

[CASE REPORT]

Acquired von Willebrand Syndrome due to Aortic Valve Stenosis in a Case with Antiphospholipid Antibody

Hiroaki Tanaka¹, Yurie Nagai¹, Chihiro Kuwabara¹, Ryo Shimizu¹,
Akihide Umeki² and Tetsufumi Yamamoto²

Abstract:

Acquired von Willebrand syndrome (AVWS) is a bleeding disorder caused by an acquired deficiency of von Willebrand factor (vWF). Some patients with AVWS show a low bleeding tendency and are diagnosed by the presence of a mild prolongation of activated partial thromboplastin time (APTT) preoperatively. Another cause of APTT prolongation is the presence of antiphospholipid antibody (aPL). We experienced a case of AVWS due to aortic valve stenosis in a patient with aPL in whom aortic valve replacement surgery was successful with vWF replacement. In patients with AVWS-associated disorders who are identified based on APTT prolongation at the preoperative examination, both vWF and aPL screening tests must be performed.

Key words: acquired von Willebrand syndrome, antiphospholipid antibody, aortic valve stenosis, aortic valve replacement surgery

(Intern Med 57: 1641-1644, 2018)

(DOI: 10.2169/internalmedicine.9860-17)

Introduction

Von Willebrand factor (vWF) is a blood glycoprotein involved in platelet aggregation and stabilization of the eighth coagulation factor. A deficiency of vWF causes bleeding disorders. A bleeding disorder due to a congenital vWF deficiency is called von Willebrand disease (VWD), and a bleeding disorder due to an acquired vWF deficiency is called acquired von Willebrand syndrome (AVWS). The underlying disorders of AVWS are lymphoproliferative (48%), cardiovascular (21%), myeloproliferative (15%), other neoplastic (5%), and autoimmune disorders (2%) (1). Several pathogenic mechanisms of AVWS have been proposed for each underlying disorder, including autoantibodies directed against vWF, leading to a more rapid clearance from the circulation or an interference with its function, the adsorption of vWF by tumor cells or platelets, and proteolytic cleavage of VWF after shear stress-induced unfolding (2-5). Some patients with AVWS show a low bleeding tendency and are diagnosed based on the presence of mild prolongation of the activated partial thromboplastin time (APTT) during a preoperative examination. In patients with AVWS-associated

disorders, vWF testing is recommended before major surgery and other interventions with a high risk of bleeding (2).

Another cause of prolongation of APTT is the presence of antiphospholipid antibody (aPL), which is associated with a thrombotic disease called antiphospholipid syndrome (APS) (6). In patients with aPL who have never suffered from a thrombotic event, however, antithrombotic therapy as primary thromboprophylaxis is not recommended.

We experienced a case of a patient with aPL who also had AVWS due to aortic valve stenosis (AS). Although the APTT value was unreliable because of the presence of aPL, aortic valve replacement surgery was successful after a vWF replacement test was performed preoperatively.

Case Report

In June, 20XX, a 78-year-old Japanese man was referred to our hospital for complete right block and severe AS determined by ultrasound cardiography. He had been treated for hypertension and hyperlipidemia and had continued smoking 40 cigarettes a day until age 56. Eight years before being referred to our hospital, a heart murmur had been detected in the subject at a family hospital. He had no history

¹Department of Hematology, Asahi General Hospital, Japan and ²Department of Cardiovascular Surgery, Asahi General Hospital, Japan

Received: July 21, 2017; Accepted: October 15, 2017; Advance Publication by J-STAGE: January 11, 2018

Correspondence to Dr. Hiroaki Tanaka, htanaka@hospital.asahi.chiba.jp

Table. Laboratory Data on Admission.

