Case Report

Systemic lupus erythematosus develop seven years after acquisition of acquired hemophilia A in a patient with palindromic rheumatism: a case report

Ching-Chi Hsieh¹, Hsin-Hua Chen¹,²,³, Der-Yuan Chen¹,²,³, Joung-Liang Lan¹,²,³

¹Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan
²School of Medicine, National Yang-Ming University, Taipei, Taiwan
³Institute of Medical Technology, National Chung-Hsing University, Taichung, Taiwan

Acquired hemophilia A is a rare disease caused by the spontaneous development of autoantibodies against coagulation factor VIII (FVIII). About half of these cases are idiopathic and 5% of them are associated with systemic lupus erythematosus (SLE). To our knowledge, in prior case reports of this cohort, acquired hemophilia A appeared concurrently with, or around 6 years after the development of SLE. Herein, we report the first case of a patient with palindromic rheumatism who developed SLE 7 years after acquisition of acquired hemophilia A.

Key words: Acquired hemophilia A, factor VIII inhibitor, systemic lupus erythematosus, palindromic rheumatism

Introduction

Acquired hemophilia A is a rare but life-threatening autoimmune bleeding disorder resulting from the presence of antibodies directly against coagulation factor VIII (FVIII). Its incidence is about 0.2-1.0 per million per year in western countries [1]. Approximately 50% of cases are caused by the underlying specific medical conditions, such as postpartum, malignancy, and autoimmune diseases. Herein, we describe a Taiwanese female patient with palindromic rheumatism (PR) who developed systemic lupus erythematosus (SLE) 7 years after acquisition of acquired hemophilia A. Compared with those who had acquired hemophilia A and SLE reported in the literature, our case is the first one who presented with SLE after acquisition of acquired hemophilia A.

Case report

A Taiwanese woman suffered from intermittent monoarthritis since the third day after delivery of her first baby in 1990, at the age of 28. The presentation was intermittent acute onset of painful swelling without local erythema over a single joint. In each episode, there was no preceding trauma. The joints involved were wrists, proximal interphalangeal joints, metacarpophalangeal joints, knees, and ankles. It happened about once per month, lasted for a few days, and subsided spontaneously without any residual pain, swelling or deformity between episodes. Before 2000, the patient did not visit a doctor for her intermittent monoarthritis and never complained of hair loss, skin rash, photosensitivity, chest pain, abdominal pain, weakness, foamy urine, psychosis, seizure, skin thickening, dry eyes, dry mouth or Raynaud’s phenomenon.

In Oct 2000 when she was 38 years old, she suffered from an acute attack of multiple ecchymosis, which developed spontaneously over all the four limbs and...
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lasted for several days. She visited the Rheumatology Clinic of Taichung Veterans General Hospital for the unexplained ecchymosis and intermittent migratory monoarthritis. Laboratory data including antinuclear antibody (ANA), rheumatoid factor (RF), anticardiolipin antibody (Ab), lupus anticoagulant (LA), anti-hepatitis C virus Ab, and anti-human immunodeficiency virus Ab were all negative. She had a regular menstrual cycle and her uric acid level was 5.6 mg/dL. X-ray of all the joints that had been involved didn’t reveal any abnormality. PR was thus diagnosed by the PR diagnostic criteria proposed by Guerne and Weisman [2]. She was then admitted for evaluation of her bleeding tendency. The coagulation profile revealed prolonged activated partial thromboplastin time (aPTT) and persistent prolongation of clotting time after mixing with normal plasma. The presence of a coagulation factor inhibitor, FVIII inhibitor: 1.5 Bethesda units (BU), was confirmed by Bethesda assay [3]. The quantification of FVIII was 2% (55-145%) (Fig. 1). No autoimmune

Figure 1. Serial changes of coagulation factor VIII in a PR patient with acquired hemophilia A who developed SLE. Abbreviations: PR = palindromic rheumatism; SLE = systemic lupus erythematosus; CyS = cyclosporine; aPTT = activated partial thromboplastin time; FVIII = coagulation factor VIII; AZA = azathioprine; MA = mycophenolic acid
disease or malignancy was found. The patient was treated with corticosteroids (hydrocortisone 1200 mg daily initially) and cyclosporine (150 mg daily), and symptoms subsided with normalization of aPTT and FVIII values. We continued cyclosporine (100 mg daily) treatment to maintain normal coagulation profiles and added sulfasalazine (1000 mg daily) for PR. Hydroxychloroquine was not given due to an allergy to this medication presenting with generalized itching skin rash. As illustrated in Fig. 1, the values of aPTT and FVIII were within normal limits, also intermittent arthritis resolved after the above medications. However, seven years later, she developed progressive hair loss, painless oral ulcer, and Raynaud’s phenomenon in Mar 2007 and intermittent microscopic hematuria and proteinuria (4.13 gm/24hr) were noted in Apr 2007. Immunological data revealed positive tests for ANA (1:2560, fine and coarse speckled pattern), anti-Sm Ab (1249 AU/mL, normal <100 AU/mL), anti-RNP Ab (2339 AU/mL, normal <100 AU/mL), and elevated level of serum anti-dsDNA Ab (279.2 WHO units/mL, normal ≤92.6 units/mL). Testing for anti-histone antibody was negative. The patient had low complement 3 (C3) (43.1 mg/dL, normal 90-180 mg/dL) and C4 (8.19 mg/dL, normal 10-40 mg/dL). HLA typing showed HLA-DRB1 0901/0803. Therefore, she fitted the 1997 American College of Rheumatology (ACR) revised SLE classification criteria (including hair loss, ANA, dsDNA and proteinuria) [4]. Cyclosporine and sulfasalazine were discontinued. We treated her SLE with corticosteroids (20 mg daily), azathioprine (50 mg daily), and mycophenolic acid (720 mg daily), and lupus disease activity declined gradually thereafter. As illustrated in Fig. 1, before and after the diagnosis of SLE, quantification of FVIII was within normal limits and no FVIII inhibitor was detected.

