Int J Clin Exp Med 2016;9(7):14870-14874
www.ijcem.com /ISSN:1940-5901/IJCEM0026321

Case Report

Acquired von Willebrand's syndrome as the first manifestation of juvenile-onset systemic lupus erythematosus with negative specific autoantibodies

Haijuan Xiao, Mingsheng Ma, Hongmei Song, Yan Liu, Wuchen Wu, Juan Xiao, Yanyan He, Min Wei

Department of Pediatrics, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China

Received February 20, 2016; Accepted May 15, 2016; Epub July 15, 2016; Published July 30, 2016

Abstract: Acquired von Willebrand's syndrome (AvWS) is a rare heterogeneous bleeding disorder that could be secondary to many underlying diseases, among which systemic lupus erythematosus (SLE) is a less common cause. We presented an uncommon juvenile-onset SLE with AvWS as the first manifestation, whose autoantibodies were all negative except for low-titer positive antinuclear antibody (ANA). Initial corticosteroid treatment before the addition of immunosuppressant had poor effects. In conclusion, von Willebrand's syndrome could be secondary to SLE and immunosuppressants are useful treatment for juvenile-onset AvWS secondary to SLE.

Keywords: Systemic lupus erythematosus (SLE), acquired von Willebrand's syndrome (AvWS), autoimmune hemolytic anemia (AIHA), membranous nephropathy (MN), autoantibody, von Willebrand factor (vWF)

Introduction

Acquired von Willebrand's syndrome (AvWS), which should be suspected in patients without a prior or family history, is a rare heterogeneous bleeding disorder characterized by mucocutaneous and/or gastrointestinal bleeding, an isolated elevated activated partial thromboplastin time (APTT), and variably low plasma levels of factor VIII (FVIII) and von Willebrand factor (vWF) [1]. Several categories of underlying disorders have been reported, such as lymphoproliferative disorders, myeloproliferative disorders, tumors, autoimmune diseases, cardiac disorders, and so on, among which systemic lupus erythematosus (SLE) appears to be less frequently associated with AvWS [1]. Most cases presented vWS when or after diagnosed as SLE, however, vWS was also reported as a herald syndrome in the patients who developed SLE later [2]. There have been at least 21 reported cases of AvWS secondary to SLE. Among these, 6 cases were explicitly less than 18 years old [2-7].

In this article, we described an uncommon juvenile-onset SLE patient with AvWS as the first manifestation, whose autoantibodies were all negative except for low-titer positive ANA. Her conditions were complicated, critical and atypical, and initial treatment had no obvious effects. We got the correct diagnosis and gave proper treatment by organized clinical thinking and renal pathological result.

Case record

A 12-year-old girl without obvious bleeding history was admitted in July 9, 2014. She experienced intermittent epistaxis and bleeding spots of double lower limbs from early-May 2014. In mid-June, she suffered from petechia of conjunctiva and oral mucosa, mild fever, and serious myalgia and swelling of limbs. There was no obvious hepatosplenomegaly. Laboratory tests revealed decreased haemoglobin (HGB, 46 g/L), prolonged APTT (60 s, *22.7-31.8*), and normal prothrombin time. Several blood biochemical parameters were increased: total bilirubin (42.2 μmol/L, *5.1-22.2*), indirect bilirubin (35.4 μmol/L), and muscle enzymes, among which creatine kinase (CK) was 1542 U/L (*24-170*). Other blood results were as follows: increased reticulocyte count (20%) and erythrocyte

sedimentation rate (ESR, 115 mm/h, *0-20*), and decreased albumin (30 g/L) and complement (C3 0.3 g/L, *0.73-1.46*; C4 0.02 g/L, *0.1-0.4*). Her urine protein was 3.08 g/24 h, and 98.4% was derived from glomerular lesion. Fecal occult blood was positive, and a few red blood cells (RBC) were found.

