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Case Report

Acquired Hemophilia A Combined with Systemic Lupus Erythematosus: A Case Report and Literature Review

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Acquired hemophilia A (AHA) is a rare hemorrhagic disorder caused by autoantibodies against factor VIII (FVIII). An 80-year-old woman presented multiple bruises on her upper and lower extremities, along with gross hematuria. Extensive ecchymosis and swelling were observed on the buttocks. She had anemia and normal platelet count. The initial coagulation results showed prolonged activated partial thromboplastin time (aPTT, 68.5 seconds) and normal prothrombin time. According to the mixing test, we observed a decreased FVIII activity (2%), increased factor VIII inhibitor (FVIII-I) titer (74.4 BU), and negative lupus anticoagulant. AHA was diagnosed based on late onset bleeding and increased FVIII-I titer. Additionally, she met the criteria for systemic lupus erythematosus (oral ulcer, photosensitivity, renal disorder, and positivity for antinuclear and anti-β 2-glycoprotein-I antibodies). She was started on oral prednisolone for FVIII-I eradication. Post-treatment, her bleeding tendency, aPTT (47.3 seconds), and FVIII-I titer decreased (1.24 BU), and FVIII activity increased (10%). **(J Rheum Dis 2017;24:309-312)**

Key Words. Hemophilia A, Acquired, Systemic lupus erythematosus

INTRODUCTION

Acquired hemophilia A (AHA) is a very rare disease associated with autoantibody expression of factor VIII (FVIII). AHA has different clinical features compared to congenital hemophilia, and it has various clinical symptoms ranging from mild bruising to severe bleeding. It often occurs at an older age (most patients are ≥50 years old), and the mortality rate is as high as 8% to 22% [1]. Accompanying conditions include autoimmune diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), malignancy, post-partum disease, and drug reaction, but about 50% of patients do not know about the underlying disease [1]. Although AHA with SLE is rarely reported in foreign countries, most patients are diagnosed as having SLE and AHA after several years [2-9]. However, in our patient, SLE was confirmed during the evaluation of an underlying disease, AHA, and it developed in an elderly patient (aged 80 years) in whom the SLE activity was not high; the patient had a sufficient response to oral prednisolone. Since a patient with AHA combined with SLE has not yet been reported in Korea, we describe such a patient with a literature review of foreign cases.

CASE REPORT

An 80-year-old woman visited the hematologic department with recurrent oral bleeding; bruises of the upper limbs, lower limbs, and hips; and hematuria. She had tuberculosis 40 years ago and had no hemorrhagic tendency during a knee operation (10 years ago). She had no history of hypertension, diabetes, hepatitis, allergies, or cancer. Upon examination, she complained of photosensitivity, and she had a painless oral ulcer. She had anemia (hemoglobin level, 10.3 g/dL) and a normal platelet count (354,000/mm^3). Results of the liver function test (aspartate aminotransferase level, 23 IU/L; alanine trans-

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aminase level, 10 IU/L; total bilirubin level, 0.98 mg/dL) were within normal range. Results of urine analysis showed proteinuria (2+, 100 mg/dL), hematuria (red blood cell count, 3～5/high power field), and cellular cast (mixed). Coagulation test results showed that only the activated partial thromboplastin time (aPTT) alone was prolonged (58.7 seconds [range, 20.9～35 seconds]) (prothrombin time, 95%; international normalized ratio, 1.02). After administering a 1:1 mixture of plasma with normal plasma, the aPTT was not corrected. The mixing test was repeated by extending it to 2 hours at 37°C, and the aPTT was still not corrected. Results of the coagulation factor assay were as follows: FVIII activity, 2% (range, 60%～150%); factor IX activity, 153% (range, 60%～140%); factor XI activity, 106% (range, 60%～140%); and von Willebrand factor activity, normal. The coagulation factor test results showed a significant decrease in FVIII activity. Additionally, the factor inhibitor assay results showed that the FVIII inhibitor (FVIII-I) titer was increased (74.4 BU). Hepatitis B, hepatitis C, and HIV antibodies were all negative.

