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CASE REPORT

A case of Stevens-Johnson syndrome with acquired hemophilia complication

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Autoimmune diseases have been observed in patients with Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN); however, acquired hemophilia, which can develop owing to autoimmune diseases, has not yet been reported SJS/TEN patients. A 74-year-old male patient, who had been treated for SJS after allopurinol exposure, was referred to our clinic due to hypotension and mucosal erosions. He was suspected to have septic shock due to widespread mucosal involvement caused by SJS, which improved after 1 week of intensive conservative treatment that included antibiotics and systemic corticosteroids. However, a rapid increase in prothrombin time (> 60 seconds) and activated partial thromboplastin time (> 120 seconds) was confirmed, and the mixture of the 2 materials did not improve decreased factor VIII activity (18.7%). The patient was diagnosed with acquired hemophilia, which was probably associated with SJS. In this case, acquired hemophilia, a fatal and rare autoimmune disease, occurred concurrently with SJS. (*Allergy Asthma Respir Dis 2024;12:204-208*)

Keywords: Drug hypersensitivity, Autoimmune diseases, Hemophilia A

INTRODUCTION

Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) is a delayed drug hypersensitivity reaction that develops after the administration of culprit drugs for several days to weeks.[1] Involvement of mucus in the oral cavity and conjunctiva in the eyes is commonly observed, and skin changes, including vesicle formation and epidermal detachment, are widespread. SJS/TEN can be fatal or life-threatening. However, there is no established treatment strategy other than discontinuing the culprit drug and controlling the symptoms.[1,2] SJS/TEN can cause acute complications, such as sepsis and organ failure, and can lead to fatal outcomes. The long-term sequelae of SJS/TEN are mainly associated with stricture and scarring of the involved skin and ocular areas.[1,3] However, the immunological changes in SJS/TEN have not yet been elucidated and may induce various complications related to SJS/TEN development. Autoimmune diseases, such as Hashimoto thyroiditis, Sjögren syndrome, and systemic lupus erythematosus, have been reported as complications of SJS/TEN[4]; however, to date, there have been no reports on the occurrence of acquired hemophilia in SJS/TEN. Herein, we present a case of acquired hemophilia that developed after the occurrence of SJS.

CASE REPORT

A 74-year-old male was referred to the allergy clinic on October 11 (day 1), 2023, presenting with confusion, diffuse mucositis, ulceration of the oral cavity, skin rash with brownish pigmentation, and diarrhea. His symptoms began 20 days before and approximately 11 days after the administration of allopurinol (100 mg/day), which was prescribed for hyperuricemia. He had continued the administration of aspirin, clopidogrel, carvedilol, losartan, and ferrous sulfate for 3 months. He had a history of chronic kidney disease that required hemodialysis for 15 years and hypertension. The patient was a 53-pack-year smoker with a recent history of acute myocardial infarction 3 months prior and stroke 23 days prior to presentation. He was hospitalized after the diagnosis of stroke, and skin eruption and oral mucositis appeared 3 days after admission and continued to worsen. On the 12th day of the hospitalization, the patient was transferred to another hospital and diagnosed with SJS. Allopurinol was discontinued, and the patient was treated with systemic corticosteroids (prednisolone, 20 mg/day). However, he was in shock and was referred to the allergy clinic after a week of systemic corticosteroid treatment. The patient's initial vital signs were blood pressure 75/47 mmHg, heart rate 75/min, respiratory