Her head magnetic resonance and echocardiography were roughly normal. Chest computed tomography showed pulmonary interstitial diseases. There were no positive infection indicators, such as T-SPOT.TB test, hepatitis B virus (HBV), Epstein-Barr virus and cytomegalovirus DNA and antibodies, and so on. Her antibodies to double-stranded DNA (anti-dsDNA), antiphospholipid antibodies, anti extracted nuclear antigens autoantibodies (anti-ENA), and anti-neutrophil cytoplasmic antibodies (ANCA) were all negative; the titer of antinuclear antibody (ANA) was 1:80. In local hospital, she received full-dose methylprednisolone (including pulse therapy), intravenous immunogloblin, blood transfusion and prothrombin complex, and antibiotics treatment from June 15, but no effects were gained.

Her conditions were serious for bleeding and severe anemia, and were not improved although early aggressive therapy had been given. We continued methylprednisolone and symptomatic treatment, and performed further tests. Abnormalities of membranes and enzymes of RBC were excluded. Coombs' tests were negative. Her APTT could be corrected by 1:1 plasma immediately and after 2 hours; coagulation factors were normal except FVIII (6.3%, *50.0-150.0*). vWF antigen was nearly completely absent (2.6%, *66.1-176.3*), and ristocetin-induced platelet aggregation (RIPA) test showed no response. There were no evidence of tumor (normal bone marrow biopsy, whole body diffusion-weighted imaging, and bone scanning) and hepatolenticular degeneration (normal ceruloplasmin). Related tests for antoantibodies were repeated, which were similar to those before.

vWS could be diagnosed based on bleeding symptoms, abnormal APTT, FVIII, and vWF antigen. We considered that her vWS was secondary for negative family and clinical history. Hemolytic anemia was obvious based on increased indirect bilirubin and reticulocyte count. We diagnosed autoimmune hemolytic anemia (AIHA) according to the fact that blood transfusion could not increase her HGB (50-60 g/L). Renal biopsy could not be performed because of abnormal coagulation. Her myalgia, swelling of arms, and increased muscle enzymes were considered as myositis. Diagnosis for her primary disease was extremely difficult. At last, SLE with negative specific autoantibodies was diagnosed based on five points: positive ANA, obviously decreased C3/C4, AIHA, explicit glomerular proteinuria, and AvWS.

We continued full-dose methylprednisolone (including the second pulse therapy). Meanwhile, intravenous cyclophosphamide pulse therapy for 6 months was administered from July 24. Her HGB and CK improved from early-August. In October 2014, her APTT were normal; ANA became negative, and Coombs' was positive (C3 positive). In January 2015, her FVIII, vWF, RIPA, ESR, and C3/C4 went back to normal. However, her proteinuria increased to 6.48 g/24 h. The patient and her parents refused renal biopsy although we strongly advised. We substituted mycophenolate mofetil for cyclophosphamide. In March 2015, her ESR increased to 66 mm/h, and proteinuria increased to 9.40 g/24 h (albumin decreased to 20 g/L). Renal biopsy was performed; the pathology showed atypical membranous nephropathy (MN) with full-house pattern by immunofluorescence (**Figure 1**). Combined with her other manifestations, we diagnosed SLE and added cyclosporine.

The patient was followed up every 2-3 months. Her ESR remained about 80 mm/h, complements were normal, and anti-dsDNA remained negative. Proteinuria decreased gradually, but was still more than 6 g/24 h. In November 2015, when her prednisone reduced to 15 mg/day, her C3 and C4 decreased to 0.697 g/L and 0.095 g/L respectively, ANA was positive again (1:640), and anti-dsDNA was positive for the first time: 1:20 (immunofluorescence) and 161 IU/ml (ELISA). ESR and proteinuria did not change obviously. We considered that her conditions relapsed along with reduction of corticosteroids, therefore, we increased prednisone dosage and added other immunosuppressant. In January 2016, her ESR was still 80 mm/h. However, complements returned to normal, anti-dsDNA decreased to 1:10 (immunofluorescence) and 0 (ELISA), and proteinuria decreased

