Characteristics of Acquired Inhibitors to Factor VIII and Von Willebrand Factor Secondary to Systemic Lupus Erythematosus: Experiences From a Chinese Tertiary Medical Center

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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 AH 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 AH 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

ORIGINAL ARTICLE

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 coagulation factor inhibitor,” or “acquired hemophilia” to select appropriate patients. If the patients also presented with malignancies, infectious disorders, pregnancy, and drugs, 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. The AHA, caused by antibodies against FVIII, is the most common pattern. The SLE accounts for 8.6% of autoimmune diseases-related AH. In AH patients with comorbidities, the ratio of SLE was 2.8%. 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.
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. 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, indirect immunofluorescence using a kit from EUROIMMUN, Hangzhou, China, and by line immunoassay using a kit from the same manufacturer. 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. 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

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
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 1. Baseline Clinical Features of 6 Acquired Hemophilia Patients Secondary to Systemic Lupus Erythematosus |
|---|---|---|---|---|---|---|
| Case | Age | Initial Bleeding Site | Bleeding Complications | SLEDAI Score | Initial aPTT, s | Initial FVIII Activity and VWF Antigen Level, % |
| | | | | | | | |
| 1 | 28 | Skin | Anemia | 4 | 155.9 | >256 |
| | | | | | VIII 1.0, VWF 245 |
| 2 | 50 | Anus | Anemia, restricted defecation | 15 | 77.8 | >32 |
| | | | | | VIII 7.1, VWF 170 |
| 3 | 28 | Skin and gingiva | Anemia | 18 | 105.0 | >128 |
| | | | | | VIII <1.0, VWF 241.5 |
| 4 | 40 | Skin and shoulder joint | Anemia | 10 | 73.4 | 105 |
| | | | | | VIII 0.4, VWF 121 |
| 5 | 44 | Skin, epistaxis, gingiva, and diffuse menstruation | Anemia, syncope | 6 | 52.1 | — |
| | | | | | VWF 1.6, VIII 10 |
| 6 | 12 | Epistaxis and hypoglossal ecchymosis | Anemia | 10 | 54.8 | — |
| | | | | | VWF 2.6, VIII 6.3 |

SLEDAI was measured at the time of diagnosis of the AH.

aPTT; the reference range was 22.7–31.8 s.

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

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.

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

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.

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| 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 | 7.9 | VIII 97.0 | Remission |
| 2 | GC + CsA/TWP/CYC + IA | 7.9 | VIII 0.1 | No response |
| 3 | GC + IVIG + CYC | 6.3 | VIII 93.0 | Remission |
| 4 | GC + IVIG+CYC + RTX | 4.3 | VIII 111.2 | Remission |
| 5 | GC + CYC | 5.3 | VWF 134.0 | Remission |
| 6 | GC + IVIG+CYC | 21.6 | VWF 123.8 | Remission |

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 immuno- suppressants such as cyclophosphamide, cyclosporin A, and Tripterygium wilfordii were administered as well. Human immuno- globulin 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’Connor22 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, mucosal and articular hemartoma, 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 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.23 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.24 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 AVS, 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. Nevertheless, 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

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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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