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rate 18/min, and body temperature 36.8°C. The whole blood count was 16,580/μL, and the blood eosinophil count was 1,326/μL in the initial laboratory test (Table 1). The levels of acute inflammatory markers, including C-reactive protein (8.46 mg/dL), procalcitonin (5.11 ng/mL), and interleukin-6 (70.9 pg/mL), were significantly elevated. Renal function test results showed increased levels (blood urea nitrogen, 58.4 mg/dL; creatinine, 5.02 mg/dL), and liver function test results, prothrombin time (PT), and activated partial thromboplastin time (aPTT) were within the normal range. The calculated severity-of-illness score was one point, and the involved body surface area was <10%. Viral markers, including herpes simplex virus, Epstein-Barr virus, human herpes virus 6, coxsackievirus, and cytomegalovirus, showed no evidence of current infection or reactivation. The HLA-B*5801 genotyping results were positive. Although no pathogens were identified in the blood culture, we presumed that the patient had septic shock on the basis of his vital signs and laboratory test results. The patient was initially treated with antibiotics (vancomycin and meropenem), systemic corticosteroids (methylprednisolone, 62.5 mg/day), inotropics, and continuous renal replacement therapy. Seven days after treatment, his septic condition and laboratory abnormalities improved (Table 1), and the skin lesions and mucosal involvement of the oral cavity slightly improved (Fig. 1). However, PT and aPTT continued to increase up to >60 seconds (reference range, 9.5–13.3 seconds) and

Table 1. The results of laboratory investigations

Variable	Oct 11	Oct 12	Oct 14	Oct 16	Oct 18	Reference range
WBC ($\times 10^9$/L)	16.7	13.7	13.0	15.7	10.1	3.5–10.5
Neutrophil (%)	80.5	71.2	87.6	86.1	82.5	40.0–80.0
Eosinophil (%)	8.0	12.4	0.2	0.1	0.4	≤7.0
Platelet ($\times 10^9$/L)	177	165	129	150	106	150–450
CRP (mg/L)	8.5	9.1	3.0	1.2	0.9	≤0.3
PCT (ng/mL)	5.1	4.6	-	-	0.9	≤0.5
IL-6 (pg/mL)	-	70.9	-	-	-	≤7.0
BUN (mg/dL)	30.4	29.3	18.6	21.4	33.9	8.0–23.0
Creatinine (mg/dL)	5.0	4.5	1.6	1.4	2.1	0.7–1.2
Bicarbonate (mmol/L)	27.9	22.8	23.3	26.1	27.8	22.0–26.0
Glucose (mg/dL)	100	200	201	186	162	70–110
AST (U/L)	29	32	21	30	31	≤32
ALT (U/L)	33	32	23	28	29	10–35

WBC, whole blood count; CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleukin 6; BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transaminase.

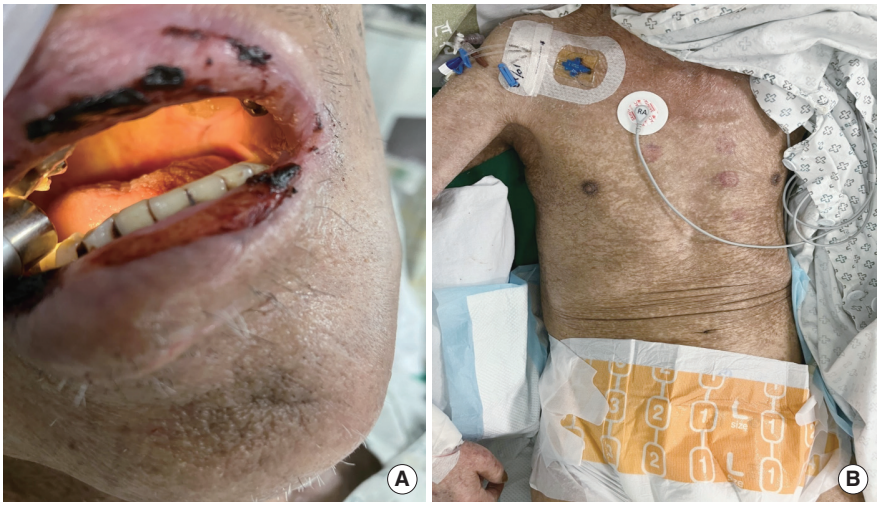

Fig. 1. (A) Crusty erosion of the mucosa of the lips and ulcers and mucositis in the oral cavity. (B) Thinned and flattened maculopapular rash with remaining brown pigmentation and scales on trunk.

