

Severe acquired von Willebrand syndrome secondary to systemic lupus erythematosus

Dear Editor,

The acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder that mimics the clinical and laboratory findings of inherited von Willebrand disease (VWD) but occurs in individuals with no previous personal or family history of bleeding. The main pathogenic mechanism is the accelerated removal of von Willebrand factor (VWF) from plasma, due to different causes such as the increased proteolytic degradation of VWF, its adsorption onto malignant cells or activated platelets or to immunoglobulins against the VWF-factor VIII (FVIII) complex.¹ The syndrome is associated with lymphoproliferative, myeloproliferative, cardiovascular and autoimmune diseases and cancer, and is more often occurring in the elderly.² The first case of AVWS secondary to systemic lupus erythematosus (SLE) was reported by Simone *et al*³ in 1968. Although this association is infrequently described in literature,^{1,3,4} even less frequent is its presentation with clinical and laboratory features resembling a severe VWD phenotype.⁵ Most cases have mild to moderate bleeding tendency, with laboratory characteristics similar to inherited VWD type 1.^{1,6,7}

The differential diagnosis between AVWS and VWD might be difficult because the personal history of bleeding (acquired or lifelong) is not always conclusive and the two diseases share similar laboratory results. A potential diagnostic biomarker, the ratio of the VWF propeptide (VWFpp) to VWF antigen (VWF:Ag) (VWFpp/VWF:Ag), is an indicator of an enhanced VWF clearance.⁸⁻¹⁰ Only 20% of patients with AVWS have autoantibodies inactivating VWF activity, indicating that mixing tests such as the Bethesda assay may be often inadequate to detect antibodies.¹¹ A tool that might be useful to confirm the laboratory diagnosis of AVWS is the ELISA that detects anti-VWF non-neutralizing antibodies.¹¹ Here, we report the case of a severe AVWS secondary to a previously undiagnosed SLE, the main laboratory features over time and the positive clinical and laboratory effect of immunosuppressive therapy. The patient was a 19 years old girl admitted to the emergency room with spontaneous gum bleeding and general malaise. The initial laboratory evaluation showed a prolonged activated partial thromboplastin time (aPTT), with a ratio of 1.51 (normal range 0.86-1.20). Haemoglobin was 10.3 g/dL (normal range 12.0-16.0 g/dL), platelet count 147 000/ μ L (normal range 130 000-400 000/ μ L), aspartate aminotransferase 47 U/L (normal range 10-33 U/L), alanine aminotransferase 108 U/L (normal range 6-41 U/L). The day after admission, the patients also declared to have suffered in the most recent past of easy bruising and heavy menstrual bleeding, but she had no lifelong personal and family history of bleeding. The laboratory assessment revealed

a pattern resembling a severe form of VWD, with very low plasma values of factor VIII (FVIII), VWF:Ag, VWF ristocetin cofactor activity (VWF:RCo) (Table 1, Baseline) and a barely detectable VWF multimeric pattern. The tests for hepatitis C and B viruses were negative. Since the patient reported a significant bleeding history only in recent times, an AVWS was hypothesized and the laboratory evaluation was guided by this hypothesis. At baseline the VWFpp/VWF:Ag was 54 (normal range 0.6-1.6), indicating a normal pro-VWF synthesis but a markedly increased plasma clearance of this moiety, as typical of AVWS. Mixing test with the Bethesda method, using the VWF:RCo and VWF:CB assays, showed the presence of a mild inhibitor against VWF:RCo (1 BU). The syndrome was confirmed by the normal intraplatelet VWF content, but the ELISA for anti-VWF antibodies demonstrated a high titre of IgG and also the presence of IgM (Table 1). Further laboratory investigations revealed the presence of high titre antinuclear antibody (1:1280, normal value <1:60), anti-native DNA antibody (1:40, normal value <1:10) and anti-double-stranded DNA antibody (311 IU/mL, normal range 0-27), some consumption of the complement fractions C3 and C4, mild anaemia and thrombocytopenia. Because these laboratory findings, together with other clinical manifestations such as muscle and joint pain, led to a novel diagnosis of SLE, she started an immunosuppressive daily treatment with prednisone 50 mg, azathioprine 100 mg and hydroxychloroquine sulphate 200 mg. After 2 weeks, a progressive increase in FVIII and VWF values with concomitant reduction in the titre of anti-VWF IgG/IgM antibodies was observed. At the follow-up (FU) day 168 the patient showed a normalization of FVIII and VWF values, and the anti-VWF IgG and IgM antibodies titre became undetectable (Table). The titre of anti-double-stranded DNA antibody decreased from 311 to 55 IU/mL and the C3 and C4 complement fraction and beta2-microglobulin became normal. A possible explanation of an AVWS secondary to SLE is the increased VWF clearance due to an anti-VWF antibody. The enhanced VWF clearance in our patient was confirmed by the markedly increased VWFpp/VWF:Ag values. By following up the patient over time, a decrease in the VWFpp/VWF:Ag was observed, along with the normalization of VWF measurements that occurred one month after the beginning of the immunosuppressive therapy. The baseline results of the VWFpp/VWF:Ag measurement facilitated the differential diagnosis between VWD and AVWS, and evaluation over time confirmed the efficacy of the immunological treatment and the remission of the underlying disease, previously undiagnosed.¹² It has been already reported that the eradication of the autoantibodies with an aggressive

