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Characteristics of Acquired Inhibitors to Factor VIII and Von Willebrand Factor Secondary to Systemic Lupus Erythematosus

Experiences From a Chinese Tertiary Medical Center

Xiao-Yu Cao, MD, Meng-Tao Li, MD,* Xuan Zhang, MD,* Yan Zhao, MD,* Xiao-Feng Zeng, MD,* Feng-Chun Zhang, MD,* Yong Hou, MD,* and Li-Xiu Zhu, MS*†*

Objective: Because acquired hemophilia (AH) is a rare entity in systemic lupus erythematosus (SLE), we aimed to investigate the clinical features of SLE-related AH in Chinese patients.

Methods: This is a medical records review study carried out at a large tertiary care hospital in China from years 1986 to 2018. We searched the case database in Peking Union Medical College Hospital using the *International Classification of Diseases*. The clinical data on SLE-related AH patients were collected.

Results: A total of 9282 SLE patients had been hospitalized. Six female SLE-related AH patients were identified. Four patients had acquired hemophilia A (AHA), and 2 patients had acquired von Willebrand syndrome. Their mean age was 33.67 ± 13.77 years. Five patients had active disease. The mean SLE disease activity index measured at the time of diagnosis of AH was 10.50 ± 5.28. The average level of activated partial thromboplastin time was 86.5 seconds. Coexistence of secondary antiphospholipid syndrome and AHA was found in one case, and pulmonary embolism was observed 3 years later. After immunosuppressive therapy and symptomatic treatment, an overall remission rate of 83.3% was achieved.

Conclusions: The frequency of SLE-related AH was low. The development of AH in SLE patients frequently occurs with active disease. The AH could be the first clinical presentation of SLE. Secondary antiphospholipid syndrome and AHA could appear in the same SLE patient. Early and aggressive treatment contributes to a favorable prognosis.

Key Words: systemic lupus erythematosus, acquired von Willebrand syndrome, acquired hemophilia A, antiphospholipid syndrome, acquired hemophilia

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From the *Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Graduate School of Peking Union Medical College, Beijing; and †Department of Rheumatology, Ningde Hospital Affiliated to Fujian Medical University, Ningde, China.

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Correspondence: Yong Hou, MD, Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 1 Shuaifuyuan, Wangfujing St, Dongcheng District, 100730, Beijing, China. E-mail: houyongjia@hotmail.com; Li-Xiu Zhu, MS, Department of Rheumatology, Ningde Hospital Affiliated to Fujian Medical University, No. 13, East Mindong Rd, Ningde, Fujian Province, 352000, China. E-mail: aries5285107@163.com.

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Acquired hemophilia (AH) is a rare disease that involves the presence of autoantibodies against endogenous coagulation factors. It can cause life-threatening bleeding. The activated partial thromboplastin time (aPTT) is prolonged in most cases.[1] The AH includes acquired von Willebrand syndrome (AVWS), acquired hemophilia A (AHA), and other diseases.[2,3] The subclinical presence of AH is extremely rare. The European Acquired Hemophilia Registry has reported that 6.6% (33/501) AHA patients did not present with bleeding.[4] The incidence of AHA was estimated to be 1 to 1.5 cases per 1,000,000 per year in the general population.[5] The real prevalence of AVWS in the general population remains undetermined.[6] The AH can be secondary to autoimmune disease, malignancy, infection, pregnancy, and drugs.[1] The etiology has not yet been elucidated clearly. In systemic lupus erythematosus (SLE)–related AH patients, the presence of inhibitory antibodies against coagulation factor VIII (FVIII) or von Willebrand factor (VWF) is involved in the pathogenesis.[7,8] The AHA, caused by antibodies against FVIII, is the most common pattern. The SLE accounts for 8.6% of autoimmune diseases-related AH.[4] In AH patients with comorbidities, the ratio of SLE was 2.8%.[9] Due to the rarity of AH in SLE patients, we carried out a retrospective analysis in the highest ranked rheumatology center in China. The aim of this case series is a preliminary exploration of the distinct clinical presentations of AH in Chinese SLE patients.