Results of immunologic tests showed that the antinuclear antibody (ANA 1: 160, speckled) was positive and the anti-β-2 glycoprotein-I (GPI) immunoglobulin (Ig)M antibody (22 IU/L), and anti-ribonucleoprotein antibody (1.13 AAU) were positive. Results for the anti-cardiolipin antibody, anti-β-2 GPI IgG antibody, anti-DNA antibody, and lupus anticoagulant were negative.

She met the criteria for SLE (i.e., oral ulcer, photosensitivity, renal disorder, ANA positivity, and anti-β-2 GPI IgM antibody positivity). Although a renal biopsy was needed to further evaluate the renal disorder, the examination was not performed because of the patient's old age and hemorrhagic tendency. We diagnosed her as having AHA combined with SLE based on her bleeding tendency, decreased FVIII activity, increased FVIII-I titer, and SLE criteria.

Before treatment, the aPTT was 68.5%, so we started oral prednisolone (5 mg) to eradicate the FVIII-I. Two weeks later, the aPTT was 57.5 seconds, but the patient's symptoms were not improved; thus, we increased the prednisolone dose to 10 mg. One month later, the aPTT was corrected to 47.4 seconds, but the bleeding tendency did not improve; thus, the prednisolone dose was increased to 15 mg. The bleeding tendency decreased 1 month later, but the bruise on the left forearm remained, so the prednisolone dose was increased to 20 mg. Four months after starting treatment, the bleeding tendency improved, aPTT decreased to 47.3 seconds, FVIII activity increased to 10%, and FVIII-I titer increased to 1.24 BU. The SLE disease activity index at the time of SLE diagnosis was 6, but it decreased to 2 after treatment. To reduce steroid requirements, we planned to administer an anti-malarial drug, but the patient refused this treatment; thus, we maintained steroid therapy alone. Currently, the patient is being followed up with at the outpatient clinic, and prednisolone is being tapering.

DISCUSSION

AHA may be suspected when there is increased FVIII activity and a decreased FVIII-I titer, as well as a prolonged aPTT and hemorrhagic tendency in an elderly patient without a family history of hemophilia. Among 215 non-hemophilic patients with FVIII-I, about half of them did not have any underlying disease, whereas some patients had autoimmune diseases, such as RA (7.9%) and SLE (5.7%) [1]. In the present case, there was no familial history of congenital hemophilia, and the patient was admitted to our hospital with complaints of multiple bruises. Based on the results of FVIII and FVIII-I tests, acquired hemophilia was diagnosed, and SLE was diagnosed simultaneously during the evaluation of underlying diseases.

The treatment of acquired hemophilia has two main goals: to correct acute hemorrhage and remove autoantibodies [10]. The FVIII, recombinant activated factor VII, and activated prothrombin complex concentrate may be used to treat acute bleeding [4]. However, the concentrates used in hemostasis treatment are difficult to obtain and are very expensive, so the cost and side effects should be considered [10]. There are also several reports of using immunosuppressant therapy to eliminate autoantibodies [11]. Plasmapheresis, intravenous immunoglobulin (IVIG), and combination therapy with steroids and cyclophosphamide (CYC) are recommended for removing the FVIII-I. Among these treatments, combination therapy with a steroid and CYC is commonly used [11-13]. Porru et al. [6] described a patient who did not respond to IVIG, methylprednisolone pulse therapy, and plasma exchange, but treatment with CYC pulse therapy (0.5 g/m every 2 weeks) was effective. In the present patient, there was a hemorrhagic tendency (i.e., skin purpura and anemia), but it was not acute massive bleeding and her vital signs were stable. Thus, we did not treat hemostasis, but we started treatment with prednisolone for autoantibody

elimination (i.e., the removal of FVIII-I). Although she was elderly, we planned to use CYC if she did not respond to steroid therapy. Fortunately, the FVIII-I titer decreased with prednisolone. She responded well to oral steroids. Additionally, she had relatively benign clinical features, which may have been because the lupus activity was low when the symptoms of AHA developed in this elderly patient with SLE. A PubMed search of full-text articles revealed 8 reported cases of SLE with AHA in English that satisfied the diagnostic criteria of SLE. These cases, along with ours, are presented in Table 1. Although SLE is common in women, most patients with SLE with AHA are women, with ages ranging from 19 to 80 years. Most patients initially diagnosed as having SLE also had a hemorrhagic tendency and confirmed AHA. However, only 3 patients including ours were diagnosed as having AHA during evaluation of their hemorrhagic tendency, and SLE was confirmed during the evaluation of underlying diseases. In these patients, 8 of 9 were ANA-positive, and the occurrence of AHA was not related to SLE activity. The relationship between AHA and the lupus anticoagulant, and anticardiolipin antibody is unclear, and the response to treatment seems unrelated to the potency of the FVIII inhibitor or SLE activity. In Korea, AHA with autoimmune disease has only been reported in patients with RA [14]. However, AHA with SLE has not been reported. Although our patient was elderly, SLE was diagnosed during the evaluation of an underlying disease, AHA, which was successfully treated with oral prednisolone.