Discussion

PR is characterized by recurrent episodes of acute arthritis of short duration, leaving no residual clinical and radiographic changes. In the long term, a substantial proportion of patients will develop rheumatoid arthritis (RA) or other connective tissue diseases. Gonzalez-Lopez et al. reported that 3 (2%) of 127 patients with PR, with disease duration of 6 ± 6 years, subsequently developed SLE who were followed up 40 ± 45 months by rheumatologists [5]. The patient presented with PR 17 years prior to development of SLE. However, the symptoms of PR disappeared after treatment with corticosteroid, sulfasalazine, and cyclosporine for acquired hemophilia A 7 years prior to development of SLE, when ANA was negative. Both PR and acquired hemophilia A could be related to subsequent SLE. As yet, no previous reports have mentioned the correlation between PR and acquired hemophilia A.

The clinical picture of acquired hemophilia is dominated by severe hemorrhage in the majority of patients, with an inhibitor-related mortality rate of up to 22%. Heparin contamination and the presence of LA should be ruled out. Prolonged aPTT that is not corrected by a 1:1 mix of patient and reference plasma is characteristic for both acquired hemophilia A and presence of LA. In a cohort of 1000 patients with SLE, 15% of them had LA [6]. However, patients with LA should present with vascular thrombosis or pregnancy morbidity, which the patient didn’t present with, rather than bleeding tendency. Instead of LA, FVIII inhibitor was detected by Bethesda assay in our patient. In the Bethesda assay, serial dilutions of patient plasma are incubated with pooled normal plasma at 37°C for two hours; FVIII activity is then measured using a clotting assay as one would in the patient with hereditary FVIII deficiency. The reciprocal dilution of patient plasma that results in 50 percent FVIII activity is defined as one BU. The stronger the inhibitor, the greater the dilution required to allow for FVIII activity. In our patient, FVIII inhibitor was no longer detected by Bethesda assay after treatment for acquired hemophilia A. In addition to corticosteroid and cyclosporine, which were used in our patient, previous studies in a prospective randomized trial showed that cyclophosphamide is effective as a second-line therapy for many of those who are steroid-resistant [7], and that successful treatment and long-lasting remission was achieved in SLE patients with acquired FVIII inhibitors [7,8]. Recently, a chimeric anti-CD20 monoclonal antibody (rituximab) has been used in the treatment of acquired hemophilia, showing promising results [9]; but, large prospective randomized trials are needed to confirm these positive preliminary results.

A survey of 215 patients with inhibitors against FVIII revealed that 7.9% of the cases had RA and 5.6% had SLE [10]. The association of SLE and acquired hemophilia has been reported in several articles. Ten cases were available and all of them had acquired hemophilia A, which appeared either concurrently with or following SLE [11,13]. Most of these cases appeared around 6 years later, and one case developed 21 years later [12]. In contrast, our patient developed SLE seven years after presentation of acquired hemophilia A.
Perhaps the high mortality of acquired hemophilia A or usage of immunosuppressive agents (cyclosporine) abrogated the probability of further development of SLE. Sulfasalazine-induced lupus erythematosus was suspected initially. However, it is usually accompanied by positive ANA as well as positive anti-histone antibodies (95%) with an absence of anti-dsDNA (<5%) [14]. In addition, increased risk of sulfasalazine-induced SLE was observed in patients with HLA-DRB1 0301. Our patient had a negative anti-histone antibody test, a positive anti-dsDNA test and HLA-DRB1 0901/0803, and clinical features of SLE persisted despite the withdrawal of sulfasalazine. Therefore, sulfasalazine-induced SLE was presumed to be less likely. After treatment for SLE was initiated, disease activity of SLE declined markedly and the FVIII level was kept within normal limits (Fig. 1). No significant correlation between SLE activity and degree of acquired hemophilia A has been reported. Previous reports showed that FVIII inhibitors were eliminated with improvement of symptoms in the majority of cases, but a small minority died of multiple organ failure or SLE flare-up [11,12]. Consistent with previous reports, FVIII inhibitor was not detected in our patient throughout the course of SLE.

**Conclusion**

SLE can develop not only concurrently with or before acquisition of acquired hemophilia A, but also several years after remission of acquired hemophilia A.

**References**

一位反覆性風濕症患者於罹患後天性A型血友病七年後發生紅斑性狼瘡：病例報告

謝景吉 1 陳信華 1,2,3 陳得源 1,2,3 藍忠亮 1,2,3

1台中榮民總醫院內科部
2國立陽明大學醫學院
3國立中興大學生物科技研究所

後天性A型血友病是一種由於自發性製造對抗第八凝血因子之自體抗體而造成的罕見疾病。這種病症中大約半數是不明原因的，而大約百分之五和紅斑性狼瘡有關。就我們所知，在之前此類病患的個案報告中，所有的患者其後天性A型血友病皆是和紅斑性狼瘡同時發生，或是在診斷紅斑性狼瘡數年後才發生。在此我們報告第一例反覆性風濕症患者於罹患後天性A型血友病七年後才發生紅斑性狼瘡。

關鍵詞：後天性A型血友病、第八凝血因子抗體、紅斑性狼瘡、反覆性風濕症