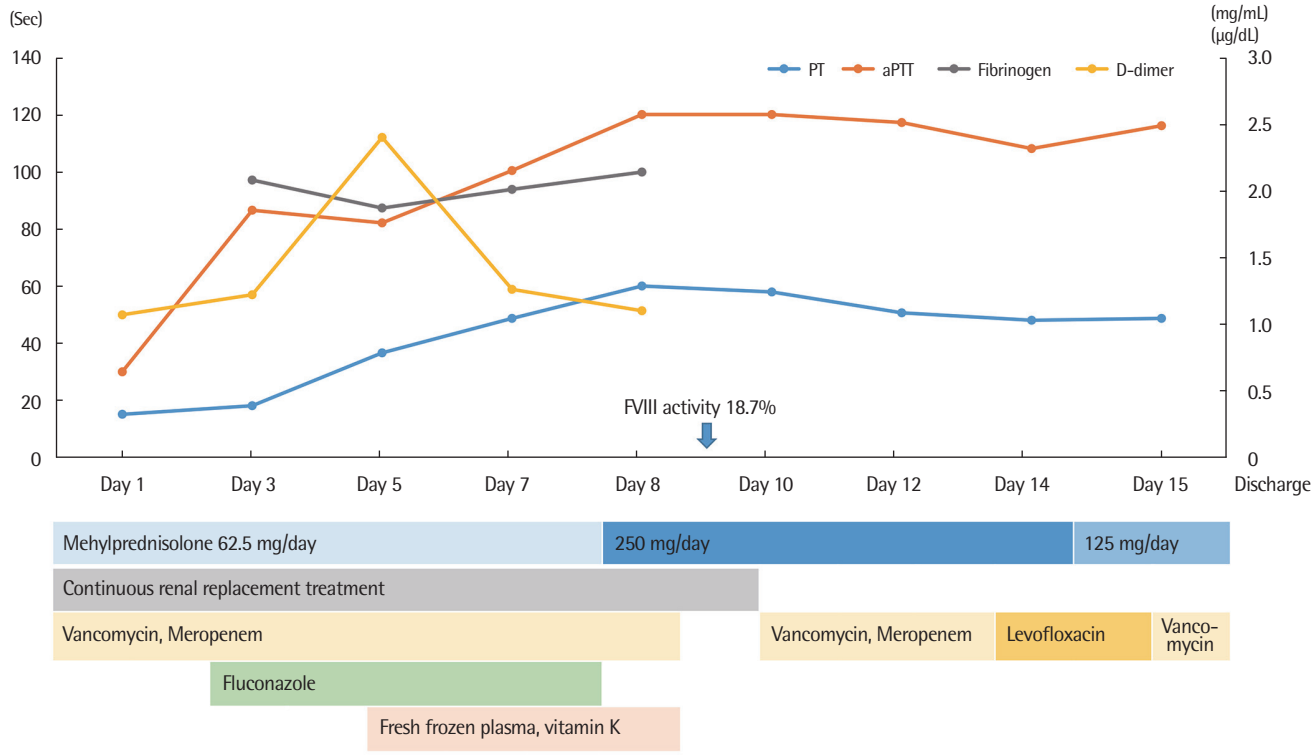

Fig. 2. Timeline of treatment and values of the blood coagulation test. PT and aPTT are along the left axis. Fibrinogen and D-dimer are along the right axis. The unit of fibrinogen is mg/dL, and that of D-dimer is μg/mL. PT, prothrombin time; aPTT, activated partial thromboplastin time.