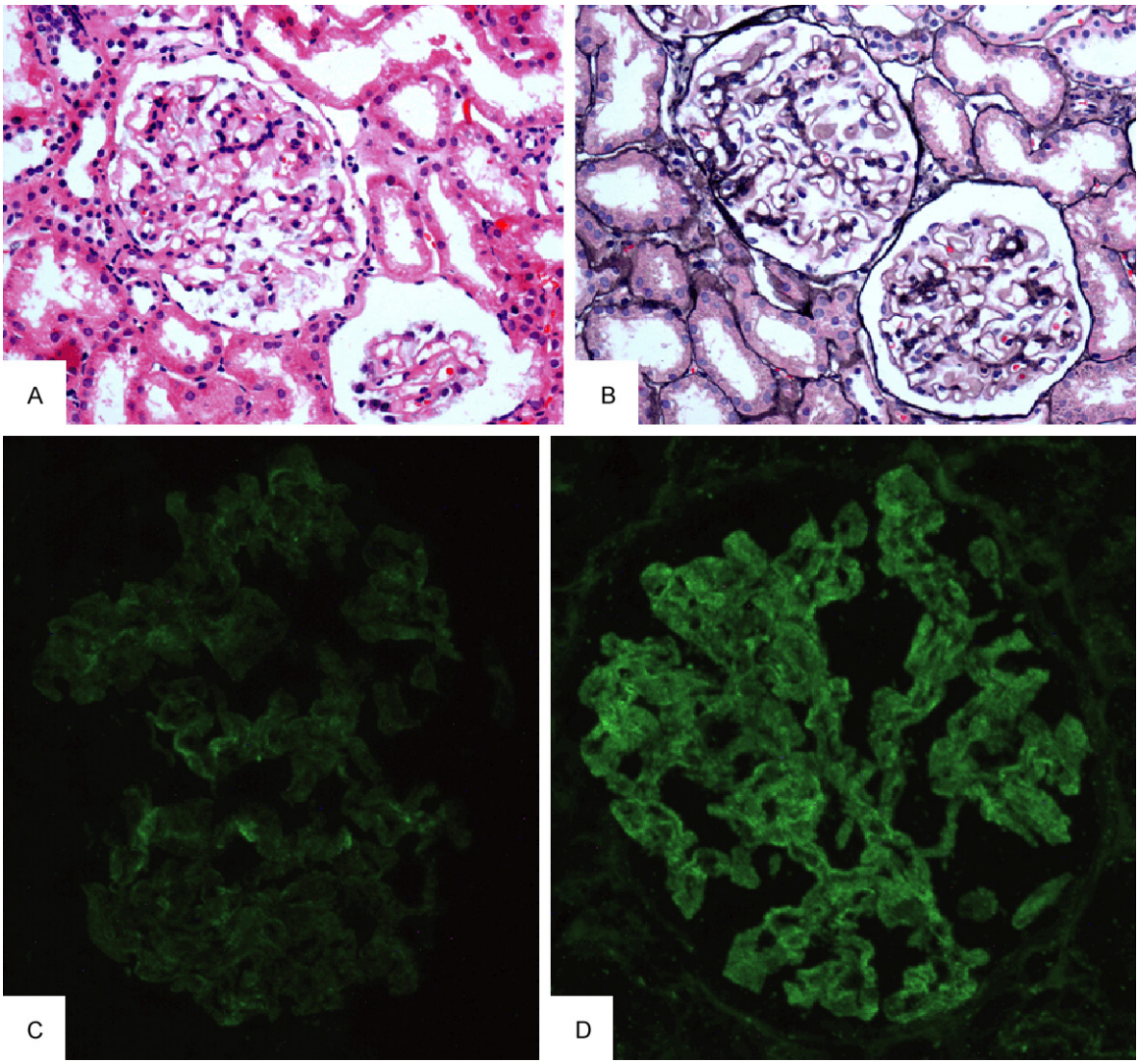

Figure 1. Renal pathological results. Segmental mesangial cells proliferation and mesangial matrix expansion were shown by hematoxylin-eosin (HE) staining (A: ×200). Diffusely thickened glomerular basement membrane and a number of spikes on the epithelial side were shown by periodic acid-silver methenamine (PASM) (B: ×200). Granular capillary loop and mesangial deposits staining for C1q (C: 1+, diffuse and global), IgG (D: 2+, diffuse and global), and C3 (1-2+, diffuse and global) were shown by immunofluorescence microscopy.

to 3.06 g/24 h. This patient had received effective treatment.