METHODS

Patient Selection

The Ethics Committee of Peking Union Medical College Hospital (PUMCH) approved the study. Written informed consent was obtained from all patients. Clinical data of patients hospitalized in PUMCH between 1986 and 2018 were collected. The database in PUMCH applies the *International Classification of Diseases* (*ICD*). We used the search terms "systemic lupus erythematosus" or "lupus" in combination with "acquired hemophilia A," "factor VIII inhibitor," "acquired factor VIII deficiency," "acquired von Willebrand syndrome," "acquired von Willebrand factor deficiency," "acquired von Willebrand disease," "acquired coagulation factor inhibitor," or "acquired hemophilia" to select appropriate patients. If the patients also presented with malignancies, infectious disorders, pregnancy, hypothyroidism, or special drug therapy, they were excluded (Fig.). The inclusion criteria for SLE-related AH were as follows: (*a*) the patients met the Systemic Lupus International Collaborating Clinics classification criteria for SLE[10]; (*b*) after excluding the other possible causes, AH was diagnosed based on the positive inhibitor against coagulation factor, the apparently reduced activity of coagulation factor, and final confirmation by a specialist with expertise in AH. The

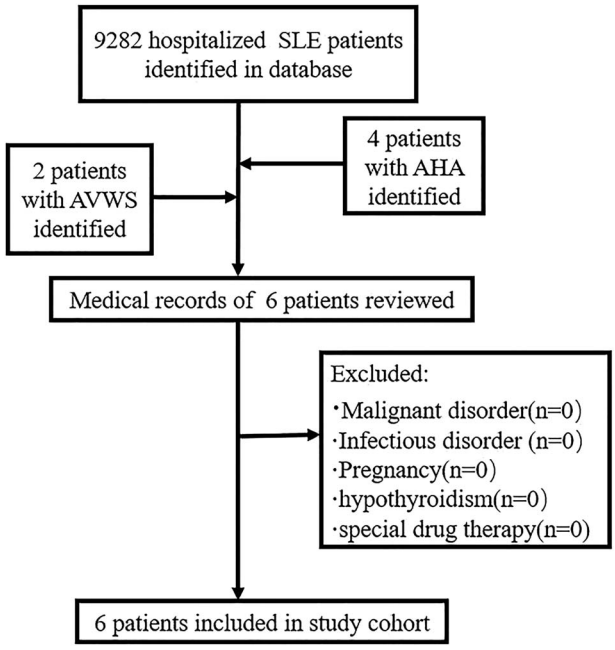

FIGURE. Flowchart of patient disposition.

exclusion criteria for SLE-related AH were the complication with malignancies, infectious disorders, pregnancy, hypothyroidism, or special drug therapy. Antiphospholipid syndrome (APS) was diagnosed according to the revised Sapporo classification criteria for APS.[11]

The diagnosis of AHA was based on the consensus guidelines.[12] In detail, (*a*) patients often presented with recent onset of hemorrhage; (*b*) the patient did not have a personal or family history of bleeding; (*c*) the laboratory examination showed a normal prothrombin time and a prolonged aPTT, which could not be corrected by mixing tests with normal plasma; (*d*) the positive FVIII inhibitor was examined using Bethesda assay; (*e*) after consultation with an expert specialized in AH, a final diagnosis of AHA was made.

A diagnosis of AVWS was made if patients fulfilled the following criteria proposed in 2009,[13] namely, the following: (*a*) patients had an acquired bleeding diathesis, such as epistaxis, mucosal bleeding, or menorrhagia; (*b*) the personal and family history of bleeding disorders was negative; (*c*) laboratory tests showed VWF antigen (Ag) levels were very low and revealed a prolonged aPTT, normal platelet count, and reduced or absent platelet aggregation upon addition of 1.2 mg/mL ristocetin; (*d*) the Bethesda assay for FVIII inhibitor was negative.

Laboratory Testing

Freshly drawn venous blood was collected in a vacuum blood tube containing the anticoagulant trisodium citrate. Assays were carried out by experienced laboratory personnel, using kits to measure FVIII, FVIII inhibitor, and VWF Ag levels that had been purchased from HemosIL Reagents, Instrumentation Laboratory Company (IL), Bedford, MA. The detection of FVIII was based on the aPTT assay and an IL coagulation system. The VWF Ag levels in human citrated plasma were quantified by automated latex-enhanced immunoassay on an IL coagulation system. FVIII inhibitory antibody levels were measured by the Bethesda method,[14] and the reference range was defined as lower than 0.6 Bethesda units (BU)/mL. The reference range of VWF Ag levels was 42% to 140.8% for individuals with O-type blood and 66.1% to 176.3% for individuals without O-type blood. The reference range of FVIII activity was 50% to 150%. The total coefficients of variation of FVIII, FVIII inhibitor, and VWF Ag levels were 3.5%, 3.5%, and 3%, respectively. The detection limit of VWF Ag was 2.2%. The lupus anticoagulant (LA) levels were measured by a 3-step functional coagulation assay. The HemosIL dilute Russell viper venom time screen and confirm kit was purchased from IL.[15] The anti-β2GP1 and anticardiolipin antibodies (IgA, IgG, and IgM) were detected using a chemiluminescent enzyme-linked immunosorbent assay kit (YHLO Biotech Co, Ltd, Shenzhen, China). The antinuclear antibodies were examined with two different methods, that is, by indirect immunofluorescence using a kit from EUROIMMUN, Hangzhou, China,[16] and by line immunoassay using a kit from the same manufacturer.[17] The extractable nuclear antigen levels were measured in two different assays, that is, immunoblotting assay using a kit from Blot Biotech Co, Ltd, Shenzhen, China, and double immunodiffusion assay using antigen from the same manufacturer.[18] The Laboratory of Rheumatology and Clinical Immunology in our center is a key laboratory of the Chinese Ministry of Education and has obtained 15189 certification from the International Organization for Standardization.