TABLE 1 Laboratory assessment

Days of FU	FVIII:C, IU/dL	VWF:Ag, IU/dL	VWF:RCo, IU/dL	VWF:CB, IU/dL	VWFpp/VWF:Ag	Anti-VWF IgG titration	Anti-VWF IgM titration
Baseline	3	2	0.5 ^b	<1	54	1:640	1:40
50 ^a	10	3	0.5 ^b	NT	60	1:1280	1:80
62	36	12	13	NT	9.4	1:640	1:20
78	149	73	71	73	2.05	1:160	1:20
125	190	123	122	161	1.17	1:40	<1:20
168	118	70	63	NT	NT	<1:20	<1:20
Normal range	50-147	40-169 ^c 55-165 ^d	41-160 ^c 53-168 ^d	45-170 ^c 56-174 ^d	0.6-1.6	<1:20	<1:20

BU, Bethesda Unit; FU, follow-up; FVIII:C, FVIII coagulant activity; IU, International Unit; NT, not tested; VWF, von Willebrand factor; VWF:Ag, VWF antigen; VWF:CB, VWF collagen binding; VWF:RCo, VWF ristocetin cofactor activity; VWFpp/VWF:Ag, VWFpp to VWF:Ag ratio.

^aImmunosuppressive therapy started at day 45;

^bchemiluminescent based assay;

^cO blood group;

^dnon-O blood group.

immunosuppression therapy is critical for the treatment of underlying autoimmune disorders,¹ as confirmed herewith. In this patient mixing tests revealed a neutralizing antibody at a low titre (1BU), but high titre anti-VWF IgG and IgM were shown by the ELISA assay.

In conclusion, we described herein a rare case of severe AVWS secondary to SLE. When the differential diagnosis between AVWS and VWD is challenging, the use of VWFpp/VWF:Ag and the ELISA for the detection of anti-VWF antibodies may facilitate the diagnosis. Also, the successful treatment points out the importance of a therapy aimed at resolving the underlying disease and therefore the acquired bleeding syndrome.

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AUTHOR CONTRIBUTION

FS and LB wrote the manuscript. PC performed the assays. MC collected clinical data. EB and FP discussed the results and critically revised the manuscript.

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REFERENCES

- Franchini M, Lippi G, Favaloro EJ. Advances in hematology. Etiology and diagnosis of acquired von Willebrand syndrome. *Clin Adv Hematol Oncol*. 2010;8:20-24.
- Federici AB, Rand JH, Bucciarelli P et al. Acquired von Willebrand syndrome: data from an international registry. *Thromb Haemost*. 2000;84:345-349.
- Simone JV, Cornet JA, Abildgaard CF. Acquired von Willebrand's syndrome in systemic lupus erythematosus. *Blood*. 1968;31:806-812.
- Taveras AS, Alexis K, Sridharan A et al. Acquired Von Willebrand's syndrome in systemic lupus erythematosus. *Case Rep Hematol*. 2014;2014:208597.