>120 seconds (26.2–37.2 seconds) on admission day 8, although transfusion of fresh frozen plasma and vitamin K replacement had been continued (Fig. 2) and the PT/aPTT mixing test was not corrected. Mild gum bleeding was detected; however, no major bleeding events occurred. The thrombin time (18.8 seconds) was within the normal range (<21.0 seconds), and factor VIII (FVIII) activity (18.7%; reference range, 60%–140%) decreased without FVIII inhibitor antibody detection. The patient tested positive for lupus anticoagulants, but negative for antiphospholipid and anticardiolipin antibodies. He was diagnosed with acquired hemophilia and started on steroid pulse therapy on day 7 of admission (methylprednisolone 250 mg/day). He was transferred to the hematology department and continued systemic corticosteroid treatment (methylprednisolone 250 mg/day) for 7 days, and methylprednisolone was then reduced to 125 mg/day. However, no improvement in aPTT prolongation was observed, and the patient was voluntarily transferred to another hospital on admission day 16.

This study was approved by the Institutional Review Board of Inje University Haeundae Paik Hospital (HPIRB 2023-12-016), and the requirement for informed consent was waived.

DISCUSSION

Acquired hemophilia is a rare autoimmune disorder caused by the development of autoantibodies against antihemophilic factors, and the most frequently related factor is FVIII.[5,6] In half of the cases, autoantibodies are associated with underlying conditions such as malignancy, postpartum state, dermatologic disorders, infection, and drugs, and immunologic disorders are considered the most significant predisposing factors. However, the other half of cases are idiopathic.[5,7]

In this case, the patient showed aPTT prolongation without response to replacement with fresh frozen plasma and vitamin K. aPTT was not corrected by the mixing test, which meant that an inhibitor to factor existed, and the activity of FVIII was moderately decreased by up to 18.7%. The thrombin time was within the normal range, and coagulopathy due to heparin was excluded. Disseminated intravascular coagulation was excluded on the basis of normal fibrinogen and D-dimer levels. Thus, we clinically diagnosed the patient with acquired hemophilia.

Drugs, such as antibiotics and antiplatelet agents are potential causes of acquired hemophilia. The epidemiology, natural history,

and clinical relevance of drug-induced hemophilia remain unclear. In a systematic review, immunomodulating agents such as interferon-α and fludarabine were associated with acquired hemophilia, but it was difficult to understand the relationship between acquired hemophilia and other drugs, such as antibiotics, anticonvulsants, and clopidogrel.[8] In a recent analysis using the information component to identify drug-induced acquired hemophilia in the World Health Organization global database,[9] clopidogrel, alemtuzumab, and omalizumab were the most significant drugs associated with drug-induced acquired hemophilia. The mean time to onset of drug-induced acquired hemophilia from start of a drug was 30 days, and the range was 9.5 days to 73.75 days. In this case, the patient started antiplatelet therapy (aspirin and clopidogrel), beta-blockers, and aldosterone receptor antagonists 3 months prior, and antibiotics and antifungal agents were started 7 days prior to the onset of acquired hemophilia. Although drug-induced acquired hemophilia cannot be excluded, temporal causality of the drugs administered in this case was not significant.

The management of acquired hemophilia usually depends on clinical judgment and involves hemostasis and eradication of the inhibitor.[5,10] In our case, the patient showed mild bleeding in the oral cavity, but no major bleeding was observed. High-dose steroid treatment after steroid pulse treatment was continued to eradicate autoantibodies; however, aPTT proliferation did not significantly improve during the patient's stay in our hospital. Corticosteroids are typically recommended as first-line immunosuppressant therapy, and second-line therapy (cyclophosphamide or rituximab) can be considered if there is a lack of treatment response after 3–5 weeks of corticosteroid therapy.[10] In this case, the observed treatment duration of corticosteroids was just a week, which was too short to assess the treatment response.