Discussion

To our knowledge, this is the first juvenile-onset SLE with negative specific autoantibodies, whose first manifestation was AvWS. Her conditions (bleeding, severe anemia, proteinuria, myalgia) were so complicated and critical that definite primary diagnosis and timely treatment were urgently needed. However, atypical clinical features (corrected APTT by 1:1 plasma, negative Coombs' tests, and negative specific autoantibodies) and poor effects of initial corticosteroid treatment enhanced the difficulty for right diagnosis and therapies. We diagnosed SLE by excluding other possible diseases such as infectious diseases and tumors and grasping clinical key points. Her conditions were not improved until powerful immunosuppressant was added. Renal pathology confirmed the diagnosis, and positive anti-dsDNA in the follow-up supported SLE further.

vWF, which is a glycoprotein performing two critical functions (a carrier for FVIII in the circulation rendering its stability, a bridging mole-

cule for platelet adhesion and aggregation), is synthesized normally in most AvWS patients; low levels of vWF result from accelerated removal from the plasma via several mechanisms [8]. In autoimmune diseases, specific autoantibodies bind to vWF, form immune complexes, and increase the clearance of vWF by Fc bearing cells of the reticuloendothelial system [8]. As for this patient, we inferred the presence of autoantibody to vWF, which, however, could not be detected in our hospital.

In fact, the result that her APTT could be corrected by 1:1 plasma did not support secondary diseases. We considered this might be caused by the difference between internal environment and in vitro tests. This patient was diagnosed as AIHA, but her Coombs' tests were negative. In fact, about 2-10% of AIHA patients are Coombs' negative, which is due to IgG sensitization below the detection threshold, low-affinity IgG antibody, sensitization by IgA or IgM alone, and other factors [9]. After treatment, her Coombs' test became C3 positive, which might be the result of mass of complement consumption early in the illness. The specific autoantibodies for SLE in our patient remained negative for more than 1 year. Anti-dsDNA did not become positive until her conditions relapsed. We considered that her autoantibodies deposited on the kidney in the early stage of disease, which could not be detected in the blood. However, the reason that anti-dsDNA became positive in the blood afterwards was not clear.

MN is an immune complex-mediated cause of nephritic syndrome, the etiology of which may be primarily autoimmune (idiopathic) or instead secondary to infections, systemic autoimmune processes, drugs, malignancy, or even dietary antigens [10]. In typical/idiopathic MN, thickened appearance of the glomerular basement membrane (GBM), spikes on Jones' silver stain, the granular capillary loop pattern on immunofluorescence microscopy, and the subepithelial electron dense deposits by electron microscopy could be seen. Mesangial cells proliferation and mesangial immune complex deposits (C1q, IgG, C3, and so on) are clues to the secondary MN [11]. Only according to the renal pathology, we could diagnose secondary MN, among which SLE and HBV infection are the most commonly reported causes in the pediatric population [10]. However, there was no evidence for HBV infection for this pathient.

There have been reports about ANA-negative SLE patients, however, reports of SLE with positive ANA and negative specific autoantibodies are rare. After all, positive anti-dsDNA, anti-Smith (anti-Sm), and antiphospholipid antibodies are critical to SLE [12]. According to the 1997 American College of Rheumatology (ACR) classification criteria for SLE, this patient only satisfied three clinical or laboratory criteria and could not be diagnosed as SLE [12]. However, according to 2009 Systemic Lupus International Collaborating Clinics (SLICC) classification system, SLE could be diagnosed by urine protein, hemolytic anemia, positive ANA, and decreased complement [13]. Anyhow, doctors should be cautious to diagnose SLE when specific autoantibodies are negative; related pathological results are helpful. Based on the renal pathology and other clinical manifestations in our patient (AvWS, AIHA, glomerular proteinuria, myositis, positive ANA, and decreased complement), SLE was the only possible diagnosis.

