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CASE REPORT

Acquired hemophilia in a patient with systemic lupus erythematosus: a case report and literature review

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Abstract We report the case of a 38-year-old female patient with systemic lupus erythematosus (SLE) who developed acquired hemophilia caused by factor VIII (FVIII) inhibitors. She manifested spontaneous bleeding symptoms such as ecchymoses and hematuria. Laboratory findings showed an isolated prolongation of the activated partial thromboplastin time, reduced FVIII activity, and a high titer of FVIII inhibitors. She was successfully treated with oral predonisolone and cyclosporine in combination with steroid and cyclophosphamide pulse therapy.

Keywords Acquired hemophilia · Factor VIII inhibitor · Systemic lupus erythematosus · Bleeding

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Introduction

Acquired hemophilia is a rare disease caused by the spontaneous development of autoantibodies against coagulation factor VIII (FVIII), with an incidence of at least 0.2–1.0 per million per year [1]. Approximately 50% of cases are caused by underlying specific medical conditions such as postpartum, malignancy, and autoimmune diseases. A survey of 215 patients with inhibitors against FVIII revealed that 7.9% of the cases had rheumatoid arthritis (RA) and 5.6% had systemic lupus erythematosus (SLE) [2]. Here, we describe an SLE patient who developed acquired hemophilia due to the presence of a high FVIII inhibitor level. Combination therapy with steroids, cyclosporine (CsA), and cyclophosphamide (CY) was effective in suppressing and controlling the FVIII inhibitor. We also review the literature on acquired hemophilia associated with SLE, including our case.

Case report

A 38-year-old Japanese woman presented with polyarthralgia, fever, and leukopenia consulted a hospital in August 2004. She was diagnosed with SLE, based on the presence of antinuclear antibodies (ANA), an immunological disorder (anti-Sm and anti-double stranded DNA antibodies), a hematological disorder (leukopenia), and arthritis. At this time, coagulation data were within normal ranges. She was initially treated with 25 mg/day of predonisolone (PSL) and the dose was tapered gradually.

In June 2005, coagulation studies demonstrated a prolonged activated partial thromboplastin time (APTT) of 89.9 s. In August 2005, she presented with spontaneous ecchymoses in the right elbow and left ankle as well as

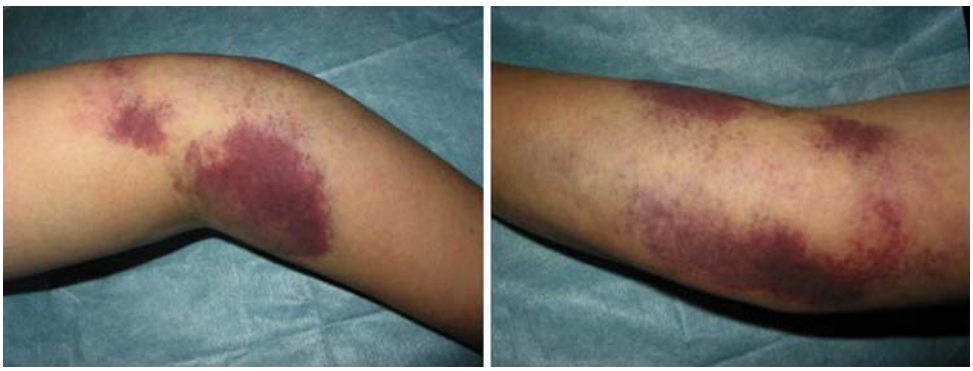

Fig. 1 Ecchymosed lesions in the right arm of the patient

occasional subcutaneous hemorrhages on the trunk. Her FVIII level was found to be greatly reduced to <1%; further, the other coagulation data were normal, and she tested negative for lupus anticoagulant (LAC). This suggested the development of an autoantibody against FVIII. Oral CsA was subsequently administered in November 2005; however, she continued to experience ecchymoses in the right arm around her elbow and developed thoracic herpes zoster, requiring hospital admission for treatment.