Complete blood cell count		Serological test (normal range)		Coagulation test	
White blood cell	7.3×10 ⁹ /L	C-reactive protein	0.04 mg/dL	PT	11.8 s
Neutrophil	74.5 %	LA APTT coagulation time	71.9 (-55.5) s	PT-INR	1.04
Lymphocyte	16.0 %	LA PL neutralization time	18.2 (-6.3) s	APTT	61.3 s
Monocyte	7.0 %	LA dRVVT	1.12 (-1.3) s	Fibrinogen	231 mg/dL
Basophil	0 %	aCL β2GPI	<1.2 U/mL	FDP	<2.5 μg/mL
Eosinophil	2.5 %	aCL IgG	<8 U/mL	Antithrombin III	79 %
Hemoglobin	12.7 g/dL	aCL IgM	<5 U/mL	FV	62 %
Platelet count	178.0×10 ⁹ /L			FVIII	75 %
				FIX	82 %
				FXI	72 %
				FXII	107 %
				APTT cross-mixing test	inhibitor pattern
				vWF multimer analysis	normal pattern
vWF replacement test					
				APTT (s)	vWF:Ag (%)
				58.6	61
				56.4	327
					vWF:RCo (%)
					8
					262

LA: lupus anticoagulant, APTT: activated partial thromboplastin, PL: phospholipid, dRVVT: diluted Russell's viper venom time test, aCL: anti-cardiolipin antibody, β2GPI: β2 glycoprotein I complex antibody, PT: prothrombin time, INR: international normalized ratio, FDP: fibrinogen degradation product, F: coagulation factor, vWF: von Willebrand factor, Ag: antigen, RCo: ristocetin cofactor

of hemorrhagic episodes. Hemostasis had been good when a skin incision drainage operation was performed at age 30.

The following laboratory findings were obtained at our hospital (Table): white blood cell count, 7.3×10⁹/L; red blood cell count, 419×10⁹/L; hemoglobin, 12.7 g/dL; platelet count, 178×10⁹/L; total protein, 7.3 g/dL; aspartate transaminase, 29 IU/mL; alanine aminotransferase, 40 IU/mL; lactate dehydrogenase, 217 IU/L (normal range, 124-226 IU/L); total bilirubin, 0.9 mg/dL; creatinine, 0.99 mg/dL; and C-reactive protein 0.04 mg/dL. His blood type was O. The coagulation findings were as follows: prothrombin time (PT), 11.8 seconds; PT-international normalized ratio, 1.04;

APTT, 61.3 seconds; fibrinogen, 231 mg/dL; fibrinogen degradation products <25 μg/mL; antithrombin III, 79%; coagulation factor V, 62%; coagulation factor VIII, 75%; coagulation factor IX, 82%; coagulation factor XI, 72%; coagulation factor XII, 107%; von Willebrand factor antigen (vWF:Ag), 61% (normal range, 50-155%); ristocetin cofactor (vWF:RCo), 8% (normal range, 60-170%); vWF multimer analysis, normal pattern; APTT cross-mixing test, inhibitor pattern; Lupus anticoagulant (LA) APTT coagulation time method, 71.9 seconds (normal range, -55.5 seconds); LA phospholipid neutralization method, 18.2 (normal range, -6.3); LA diluted Russell's viper venom time test (dRVVT),

1.12 (normal range, -1.3); anti-cardiolipin β 2 glycoprotein I complex antibody (aCL. β 2GP1), <1.2 U/mL; anti-cardiolipin antibody (aCL) IgG, <8 U/mL; and aCL IgM, <5 U/mL. Test administration of a vWF-containing factor VIII preparation did not cause the value of prolonged APTT to decrease, but vWF:Ag and vWF:RCo increased the value by 327% and 262%, respectively.

Ultrasound cardiography revealed that the aortic valve was calcified and had a remarkably open restriction. The left ventricular-aortic pressure gradient (LV-Ao PG) was 76 mmHg. Cardiac catheterization revealed that there was no pressure elevation in the right heart system; the maximum value of LV-Ao PG was 74.0 mmHg, and the mean value was 50.2 mmHg. The aortic valve area was 0.78 cm².

Aortic valve replacement surgery was performed after the administration of 5,000 units of a vWF-containing factor VIII preparation. In the coagulation test performed immediately after replacement of the vWF, prolonged APTT was still present (57.2 seconds), but the value of vWF:RCo was confirmed later to have increased to 116%. During the operation, transfusion of 12 units of fresh-frozen plasma (FFP) improved the prolonged APTT to 39.5 seconds, which lasted for 2 days. During and after surgery, no abnormal bleeding was observed. The patient was discharged without adverse events 12 days after the surgery. Although mildly prolonged APTT continued, the vWF:Ag was 155%, and the vWF:RCo was 122% at 2 months postoperatively. At two years after the operation, he was doing well and had not suffered from any exacerbation of cardiac disease, bleeding, or thrombotic events.

