzyme inhibitor.

Her hemolysis and hypocomplementemia were apparently improved after the initiation of PE. On hospital day 5, we interrupted PE after obtaining normal ADAMTS13 inhibitor (8 U/mL, Bethesda method) and activity (88%) results, which excluded the possibility of thrombotic thrombocytopenic purpura (TTP). However, hemolytic anemia recurred on hospital day 8. Five additional sessions of PE allowed the hemolysis to stabilize again, and a direct Coombs test was now negative. IHD was able to be suspended on hospital day 21 after an increase in urine output. On hospital days 21 and 41, her haptoglobin levels were decreased, even though her hemoglobin levels were stable. On hospital day 21, we performed a transfusion for a renal biopsy, which might have increased her hemoglobin. On hospital day 41, her hemoglobin had decreased from 9.4 g/dL to 8.4 g/dL, accompanying a decrease in her haptoglobin levels. Both her hemoglobin and haptoglobin levels subsequently recovered spontaneously. These findings suggested that slight hemolysis had recurred.

A renal biopsy was performed on hospital day 28. A total of five glomeruli were observed by light microscopy. No endocapillary proliferative lesions or thrombi were observed in the glomeruli (Fig. 3A). Interstitial fibrosis and tubular atrophy were moderate, and the detachment of epithelial cells and expansion of the tubular lumen were shown in the proximal tubules, indicating acute tubular injury (ATI) (Fig. 3B). No onion-skin lesions were observed in any vessel. In addition, few casts were observed. Berlin blue iron staining revealed traces of hemosiderin deposits in the tubular cells (Fig. 3C). Immunofluorescence studies were negative for immunoglobulin and complements. Electron microscopy showed mild glomerular subepithelial edema and no electron-dense deposits (Fig. 3D). Based on these findings, she was diagnosed with AKI due to ATI.

Eventually, her serum creatinine level recovered to the baseline value, and her serum complement C3 and C4 levels and CH50 also recovered to 62.1 mg/dL, 12.9 mg/dL and 36 U/mL, respectively. Her NAG, β2 microglobulin and NGAL levels were decreased to 26.3 U/gCr, 3,464 μg/gCr and 52.6 ng/mL, respectively. Her hemoglobin level and platelet count also remained stable, even when the PSL dosage was gradually reduced to 30 mg. She was discharged on hospital day 66.

Discussion

We herein report a case of AKI caused by severe hemoly-

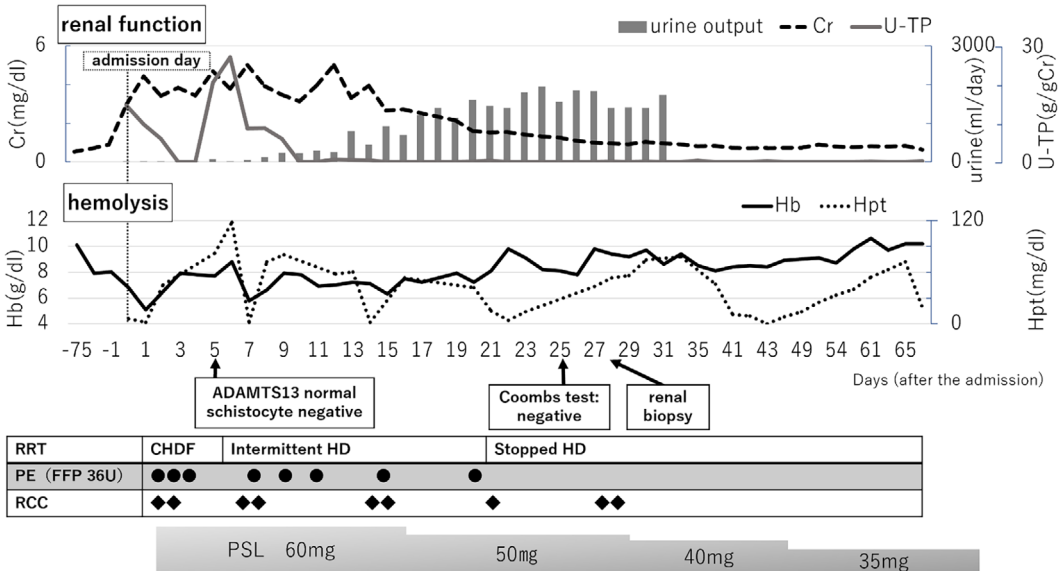

Figure 2. **Clinical course. Cr: creatinine, Hb: hemoglobin, U-TP: urinary protein, RRT: renal replacement therapy, CHDF: continuous hemodiafiltration, HD: hemodialysis, PE: plasma exchange, FFP: frozen fresh plasma, PSL: prednisolone, Hpt: haptoglobin, RCC: red cells concentrates**