The association between SJS and autoimmune disorders remains unclear. Several cases of SJS/TEN with autoimmune diseases have been reported.[4] Fan et al.[11] reported a case of a 32-year-old female with TEN and SLE. They collected 30 cases of SJS/TEN with SLE from the literature. The culprit drugs included antibiotics, hydroxychloroquine, nonsteroidal anti-inflammatory drugs, and immune suppressants. Many of them were young adults or adolescents, with 3 patients over 65 years of age. A retrospective study of the long-term complications of SJS/TEN demonstrated that SLE, Hashimoto thyroiditis, Sjögren syndrome, and interstitial lung disease developed after SJS/TEN.[4] Variants of *CTLA-4* were found on the surface of activated and regulatory T (Treg) cells, which are related to autoimmune diseases. A single-nucleotide polymorphism of *CTLA-4* was associated with patients with acquired hemophilia in previous studies.[12] Schep et al.[13] reported that patients with hemophilia A had low levels of Breg and Treg marker expression. Dysregulation of Treg cells may also be induced during SJS/TEN. Different frequencies of the Treg subpopulations and interferon-γ-secreting activity were observed between patients with SJS/TEN and healthy controls,[14] and this may affect the development of autoimmune diseases in patients with SJS/TEN.

To the best of our knowledge, no cases of acquired hemophilia following SJS/TEN have been reported. The possibility of other causes seemed insignificant, and we assumed that acquired hemophilia occurred in relation to SJS. This case suggests that various immunological changes occur in SJS/TEN, which can result in fatal autoimmune diseases such as acquired hemophilia (although rare).

REFERENCES

1. Lerch M, Mainetti C, Beretta-Piccoli BT, Harr T. Current perspectives on Stevens-Johnson syndrome and toxic epidermal necrolysis. Clin Rev Allergy Immunol 2018;54:147-76.
2. Kumar R, Das A, Das S. Management of Stevens-Johnson syndrome-toxic epidermal necrolysis: looking beyond guidelines! Indian J Dermatol 2018; 63:117-24.
3. Shanbhag SS, Chodosh J, Fathy C, Goverman J, Mitchell C, Saeed HN. Multidisciplinary care in Stevens-Johnson syndrome. Ther Adv Chronic Dis 2020;11:2040622319894469.
4. Yang CW, Cho YT, Chen KL, Chen YC, Song HL, Chu CY. Long-term sequelae of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis. Acta Derm Venereol 2016;96:525-9.
5. Tiede A, Collins P, Knoebl P, Teitel J, Kessler C, Shima M, et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica 2020;105:1791-801.
6. Kessler CM, Knöbl P. Acquired haemophilia: an overview for clinical practice. Eur J Haematol 2015;95:36-44.
7. El Demerdash DM, Ayad A, Tawfik N. Acquired hemophilia A (AHA): understanding, underdiagnosed, undertreated medical condition. Egypt J Intern Med 2022;34:12.
8. Franchini M, Capra F, Nicolini N, Veneri D, Manzato F, Baudo F, et al. Drug-induced anti-factor VIII antibodies: a systematic review. Med Sci Monit 2007;13:RA55-61.
9. Konstantinov K, Dolladille C, Gillet B, Alexandre J, Aouba A, Deshayes S, et al. Drug-associated acquired hemophilia A: an analysis based on 185 cases from the WHO pharmacovigilance database. Haemophilia 2023; 29:186-92.
10. Pishko AM, Doshi BS. Acquired hemophilia A: current guidance and experience from clinical practice. J Blood Med 2022;13:255-65.
11. Fan WY, Zhai QR, Ma QB, Ge HX. Toxic epidermal necrolysis with systemic lupus erythematosus: case report and review of the literature. Ann Palliat Med 2022;11:2144-51.
12. Sakurai Y, Takeda T. Acquired hemophilia A: a frequently overlooked au-

toimmune hemorrhagic disorder. J Immunol Res 2014;2014:320674.
13. Schep SJ, Schutgens REG, Fischer K, Voorberg J, Boes M. Role of regulatory cells in immune tolerance induction in hemophilia A. Hemasphere 2021;5:e557.
14. Yoshioka N, Suto A, Abe R, Saito N, Murata J, Hayashi-Ujiie I, et al. Disturbed balance in three subpopulations of CD4(+)Foxp3(+) regulatory T cells in Stevents-Johnson syndrome and toxic epidermal necrolysis patients. Clin Immunol 2013;148:89-91.