In conclusion, AvWS could be the first manifestation of juvenile-onset SLE with negative specific autoantibodies. When clinical features are complex and atypical, organized clinical thinking and related pathology are important for the right diagnosis. Immunosuppressants are very useful treatment for AvWS secondary to SLE, especially when initial corticosteroid treatments have no obvious effects.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hongmei Song, Department of Pediatrics, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, No. 1, Shuaifuyuan, Dongcheng District, Beijing 100730, China. E-mail: songhm1021@hotmail.com

References

[1] Federici AB. Acquired von Willebrand syndrome: is it an extremely rare disorder or do we see only the tip of the iceberg? J Thromb Haemost 2008; 6: 565-568.

[2] Niiya M, Niiya K, Takazawa Y, Hayashi Y, Tanio Y, Kushiro M, Tanimizu M, Hasegawa H and Tanimoto M. Acquired type 3-like von Wille-

brand syndrome preceded full-blown systemic lupus erythematosus. Blood Coagul Fibrinolysis 2002; 13: 361-365.

[3] Simone JV, Cornet JA and Abildgaard CF. Acquired von Willebrand's syndrome in systemic lupus erythematosus. Blood 1968; 31: 806-812.

[4] Gazengel C, Prieur AM, Jacques C, Buriot D, Nedellec J and Josso F. Antibody-induced von Willebrand syndrome: inhibition of VIII VWF and VIII AGN with sparing of VIII AHF by the autoantibody. Am J Hematol 1978; 5: 355-363.

[5] Igarashi N, Miura M, Kato E, Matsuda T, Itoh K, Abildgaard CF, Shimizu M, Koizumi S, Sato T and Taniguchi N. Acquired von Willebrand's syndrome with lupus-like serology. Am J Pediatr Hematol Oncol 1989; 11: 32-35.

[6] Soff GA and Green D. Autoantibody to von Willebrand factor in systemic lupus erythematosus. J Lab Clin Med 1993; 121: 424-430.

[7] Jimenez AR, Vallejo ES, Cruz MZ, Cruz AC, Miramontes JV and Jara BS. Rituximab effectiveness in a patient with juvenile systemic lupus erythematosus complicated with acquired Von Willebrand syndrome. Lupus 2013; 22: 1514-1517.

[8] Federici AB, Rand JH, Bucciarelli P, Budde U, van Genderen PJ, Mohri H, Meyer D, Rodeghiero F, Sadler JE; Subcommittee on von Willebr and Factor. Acquired von Willebrand syndrome: data from an international registry. Thromb Haemost 2000; 84: 345-349.

[9] Segel GB and Lichtman MA. Direct antiglobulin ("Coombs") test-negative autoimmune hemolytic anemia: a review. Blood Cells Mol Dis 2014; 52: 152-160.

[10] Ayalon R and Beck LH Jr. Membranous nephropathy: not just a disease for adults. Pediatr Nephrol 2015; 30: 31-39.

[11] Larsen CP, Messias NC, Silva FG, Messias E and Walker PD. Determination of primary versus secondary membranous glomerulopathy utilizing phospholipase A2 receptor staining in renal biopsies. Mod Pathol 2013; 26: 709-715.

[12] Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997; 40: 1725.

[13] Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, Bruce IN, Isenberg D, Wallace DJ, Nived O, Sturfelt G, Ramsey-Goldman R, Bae SC, Hanly JG, Sanchez-Guerrero J, Clarke A, Aranow C, Manzi S, Urowitz M, Gladman D, Kalunian K, Costner M, Werth VP, Zoma A, Bernatsky S, Ruiz-Irastorza G, Khamashta MA, Jacobsen S, Buyon JP, Maddison P, Dooley MA, van Vollenhoven RF, Ginzler E, Stoll T, Peschken C, Jorizzo JL, Callen JP, Lim SS, Fessler BJ, Inanc M, Kamen DL, Rahman A, Steinsson K, Franks AG Jr, Sigler L, Hameed S, Fang H, Pham N, Brey R, Weisman MH, McGwin G Jr and Magder LS. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012; 64: 2677-2686.