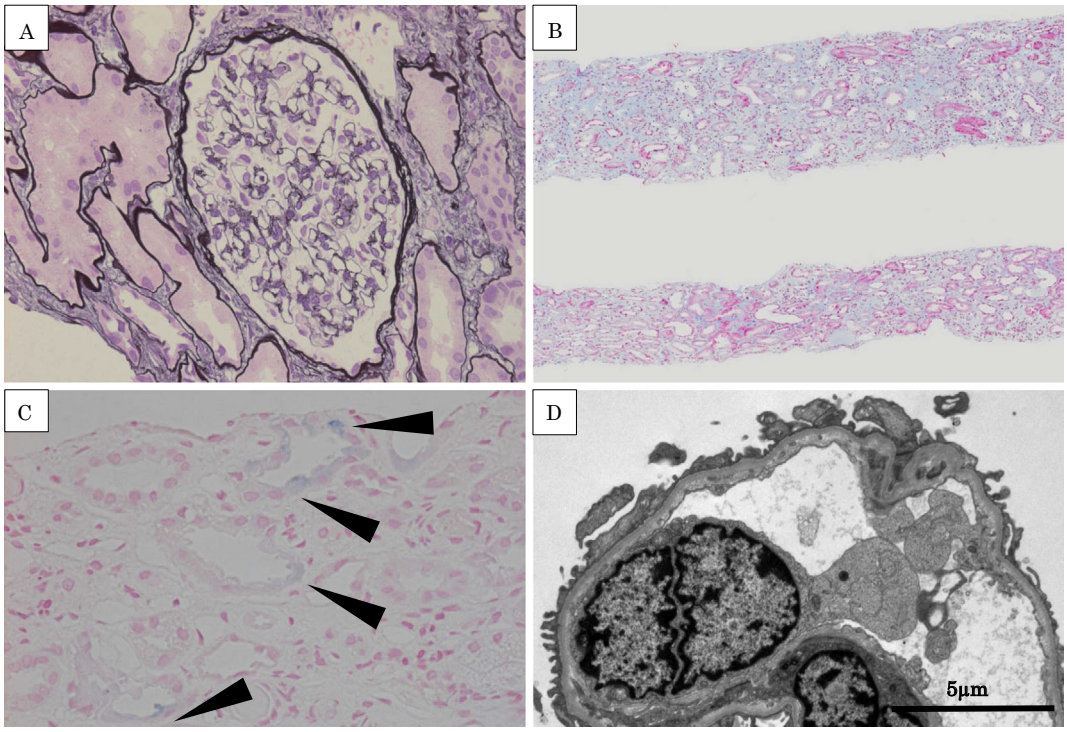

Figure 3. **The finding of the renal biopsy specimens. (A-C) Light micrographs findings. (A) No glomerular lesions nor thrombi were observed. (Periodic acid-Schiff staining; original magnification ×400). (B) Moderate interstitial fibrosis with tubular atrophy and detachment of epithelial cells was noted. The casts were seldomly observed. (Masson Trichrome staining; original magnification ×40). (C) Hemosiderin deposits in the tubular cells (arrowheads) were partially observed. (Berlin Blue staining; original magnification ×400). (D) Electron micrographs findings. Mild glomerular subepithelial edema was noted but no electron dense deposits were shown.**

sis from ES with SLE and SSc. ES, which led to severe hemolytic anemia, DIC and ATI, recovered with the administration of a glucocorticoid and blood purification therapy.

The present patient was diagnosed with ES, comprising AIHA and ITP, complicated by DIC. The laboratory findings of patients with warm AIHA include a positive direct Coombs test and the finding of hemolytic anemia without alloimmune or drug-induced immune hemolysis. Our patient

presented with thrombocytopenia and hemolytic anemia with a few schistocytes but had no etiology causing thrombotic microangiopathy (TMA) (e.g., TTP, Shiga-toxin-producing *E. coli*-HUS or atypical HUS). Although she was diagnosed with SSc and was positive for anti-phospholipid antibodies, a renal biopsy showed no endocapillary proliferative lesions or thrombi in the glomeruli, which excluded TMA and antiphospholipid antibody syndrome. The elevated PA-IgG level and increased number of megakaryocytes in the bone marrow led to the diagnosis of ITP. This case also met the criteria for DIC. DIC due to hemolysis has been generally attributed to transfusion-related hemolytic reactions and not AIHA or ES (14, 15). The present findings suggested that severe hemolysis caused by ES eventually caused DIC in our patient.