On admission, physical examination revealed significant subcutaneous hemorrhages (ecchymoses) in the right lower leg and around the swollen right elbow as well as the left ankle joints. A skin rash with blisters was also observed on the left side of her chest wall. The laboratory findings were as follows: hemoglobin, 11.8 g/dl; white blood count, 7,320/μl; platelet count, 287 × 10^3/μl; international normalized ratio of prothrombin time (PT), normal (0.87); APTT, 90.4 s; FVIII activity, 0.1%; and FVIII inhibitor, 1,320 Bethesda units (BU)/ml. Neither LAC nor anticardiolipin antibody was detected. Urinalysis did not reveal any abnormality at this time. She had no past or family history of bleeding and was diagnosed with acquired hemophilia caused by the FVIII inhibitors. Blood chemistry tests revealed a positive ANA (1:320 titer) with a homogeneous pattern, anti-double stranded DNA antibodies (13 IU/ml, normal < 10 IU/ml), and anti-SS-A/Ro (117 index) and anti-SS-B/La antibodies (247 index). A definite diagnosis of Sjögren's syndrome was not established at this time. The total hemolytic complement (CH50) activity was 9 U/ml (normal range 20–50 U/ml). These data suggested that SLE was in the active state (SLE disease activity index, SLEDAI = 8). Magnetic resonance imaging of her right arm obtained on the 17th hospital day demonstrated no significant hemarthrosis in the elbow joint.

Prior to the treatment for acquired hemophilia, she was initially treated for thoracic herpes zoster with acyclovir. After clinical improvement of herpes zoster, she was subsequently treated with intravenous methylprednisolone pulse therapy (1 g/day for three days) followed by 60 mg/day (1 mg/kg) of oral PSL in combination with oral CsA

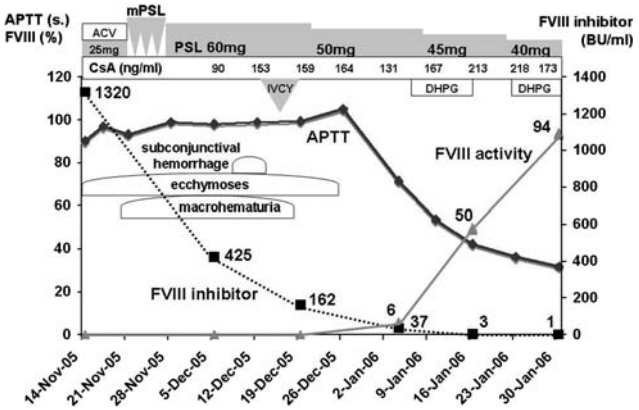

Fig. 2 Clinical course of the present case. *APTT* activated partial thromboplastin time, *FVIII* factor VIII, *BU* Bethesda units, *ACV* acyclovir, *mPSL* methylprednisolone (1,000 mg/day), *PSL* prednisolone, *CsA* cyclosporine, *IVCY* intravenous cyclophosphamide (500 mg/mm^2), *DHPG* ganciclovir (500 mg/day)

administration. The dose of CsA was then gradually increased to 200 mg/day with the trough level around 150–200 ng/ml. However, in addition to ecchymoses (Fig. 1), other bleeding symptoms such as subconjunctival hemorrhage and macrohematuria appeared and persisted, and so 900 mg (500 mg/m^2) of intravenous pulse CY (IVCY) was then administered. Thereafter, the inhibitor level was gradually reduced with an improvement in FVIII activity. There was a parallel disappearance of the bleeding symptoms. As the patient tested positive for cytomegalovirus antigenemia during the course of the therapy, she was administered two courses of ganciclovir therapy for 7–10 days. In January 2006, after ten weeks of therapy, the FVIII activity was 94%; FVIII inhibitor concentration, 1 BU/ml; and APTT value, normal (32.0 s). An added benefit was the substantial improvement in her SLE activity, i.e., the ANA titer, anti-DNA antibody titer, and CH50 activity decreased to 1:80 titer, <5 IU/ml, and 52 U/ml, respectively. Figure 2 summarizes the patient's clinical course. There has been no recurrence of the disease after a two-year follow up, and her SLE is in a quiescent state due to treatment with PSL (7.5 mg/day) and CsA (150 mg/day).