5. Gavva C, Patel P, Shen YM, Frenkel E, Sarode R. A case of auto-immune severe acquired von Willebrand syndrome (type 3-like). *Transfus Apher Sci.* 2017;56:431-433.
6. Michiels JJ, Berneman Z, Gadisseur A et al. Immune-mediated etiology of acquired von Willebrand syndrome in systemic lupus erythematosus and in benign monoclonal gammopathy: therapeutic implications. *Semin Thromb Hemost.* 2006;32:577-588.
7. Shetty S, Kasatkar P, Ghosh K. Pathophysiology of acquired von Willebrand disease: a concise review. *Eur J Haematol.* 2011;87:99-106.
8. van Genderen P, Boertjes RC, van Mourik JA. Quantitative analysis of von Willebrand factor and its propeptide in plasma in acquired von Willebrand syndrome. *Thromb Haemostas.* 1998;80:495-498.
9. Haberichter SL, Balistreri M, Christopherson P et al. Assay of the von Willebrand factor (VWF) propeptide to identify patients with type 1 von Willebrand disease with decreased VWF survival. *Blood.* 2006;108:3344-3351.
10. Stufano F, Boscarino M, Bucciarelli P et al. Evaluation of the Utility of von Willebrand Factor Propeptide in the Differential Diagnosis of von Willebrand Disease and Acquired von Willebrand Syndrome. *Semin Thromb Hemost.* 2018;10-1660481.
11. Franchi F, Biguzzi E, Stufano F, Siboni SM, Baronciani L, Peyvandi F. A two-step approach (Enzyme-linked immunosorbent assay and confirmation assay) to detect antibodies against von Willebrand factor in patients with Acquired von Willebrand Syndrome. *Thromb Res.* 2014;134:1316-1322.
12. Lee A, Sinclair G, Valentine K, James P, Poon MC. Acquired von Willebrand syndrome: von Willebrand factor propeptide to von Willebrand factor antigen ratio predicts remission status. *Blood.* 2014;124:e1-e3i.

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Does haemophilia slow down the development of liver fibrosis?

Dear Editor,

Haemophilia is an X-linked recessive bleeding disorder, resulting from deficient or dysfunctional coagulation factor VIII (haemophilia A) or IX (haemophilia B). Depending on the severity of their factor deficiency, patients present with a range of bleeding diathesis from traumatic injury or surgically induced bleeding to spontaneous haemorrhage in the soft tissues, joints or muscles.

Before the 1960s, the prognosis of severe haemophilia A patients was just 11 years or less,¹ then the introduction of fresh-frozen plasma, cryoprecipitate, and finally blood-pooled clotting factor concentrates considerably improved the survival and quality of life of patients with haemophilia or with other bleeding disorders.² However, the epidemic of HCV and human immunodeficiency virus (HIV) then erupted with severe consequences. Until the 1989 discovery of HCV,³ almost all haemophilia patients treated with clotting factor products were infected with HCV.⁴ The clinical presentation of HCV is characterized by chronic liver disease that can progress to fibrosis with development of (de)compensated cirrhosis and hepatocellular carcinoma.

An unexpected new finding was reported by Assy et al⁵ who found that liver disease following HCV infection appeared more benign in haemophilia subjects than in others. This was unexpected considering that HCV infection was one of the major causes of mortality in patients with haemophilia before the introduction of direct acting antivirals. The authors investigated the histological severity of liver fibrosis in haemophilia HCV-infected patients compared with HCV-infected patients with no bleeding disorder, demonstrating significantly lower histologic inflammatory activity and fibrosis scores in patients with haemophilia. However, the small scale of this study and high heterogeneity

of included patients render it difficult to establish a clear link between haemophilia and reduced liver damage following HCV infection.

Haemophilia A murine models that mimic patients with severe haemophilia A are currently available. These well-characterized models have been extensively employed to evaluate new treatments.⁶ In this report, we have studied the progression of chemically induced liver fibrosis by means of an haemophilia A mouse model.

The study was carried out using 12 control mice (=CTL mice) with normal factor VIII levels (8 weeks old, C57BL/6, sourced from The Jackson Laboratory, Bar Harbor, Maine, USA) and 12 haemophilia mice (=HEMO mice) with factor VIII levels <1% (7 weeks old; B6; 129S-Fg^{tm1Kaz}/J, sourced from The Jackson Laboratory). Each group was divided into subgroups receiving either thioacetamide (TAA) in their drinking water (200 mg TAA/L; CTL-TAA, and HEMO-TAA) or only water without TAA (CTL-H2O and HEMO-H2O). TAA (purchased as white crystalline powder from Sigma-Aldrich; St Louis, MO, USA) is an organosulfur compound that induces liver fibrosis while being water soluble. The mice were housed in a temperature-controlled environment (12-hour light cycle) with food and water ad libitum. In the HEMO groups, mice were housed individually to avoid injuries. The amount of water the mice consumed and their weight were monitored weekly to determine the exact dose of TAA administered. After 25 weeks, the mice were sacrificed and their livers harvested. Three haemophilia mice died unexpectedly before Week 25 due to external haemorrhages (two in the HEMO-H2O group; one in the HEMO-TAA group) and were excluded from analysis.

At the time of harvest, liver sections were fixed in formalin and embedded in paraffin. Slices were stained with PicroSirius Red then