Criteria for Clinical Remission

Three criteria were used to assess the therapeutic effects. First, bleeding did not recur after 1 year. Second, coagulation factor activity recovered to normal levels. Third, inhibitory antibody detection was negative. If the patients satisfied the above conditions, clinical remission was determined.[13,19]

Statistical Analysis

We used the Statistical Package for the Social Sciences version 19.0 statistical software (IBM Corp, Armonk, NY) to perform all statistical analyses. Number or percentage was used for categorical variables. Continuous variables were tested using K-S normal distribution. Mean ± standard deviation was used for data that were consistent with the normal distribution.

RESULTS

Of 9282 total patients who were hospitalized between 1986 and 2018, only 6 patients presented with AH secondary to SLE. The percentage of SLE-related AH in hospitalized SLE patients was 0.06%, reflecting the rarity of SLE-related AH. The results of clinical assessments and laboratory analyses are shown in Table 1. All 6 patients were female. The mean age was 33.67 ± 13.77 years, ranging from 12 to 50 years. Of note, 2 patients had initially been diagnosed with undifferentiated connective tissue disease. After the onset of AH, we followed the patients for 70 and 3 months, respectively, and the diagnosis of SLE was confirmed. In these 2 patients, the SLE disease activity index (SLEDAI) score was calculated based on onset of AH, not diagnosis. Although not exactly accurate, we emphasized the assessment of the entire disease activity.

The initial manifestation of SLE was bleeding diathesis in 2 AVWS patients and 1 AHA patient. Five patients had active disease at onset of AH. The SLEDAI score was calculated at the time of diagnosis of AH and ranged from 4 to 18 with an average of 10.50 ± 5.28. There were 4 patients with AHA and 2 patients with AVWS. In the AHA patients, mean age was 36.50 ± 10.63 years, and FVIII activity was between 0.4% and 7.1%. The VWF Ag level was not reduced. The mucocutaneous zone was the most common bleeding area. Hemorrhage of the shoulder joint and bulbar conjunctiva was also observed. The

TABLE 1. Baseline Clinical Features of 6 Acquired Hemophilia Patients Secondary to Systemic Lupus Erythematosus

Case	Age	Initial Bleeding Site	Bleeding Complications	SLEDAI[a] Score	Initial aPTT,[b] s	Titer of FVIII[c] Inhibitor, BU/mL	Initial FVIII Activity[e] and VWF Antigen Level, %	SLE Manifestations	Disease Duration[f]	Antibody Positivity
1	28	Skin	Anemia	4	155.9	>256	VIII 1.0, VWF[d] 245	Arthritis, butterfly erythema	8 y	Antinuclear/anti-dsDNA
2	50	Anus	Anemia, restricted defecation	15	77.8	>32	VIII 7.1, VWF 170	Nonscarring alopecia, nodal erythema, serositis, pulmonary arterial hypertension, autoimmune hepatitis	4 y	Antinuclear/anti-SSA/anti-SSB/antiphospholipid (lupus anticoagulant, anti-β2GP1 antibody, and anticardiolipin antibody)
3	28	Skin and gingiva	Anemia	18	105.0	>128	VIII <1.0, VWF 241.5	Nonscarring alopecia, hematuresis, neuropsychiatric SLE, incomplete intestinal obstruction, pancreatitis	7 y	Antinuclear/anti-dsDNA
4	40	Skin and shoulder joint	Anemia	10	73.4	105	VIII 0.4, VWF 121	Thrombocytopenia, serositis	0	Antinuclear/anti-dsDNA
5	44	Skin, epistaxis, gingiva, and profuse menstruation	Anemia, syncope	6	52.1	—	VWF 1.6, VIII 10	Nonscarring alopecia, arthritis	0	Antinuclear/anti-dsDNA/anti-smith/anti-RNP
6	12	Epistaxis and hypoglossal ecchymosis	Anemia	10	54.8	—	VWF 2.6, VIII 6.3	Proteinuria, myositis, autoimmune hemolytic anemia	0	Antinuclear

[a]SLEDAI was measured at the time of diagnosis of the AH.