Similar with other diseases, the early diagnosis of AHA, is important for the prognosis. In a cohort study in the United Kingdom, 87% of patients had major bleeding events, and 22% of them died [1]. In the elderly, the prognosis depends on age, underlying disease, and elimination of autoantibodies [14]. Therefore, a rapid diagnosis and effective treatment decisions are more important in elderly patients. If the aPTT is abnormal with a hemorrhagic tendency in an elderly patient, it may be necessary to consider acquired hemophilia (e.g., FVIII activity) and to conduct a screening test. Additionally, the possibility of accompanying diseases, such as autoimmune disease, should be considered, because AHA can be present with an autoantibody to FVIII.

SUMMARY

This is the first case of AHA with SLE in Korea. Although

Table 1. Review of patients with acquired hemophilia A combined with systemic lupus erythematosus

Case number	Country	Age (yr) /Sex	Diagnosis sequence	Autoantibody			SLEDAI	Factor VIIIactivity (%)/ Factor VIIIinhibitor (BU)	Treatment
				ANA	Anti-DNA	APL			
1	USA [2]	45/F	SLE (2 years)→HA	+	NR	LAC+, ACL+	NR	< 1/2,857	MP/CYC pulse, PL
2	Italy [3]	19/F	SLE (4 years)→HA	1:320, homogeneous	+	LAC+, ACL−	NR (active)	3/2.8	PL, IVIG, CYC pulse/oral
3	Japan [4]	24/F	SLE (5 years)→HA	1:640	+	LAC−, ACL−	NR (inactive)	2.8/46.5	CYC, PL, AZA
4	Japan [5]	54/F	SLE (21 years)→HA	−	NR	B2GPI−	NR (inactive)	2/38.7	MP pulse, Cs
5	Italy [6]	69/F	SLE (6 years)→HA	1:640, homogeneous	−	LAC+, ACL−	2	0/307	IVIG, CYC pulse, PL
6	Japan [7]	38/F	SLE (1 years)→HA	1:320, homogeneous	+	LAC−, ALC−	8	0.1/1,320	MP/CYC pulse, PL, Cs
7	Iran [8]	37/F	Simultaneously	> 100	+	NR	11	3.9/> 200	MP/CYC pulse, PL, AZA
8	Germany [9]	71/M	Simultaneously	1:5,120, speckled	−	LAC−, ACL+, B2GPI+	NR (active)	2/4.6	PL, AZA, HCQ
Current case	Korea	80/F	Simultaneously	1:160, speckled	−	LAC−, ACL−, B2GPI+	6	2/74.4	PL

ANA: antinuclear antibody, APL: anti-phospholipid antibody, SLEDAI: SLE disease activity index, F: female, M: male, SLE: systemic lupus erythematosus, HA: hemophilia A, NR: not reported, LAC: lupus anticoagulant, ACL: anti-cardiolipin antibody, B2GPI: anti-β-2 glycoprotein-I antibody, MP: methylprednisolone, CYC: cyclophosphamide, PL: prednisolone, IVIG: intravenous immunoglobulin, AZA: azathioprine, Cs: cyclosporine, HCQ: hydroxychloroquine.

SLE combined with acquired hemophilia is very rare, early diagnosis and treatment are very important for prognosis. Therefore, blood coagulation tests must be performed to identify acquired hemophilia if the patient with SLE has a hemorrhagic tendency. Conversely, if acquired hemophilia is diagnosed, it is necessary to confirm the presence of autoimmune diseases, such as SLE, through a detailed review of system, physical examination, and immunological tests.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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