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Successful management of severe refractory acquired immune bleeding disorder: Prior to insisting surgery

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ABSTRACT

INTRODUCTION: Acquired bleeding disorders are rare and may be missed before surgery. Additionally, they may be refractory to conventional treatments.
PRESENTATION OF CASE: A 50-year-old patient experienced prolonged post-operative bleeding when his bleeding disorder was missed prior to his undergoing inguinal herniorrhaphy. Post-operative investigations revealed severe acquired von Willebrand syndrome associated with a monoclonal gammopathy of undetermined significance. A few months later, he required umbilical herniorrhaphy, but he did not respond to attempts to raise his von Willebrand factor antigen and activity levels using conventional therapies, including desmopressin, cryoprecipitate, intravenous immunoglobulin, and Von Willebrand factor concentrate. A triple therapy combination of dexamethasone, intravenous immunoglobulin, and mycophenolate mofetil was administered, with a successful and sustained response, lasting about 2 months. The surgery was performed safely, without any complications.
DISCUSSION: Conventional acquired von Willebrand syndrome treatment is usually aimed at replacing von Willebrand factor or stimulating its secretion from storage in endothelial cells. In the present case, the alternative treatment was directed against both the humoral and cell-mediated immune mechanisms.
CONCLUSION: This case of acquired bleeding disorder showed that more attention must be given to a patient's coagulation profile, even if only very minor laboratory coagulation derangements are detected prior to surgery, to avoid missing such rare disorders. The described triple therapy demonstrated good effects and may be considered for inclusion in a controlled randomized study to determine its usefulness for other surgeries delayed due to severe acquired bleeding disorders. To the best of our knowledge, this triple combination treatment has not been previously used for the treatment of severe acquired bleeding disorders that are refractory to conventional therapies.

1. Background

Surgical procedures may be postponed because of a high risk of bleeding due to severe acquired bleeding disorders. One such disorder is acquired von Willebrand syndrome (aVWS), a rare disorder that usually occurs in elderly patients, the recognition of which may be significantly delayed.[1] aVWS occurs due to decreased levels of von Willebrand factor (VWF) antigen (VWF Ag), and VWF activity (VWF Act).[2] These patients usually present with mucocutaneous bleeding, in the absence of a previous history of bleeding abnormalities, and no clinically significant family history of bleeding disorders; they may also be easily missed prior to surgery because of demonstrating only minor laboratory coagulation derangement.[3] However, such patients may also present with serious hemorrhagic complications that are challenging to manage,[4] becoming more serious when the patient needs surgery. aVWS may be associated with lymphoproliferative disorders, myeloproliferative neoplasms, solid tumors, autoimmune disorders, and cardiovascular problems,[5] and is characterized by VWF structural or functional abnormalities. In the lymphoproliferative monoclonal gammopathy of undetermined significance

Abbreviations: APTT, activated partial thromboplastin time; VWF Ag, von Willebrand factor antigen; VWF Act, von Willebrand factor activity; IgG, immunoglobulin G; aVWS, acquired von Willebrand syndrome; VWF, von Willebrand factor; MGUS, monoclonal gammopathy of undetermined significance; MMF, mycophenolate mofetil; DIM, dexamethasone, intravenous immunoglobulin, mycophenolate mofetil; VWD, von Willebrand disease.

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(MGUS) may result in antibodies being directed against VWF, resulting in its rapid inactivation or clearance from circulation; VWF might also be absorbed from the plasma by malignant cells.[6] The treatment of aVWS is normally directed against the underlying causes to enable remission.[7] The conventional treatment methods usually involve administration of desmopressin (DDVAP), cryoprecipitate, VWF concentrate, and intravenous immunoglobulin (IVIG).[8] In the present case, the patient failed to achieve a good response to the conventional therapies necessitating an alternative therapeutic approach with dexamethasone, intravenous immunoglobulin, and mycophenolate mofetil (DIM) to enable the patient to undergo required surgery.