[b]aPTT; the reference range was 22.7–31.8 s.

[c]FVIII; the reference range of factor VIII inhibitor was lower than 0.6 BU/mL.

[d]VWF; The reference range of von Willebrand factor antigen level was 42%–140.8% for individuals with O-type blood and 66.1%–176.3% for individuals without O-type blood.

[e]FVIII activity; the reference range of FVIII activity was 50%–150%.

[f]Disease duration was defined as the interval from the initial manifestation of rheumatic disease to onset of acquired hemophilia.

dsDNA indicates double-stranded DNA; RNP, ribonucleoprotein.

diagnosis of secondary APS was definite in case 2. Intriguingly, the manifestation of pulmonary embolism appeared 3 years after AH onset. The laboratory findings revealed prolonged aPTT in all patients, with a mean value of 86.5 seconds. In the 2 patients with AVWS, the results of the platelet aggregation test upon induction with 1.2 mg/mL ristocetin were 0% (reference range, 87%–102%). The VWF levels, 1.6% and 2.6%, respectively, were decreased. FVIII levels were also reduced. The FVIII activity was 10% and 6.3%, respectively.

In terms of therapeutic tools, potent immunosuppressive therapy was administered. This included glucocorticoids (GCs),

TABLE 2. Treatment and Prognosis of Patients Enrolled in the Study

Case	Treatment	APTT After Treatment, s	Factor VIII Activity or VWF Antigen Level After Treatment, %	Outcome
1	GC + CYC	27.9	VIII 97.0	Remission
2	GC + CsA/TWP/CYC + IA	117.4	VIII 0.1	No response
3	GC + IVIG + CYC	22.6	VIII 93.0	Remission
4	GC + IVIG+CYC + RTX	24.7	VIII 111.2	Remission
5	GC + CYC	25.3	VWF 134.0	Remission
6	GC + IVIG+CYC	21.6	VWF 123.8	Remission

CYC indicates cyclophosphamide; CsA, cyclosporin A; TWP, *Tripterygium wilfordii*; RTX, rituximab.

ranging from 1 mg/kg per day to pulse therapy (methylprednisolone 1 g intravenously for 3 days). In addition, rituximab and immunosuppressants such as cyclophosphamide, cyclosporin A, and *Tripterygium wilfordii* were administered as well. Human immunoglobulin for intravenous injection (IVIG) and immunoadsorption (IA) were also administered in some patients. The plasma exchange was not used in the case series. In addition, supportive therapy, that is, infusion of red blood cells and activated prothrombin complex concentrate (aPCC), was given to some patients. As shown in Table 2, clinical remission was achieved in 5 patients (83.3%).

DISCUSSION

Our case series indicate that AH rarely occurs in SLE patients. Previously, a retrospective study on AHA was conducted in a Chinese single hemophilia center. The results revealed that none of the 49 AHA patients suffered from SLE.[20] In terms of age of onset, sex, bleeding site, and residual FVIII activity, congenital hemophilia A and AHA are entirely different.[21] Congenital hemophilia A is seen in men and children, whereas AHA occurs in older people and the postpartum phase of women of childbearing age. The joint is the common bleeding site in congenital hemophilia A, whereas there are multiple bleeding sites in AHA. Residual FVIII activity is generally undetectable in congenital hemophilia A but may be detectable in AHA.

O'Connor[7] carried out a systemic review of SLE-related AHA. From 1993 to 2012, there were a total of 12 cases. The mean age was 39.33 ± 13.58 years. The ratio of female to male was 5:1. Bleeding symptoms as the initial presentation of SLE, namely, muscular and articular hematoma, were also observed. The remission rate of treatment was 83.3%. Our results are similar.

The VWF is an adhesive protein that participates in hemostasis[7] and acts as the carrier protein of FVIII. In AVWS secondary to SLE, the autoantibody against the FVIII/VWF complex is present, causing FVIII and VWF deficiency.[8] In our research, the 2 patients with AVWS accordingly exhibited reduced FVIII activity. However, the activity of FVIII in AHA patients was lower than that in AVWS patients. From the reported literatures, AH usually occurs several years after SLE diagnosis,[22,23] but in our research, 3 patients presented with bleeding as the first symptom, so they were not immediately redirected to the Department of Rheumatology. Further screening was carried out when an infusion of plasma, red blood cells, and FVIII could not control the bleeding. Then, the presence of antinuclear antibodies, low levels of complement, and the injury of multiple organs were revealed. The diagnosis of SLE was finally made. Since mucocutaneous hemorrhage and epistaxis could be due to SLE-related thrombocytopenia, the possibility that AH may cause bleeding in SLE patients is easily ignored. Coagulation function was examined when connective tissue disease patients complained of hemorrhage in clinical practice. Irrespective of whether the patients had active disease or showed remission, SLE-related AH could occur.[23] In our study, 5 of 6 patients were in the active stage of the disease.