Discussion

Because of differences in treatment policy, AVWS and VWD should be distinguished. A history of abnormal bleeding events and family history are useful for such differentiation. However, some patients with mild vWF exhibit no abnormal bleeding events for decades, and because of its low penetrance, these patients also lack a remarkable family history (2).

The mechanism underlying AVWS in patients with AS is believed to involve high shear stress occurring at the AS site that causes the structure of high-molecular-weight vWF multimers to be stretched, thereby exposing the breakpoint and promoting cleavage by ADAMTS 13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) (7). In a study of consecutive patients with severe AS, more than 80% of the patients had vWF abnormalities, and approximately 20% had suffered from bleeding episodes (8, 9). Although a decrease in high-molecular weight vWF multimers could not be proven in our case, AVWS due to AS in our patient with aPL was considered because aortic valve replacement resulted in improvement of the vWF:RCo and continued mild prolonged APTT.

To our knowledge, this is the first case report to describe AVWS due to a cardiovascular disorder in a patient with

aPL. However, patients with AS who have both aPL and AVWS may not be rare, as patients with aPL sometimes develop cardiac valve disease (10, 11). In patients with AS who exhibit APTT prolongation in preoperative examinations, both vWF and aPL screening tests must be performed.

In our case, prolonged APTT was partially improved by massive transfusion of FFP during the operation, performed by the surgeon based on the intraoperative situational judgment. Although FFP does not contain many phospholipids, we hypothesize that aPL adsorbed onto the surface of phospholipids that had contaminated the FFP.

Conclusion

We experienced a case of AVWS due to AS in a patient with aPL. Although the APTT value was unreliable because of the presence of aPL, aortic valve replacement surgery was successful with vWF replacement. In patients with AVWS-associated disorders who are found to have APTT prolongation during a preoperative examination, both vWF and aPL screening tests must be performed.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors thank Yasuhiro Matsuura of Inoue Memorial Hospital, Chiba, Japan for his valuable advice.

References

1. Federici AB, Rand JH, Bucciarelli P, et al. Acquired von Willebrand syndrome: data from an international registry. *Thromb Haemost* **84**: 345-349, 2000.
2. Tiede A, Rand JH, Budde U, Ganser A, Federici AB. How I treat the acquired von Willebrand syndrome. *Blood* **117**: 6777-6785, 2011.
3. Tefferi A, Nichols WL. Acquired von Willebrand disease: concise review of occurrence, diagnosis, pathogenesis, and treatment. *Am J Med* **103**: 536-540, 1997.
4. Franchini M, Lippi G. Acquired von Willebrand syndrome: an update. *Am J Hematol* **82**: 368-375, 2007.
5. Kumar S, Pruthi RK, Nichols WL. Acquired von Willebrand disease. *Mayo Clin Proc* **77**: 181-187, 2002.
6. Cervera R. Antiphospholipid syndrome. *Thromb Res* **151**: S43-S47, 2017.
7. Loscalzo J. From clinical observation to mechanism-Heyde's syndrome. *N Engl J Med* **367**: 1954-1956, 2012.
8. Vincentelli A, Susen S, Le Tourneau T, et al. Acquired von Willebrand syndrome in aortic stenosis. *N Engl J Med* **349**: 343-349, 2003.
9. Casonato A, Sponga S, Pontara E, et al. von Willebrand factor abnormalities in aortic valve stenosis: pathophysiology and impact on bleeding. *Thromb Haemost* **106**: 58-66, 2011.
10. Khamashta MA, Cervera R, Asherson RA, et al. Association of antibodies against phospholipids with heart valve disease in systemic lupus erythematosus. *Lancet* **335**: 1541-1544, 1990.
11. Cervera R. Coronary and valvular syndromes and antiphospholipid antibodies. *Thromb Res* **114**: 501-507, 2004.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To

view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).

© 2018 The Japanese Society of Internal Medicine
Intern Med 57: 1641-1644, 2018