Table 1 Review of reported cases with acquired hemophilia in patients with systemic lupus erythematosus (SLE)

Case no.	Author, year [reference no.]	Age/ sex	APTT (s)	FVIII level (%)	FVIII inhibitor (BU/ml)	SLE activity	Treatment (outcome)
1	Pirner et al. [4]	27/F	77	<3	1.4	Active	PSL, AZP, CY, CsA (no change), IVIG (improved)
2	Schwartz et al. [5]	40/F	NA	<1	7.2	NA	PSL, AZP, CY, porcine FVIII-C, APCC (no change), IVIG (improved)
3	Schulman et al. [6]	27/F	42	<1	16	Active	Porcine/human FVIII-C, APCC, IVIG, CY-pulse, mPSL (transient effect), CsA (improved)
4	Lafferty et al. [7]	45/F	66	<1	2,857	NA	PH, mPSL-pulse, CY-pulse, PSL, high-dose DEX, MTX (no change), IVIG (improved)
5	Trotta et al. [8]	19/F	54.6	3	2.8	Active	PH, PSL, FVIII-C, IVIG (no change), CY-pulse, CY (improved)
6	Ishikawa et al. [9]; Nishino et al. [10]	24/F	116	2.8	46.5	Inactive	PCC, APCC, mPSL-pulse, CY (improved)
7	Kornfeld et al. [11]	30/F	79	1	7.7	Active	mPSL-pulse, PSL, DEX-pulse, IVIG, CY-pulse (improved)
8	Onishi et al. [12]	54/F	77.3	<2	38.7	Inactive	mPSL-pulse, CsA, human FVIII-C (improved coagulopathy)
9	Present case	39/F	90.4	<1	1,320	Active	mPSL-pulse, PSL, CsA, CY-pulse (improved)

APTT activated partial thromboplastin time, *FVIII* factor VIII, *BU* Bethesda unit, *PSL* prednisolone, *AZP* azathioprine, *CY* cyclophosphamide, *CsA* cyclosporine, *IVIG* intravenous immunoglobulin, *NA* not available, *FVIII-C* factor VIII concentrate, *APCC* activated prothrombin complex concentrate, *PH* plasmapheresis, *DEX* dexamethasone, *MTX* methotrexate, *PCC* prothrombin complex concentrate

Discussion

Acquired hemophilia is a severe life-threatening bleeding disorder caused by inhibiting autoantibodies against a coagulation factor, most often FVIII. The estimated mortality rate is in the range of 7.9–22% [1]. In approximately 50% of cases, FVIII autoantibodies occur in patients who have underlying disorders or conditions. The most common diseases associated with acquired hemophilia are collagen vascular diseases, including SLE, RA, temporal arteritis, dermatomyositis/polymyositis, and Sjögren's syndrome [1, 2]. Among these, SLE was reported to be associated with 5.6% of cases (10 of 215 patients) [2]. The most common laboratory screening test for acquired hemophilia is an isolated prolonged APTT. Heparin contamination and the presence of LAC should be ruled out. The diagnosis is based on the demonstration of reduced FVIII levels and evidence of a FVIII inhibitor using a mixing study and/or the Bethesda assay in a patient with no previous personal or family history of bleeding [1, 3].

Among previous investigations of acquired hemophilia along with SLE, nine cases (including our case) are available, and the features of these reported cases are summarized in Table 1 [4–12]. All cases were female patients of child-bearing age with a median age of 33.9 years (range, 19–54 years). The APTT was prolonged but other laboratory screenings for hemostasis such as the platelet count and PT were normal. Similar to cases 6 and 8, the inhibiting autoantibodies could even appear in patients with quiescent SLE [9, 10, 12], which suggests that the appearance of the FVIII inhibitor and its level does not always correlate with underlying disease activity. We could not find any other possible inductive factor(s) for our SLE patient to develop acquired hemophilia, such as other disease conditions (including skin and respiratory diseases), infections, and use of certain drugs (including penicillin and its derivatives). Further, it is likely that the inhibitor level is not always associated with the severity of clinical symptom of bleeding. This may be partly due to incomplete neutralization of FVIII activity by the inhibitory autoantibodies (type II kinetics). Although in our case the inhibitor level was exceptionally high, similar to case 4, the patient made relatively favorable progress without severe life-threatening hemorrhage. Judging from the reported cases, therapy with intravenous immunoglobulin (IVIG), CsA as well as pulse therapy with steroids and CY appeared to be effective in the treatment of SLE patients with acquired hemophilia.