Although severe hemolysis caused by ES can lead to AKI there are only few reported cases of AKI caused by severe hemolytic anemia with ES (7-9). Warm AIHA is usually associated with extravascular hemolysis, and hemoglobinuria usually appears following intravascular hemolysis. Furthermore, intravascular hemolysis in AIHA followed by hemoglobinuria is rare (16, 17). In the present case, hemoglobinuria developed due to persistent severe intravascular hemolysis. A previous study reported that SLE patients with ES presented with hypocomplementemia more frequently than SLE patients without ES (6). Complement activation might proceed beyond the C3b formation step, resulting in C5 activation, the formation of the membrane attack complex (MAC) and intravascular hemolysis (18). Thus, complement pathway activation may occur in ES with concomitant SLE and might affect the severity of hemolysis.

Several mechanisms underlying AKI in severe hemolysis have been reported. When hemolysis occurs, free dimetric hemoglobin, which is produced by hemolysis, binds mainly to haptoglobin, to complexes that inhibit hemoglobin excretion through the glomeruli. After exceeding the binding capacity of haptoglobin, free dimetric hemoglobin passes through the glomeruli, where it is absorbed by the proximal tubules and turned into hemosiderin. Renal injury is caused through various mechanisms, including 1) tubular obstruction by intraluminal precipitation of hemoglobin casts, 2) direct cytotoxicity to the proximal tubular epithelium, 3) intrarenal vasoconstriction due to consumption of endothelium-derived nitric oxide, and 4) microvascular thrombosis in the kidneys by DIC (5, 19). In the present case, the characteristic findings of lupus nephritis and scleroderma renal crisis (SRC) were not present and acute tubular necrosis, and hemosiderin deposits were observed in a renal biopsy specimen. FENa was 3.79%, which suggested intrinsic AKI rather than prerenal AKI. Accordingly, the kidney injury was suggested to have been caused by direct cytotoxicity to the proximal tubular epithelium. Hemosiderin deposits in the proximal tubules were slightly observed in the renal biopsy specimen, which was obtained after the patient recovered from AKI. Hemoglobinuria and granular casts were also observed; however, hemosiderin staining of urine sediments was negative in this case. Prussian blue only stains ferric iron, which is loosely bound to protein complexes such as hemosiderin; protein complexes that strongly bind iron, such as hemoglobin, are not stained with Prussian blue (19). Although few casts were observed, hemoglobin cast nephropathy could still have developed, as the renal biopsy was performed after her AKI had improved.

PE may be effective for removing autoantibodies and restoring haptoglobin that had been consumed by severe hemolysis. In general, the therapy for ES or AIHA is glucocorticoids with or without intravenous immunoglobulins, immunosuppressant drugs or splenectomy (1, 20). PE has been used in the treatment of various immunologic disorders to remove disease-specific antibodies from the plasma. Although the therapeutic effect is inconsistent, PE has been performed for severe and refractory cases of AIHA, even with steroid treatment and red blood cell transfusion (10, 11). In our case, PE stabilized the patient's hemolytic anemia and improved both her thrombocytopenia and AKI. It is possible that PE was effective in removing autoantibodies as a supportive therapy until PSL could show efficacy, as her Coombs test result became negative and her vital function remained stable after PE therapy. In addition, a previous study reported that no iron deposition in renal tissue or hemoglobinuria was observed after the administration of haptoglobin in a hemolysis model (21). PE may contribute to the improvement of AKI not only by stabilizing hemolytic anemia but also restoring haptoglobin by FFP. Steroid treatment has been shown to be necessary for ES (1). However, the present patient had been diagnosed with systemic sclerosis, so it was possible that steroid pulse therapy induced SRC (22). We prescribed 60 mg of PSL instead of steroid pulse therapy and added an angiotensin-converting-enzyme inhibitor to prevent SRC, which worked well.

In conclusion, we encountered a rare case of ES complicated by AKI due to severe hemolytic anemia, in which the patient recovered with the administration of a glucocorticoid and blood purification therapy. When treating patients with AKI caused by severe hemolytic anemia due to ES, it is important to diagnose the underlying disease and provide proper intensive care because the condition can be fatal.

Informed written consent was obtained from the patient for publication of this case report and accompanying images.

The authors state that they have no Conflict of Interest (COI).

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