Apart from the congenital deficiency of endogenous coagulation factor, other reasons behind aPTT prolongation included AVWS, AHA, LA, and heparin therapy.[24] We reported one case with concomitant AHA and secondary APS. The main clinical manifestations of bleeding and thrombosis were seen. It is well known that APS patients have a tendency for thrombosis.[11] In contrast, spontaneous hemorrhage is a typical feature of AHA. How could these apparently different clinical pictures coexist? Ames et al[25] performed a MEDLINE literature search to investigate the cases of coexistence of LA and acquired FVIII deficiency, and they summarized the clinical presentations. When LA coexisted with FVIII inhibitor, the presentation of thrombosis dominated in 40% of cases. Accordingly, bleeding accounted for 60%. In some cases, clinical manifestations included both deep venous thrombosis and bleeding. The evolution of disease in our case was similar. The specific mechanism is not yet clear, but Ames et al deduced that the reciprocal influences on the laboratory detection of FVIII and LA may cause this phenomenon. In our case, antiphospholipid antibodies were persistently positive. We detected the LA and FVIII inhibitor in accordance with the recommended methods. From another perspective, APS patients are typically in the hypercoagulable state. However, several conditions, such as hemorrhagic infarction after thrombosis formation,[26] anticoagulant therapy, pulmonary capillaritis, thrombocytopenia, thrombotic microangiopathies, or antibodies against prothrombin, could also appear in APS patients. Therefore, the major hemorrhage could occur in 10% of APS patients.[27] In case 2 of our case series, the patient had none of the aforementioned risk factors of bleeding in APS. The potential role of APS in the presentation of AH patients should be investigated in future research.

In one case report, an SLE-related AHA patient successively developed hematoma and thrombosis.[28] Several case reports have described simultaneous thrombosis and AHA.[29–32] Two underlying mechanisms have been proposed. First, AHA may damage the blood vessels, releasing a large amount of platelet tissue factor, which directly activates factor X, leading to thrombus development. Second, the infusion of hemostatic agents may contribute to thrombus formation.[32]

To recover clotting factor activity and stop bleeding, eradication of the inhibitor is the main goal for treatment. Several AHA therapeutic options are available, including GCs taken with immunosuppressants (cyclophosphamide, mycophenolate-mofetil, and calcineurin inhibitors), rituximab combination therapy, plasma exchange, IVIG, and IA.[24,33–38] Infusion of FVIII has little beneficial effect due to the presence of FVIII inhibitor. Nevertheless, recombinant activated factor VII or aPCC is useful, by substituting the role of FVIII in the formation of the tenase complex. With the above treatment regimes, most of our cases had a favorable outcome. The effectiveness of rituximab in SLE-related AVWS has also been reported.[23,39] Sometimes, AH patients require surgical procedures or invasive procedures. The literature on preventive therapy in these AH patients is rare. Of note, Ma et al[40] researched the safety and efficacy of recombinant factor VII (rFVIIa) during the perioperative period. Up to 91% of AH patients rated the rFVIIa as very good. No adverse events were documented. The use of rFVIIa shows promise in the hemostatic management of invasive procedures. Nonetheless, physicians should strictly consider the necessity of surgical procedures in AH patients to reduce unnecessary risk.

In summary, the frequency of SLE-related AH is low. The development of AH in SLE patients frequently occurs with moderate to severe active disease, and most frequently occurs in middle-aged women. Mucocutaneous hemorrhage was common. The AHA had low FVIII levels but not low VWF levels. In AVWS patients, VWF levels were low, accompanied by reduced FVIII levels. Recognizing this hemorrhagic disorder as early as possible is important in clinical practice, as prompt treatment can avoid potentially disastrous outcomes. The AHA and secondary APS can be concomitant in SLE patients. During disease development, thrombosis or bleeding can be the primary clinical manifestation. Larger cohort studies are warranted in the future.

KEY POINTS

In clinical practice, physicians should be aware of the possibility of AH when patients with SLE complain of bleeding. In the

SLE patient, AHA and secondary APS could subsequently develop. At different phases of the disease, the predominating clinical presentation could be thrombosis or hemorrhage.

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