Treatment of acquired hemophilia consists of controlling bleeding and eliminating the inhibitors [3]. Human or porcine FVIII, prothrombin complex concentrates, or recombinant human factor VIIa may be required to control bleeding. Since our patient showed relatively minor bleeding episodes without severe hemorrhage, we did not consider administration of coagulation factor concentrates. Elimination of the inhibitor is usually achieved through long-term immunosuppression of antibody formation with corticosteroids, cytotoxic agents, such as CY and CsA, or combination therapy, as well as IVIG therapy and/or plasmapheresis or immunoadsorption [6, 13–17]. Single-agent PSL has a reported response rate of approximately 30% in patients [13, 18]. However, patients with acquired hemophilia associated with autoimmune disorders usually have a high titer of inhibitors that rarely resolve

spontaneously or with steroids alone [1]. The regimen most commonly used to eliminate antibodies against FVIII in acquired hemophilia consists of PSL and CY, which results in a response rate of 60–70% [13, 19]. Recently, a chimeric anti-CD20 monoclonal antibody (rituximab) has been used in the treatment of acquired hemophilia, showing promising results [20–22].

Our SLE patient who presented with bleeding showed clinical improvement following the initiation of immunosuppressive treatment that included CY and CsA. Previous studies in a prospective randomized trial have shown that CY is effective as a second-line therapy for many of those who are steroid-resistant [13], and that successful treatment and long-lasting remission was achieved in SLE patients with acquired FVIII inhibitors [8, 11]. On the other hand, CsA, alone or with PSL as salvage therapy or as a first-line treatment, has been shown to be effective for acquired hemophilia [23–29]. It can be administered to patients who do not respond to standard immunosuppressive regimens and is also effective in patients with underlying SLE [3, 6, 12], such as in our case. CsA inhibits cell-mediated reactions and may play a role in the induction of immune tolerance against FVIII. Moreover, CsA generally does not affect hematopoiesis, and most of the CsA-treated reported cases showed no obvious side-effects, such as nephrotoxicity, under careful clinical monitoring. Rituximab therapy has been shown to be quite effective in the treatment of several immune disorders resulting from autoantibodies, including SLE [30, 31]. A recent report demonstrated that patients with inhibitor titers greater than 100 BU/ml did not respond to rituximab alone [22]. Another report proposed the use of rituximab as first-line therapy in combination with PSL and CY or repeated courses of rituximab for patients with an inhibitor titer of greater than 30 BU [32]. Previous reports along with our case indicated that for patients with high titers, combination treatment with CY plus steroids, including pulse therapy (in combination with rituximab), should be used for the induction of disease remission. Furthermore, CsA may be beneficial in the induction and/or maintenance of disease remission, particularly in patients with SLE-associated acquired hemophilia. In cases with potentially severe and fatal bleeding, immediate infusion of coagulation factor concentrates or bypassing concentrates (as well as subsequent plasmapheresis or immunoadsorption) may also be considered.

In summary, our case demonstrated the association between the acquired FVIII inhibitor and SLE and a remarkable response to immunosuppressive therapy, including corticosteroids, CY, and CsA. In autoimmune diseases such as SLE, when a patient presents with bleeding tendency along with a prolonged APTT, the occurrence of acquired hemophilia due to the development of FVIII inhibitors should be suspected, and rapid recognition of the inhibitor is critical. This case highlights the importance of rapid diagnosis and effective treatment (including CY and CsA) to obtain a favorable outcome. Further investigation will be necessary to determine the optimal combination therapy for the treatment of SLE-associated acquired hemophilia depending on the level of the inhibitor and the severity of the disease.

Conflict of interest We declare that we have no conflict of interest.

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