2. Presentation of case

A 50-year-old man underwent elective, right inguinal herniorrhaphy in April 2009, complicated by prolonged bleeding from the wound site. This necessitated hospital readmission for surgical exploration of the wound and treatment with cryoprecipitate and vitamin K. The bleeding gradually resolved and, after 2 weeks of hospitalization, he was discharged and referred to a hematology clinic. The laboratory results revealed a prolonged bleeding time of 5.30 (normal, 1–4) minutes, an activated partial thromboplastin time (APTT) of 62 (normal, 33–39) second, an APTT mixing study of 55 s, a factor VIII level of 7.22% (reference, 50–150%) of the normal, a VWF Ag of 7% (reference, 61–158%) of the normal, a VWF Act of 27% (reference, 38.1–152.2%) of the normal, and a normal international normalized ratio (INR); other coagulation factors, and renal and liver functions were also normal. The patient had not previously experienced significant bleeding symptoms, including in 1998 when he underwent multiple dental extractions without undue blood loss. The patient did not have a family history of bleeding disorders; his parents were not consanguineous and none of his 7 siblings or 4 children exhibited any bleeding tendency. Apart from hypertension, for which he was taking amlodipine (10 mg, once daily), he did not have a remarkable medical history.

In June 2011, the patient was scheduled for umbilical herniorrhaphy surgery. Prior to surgery, repeat testing confirmed von Willebrand disease; the patient again demonstrated significantly reduced levels of factor VIII 0.08 (normal, 0.45–1.8 U/mL) and VWF Ag 0.11 (normal, 0.5–2.00 U/mL). The Platelet Function Analyzer-100 closure time was extended beyond 300 s for the collagen/epinephrine-coated membrane (normal, 75–165 s); serum protein electrophoresis revealed monoclonal immunoglobulin G (IgG)-lambda paraprotein levels of 8 (normal, 7.5–18) g/L and beta-2-microglobulin levels of 1.38 (normal, 1–2.20) g/L. As a result, the patient was diagnosed with aVWS associated with MGUS. The low level of VWF was confirmed to be due to accelerated clearance of VWF; the administration of a test dose of VWF concentrate resulted in its rapid disappearance from circulation. Prior to surgery, the patient was administered VWF concentrate and IVIG (1 g/kg/day) for 1 day, to restore his VWF function during surgery, producing a significant rise in VWF and factor VIII levels. An additional dose of VWF concentrate was administered the next day in anticipation that the VWF levels would improve sufficiently to allow the surgery to proceed. However, the surgery could not be performed because the rise in his VWF level was insufficient. The patient returned to our hospital after 45 days. Serum immunoglobulin electrophoresis and immune fixation tests done which demonstrated monoclonal lambda-type IgG (30.1 g/L; normal, 7.5–18.0 g/L), IgA (3.76 g/L; normal, 0.9–4.5 g/L), and IgM (1.03 g/L; normal, 0.6–2.5 g/L). Bence–Jones proteins and bone lytic lesions were not detected in this patient. The patient's coagulation profile had a normal INR of 0.09 and an APTT of 29 (normal, 33–39) second.

In March 2012, the patient was again scheduled for surgery, after it had been postponed several times over the previous 3 years, because of the high risk of bleeding. The patient was prescribed oral dexamethasone (40 mg/day) and omeprazole (20 mg/day) for 4 days, together with IVIG (0.4 mg/kg) for 5 days; however, the surgery was postponed by the patient. The treatment effect on VWF Ag, and VWF Act lasted only for 10 days. When the treatment was attempted again, mycophenolate mofetil (MMF, 1000 mg, twice

Table 1
Comparison of the effect of three lines of treatment on the patient.

Treatment		Day	APTT	FVIII (% of normal)	VWF Ag (% of normal)	VWF Act (% of normal)	IgG (g/L)	Note
1. I & VWF con	BL1	1	29	0.08	0.11	ND	30	Not effective
2. D & I	BL2	1	36	15	0	0	15.1	Short Effective
		4	27	89	29	51	ND	
		6	26	150	95	108	ND	
		10	24	221	147	146	ND	
		20	26	81	51	38	ND	
3. DIM	BL3	1	ND	66	30	15	ND	Longer sustained
		2	26	110	56	38	ND	Effective for
		3	ND	78	56	39	17.9	
		9	27	221	240	151	ND	
		21	23	258	330	210	ND	
		28	24	ND	244	144	ND	
MMF reduction to 1000 mg		30	ND	130	101	70	ND	Back to base line when
MMF discontinuation		60	32	36	18	14	ND	MMF stopped
No treatment		360	34	36	18	0	12.7	
Normal ranges			26–37	50–150	61–158	38.1–152.2	7.5–18.0	

BL1: Base line just before I & VWF con treatment.
BL2: Base line just before D & I treatment.
BL3: Base line just before DIM treatment.
APTT: activated partial thromboplastin time.
FVIII: factor VIII.
VWF Ag: von Willebrand factor antigen.
VWF Act: von Willebrand factor activity.
VWF Con: VWF: concentrate.
D: dexamethasone.
I: immunoglobulin G.
MMF: mycophenolate mofetil.
ND = not done.