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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.

daily) was added to the previous drug regimen. DIM gave a prolonged and sustained effect lasted for about 2 months. The patient's VWF Ag, VWF Act, and factor VIII levels fell after the MMF dose was reduced to 500 mg twice daily, and returned to the baseline level after discontinuing MMF (Table 1).

3. Discussion

The biosynthesis of VWF is restricted to endothelial cells and megakaryocytes, from which it is constitutively secreted into the blood or subendothelial matrix. VWF may also be stored in Weibel–Palade bodies in endothelial cells, and released upon stimulation or via an unstimulated, but regulated, basal pathway.[9] The APTT, in patients with congenital or acquired Von Willebrand disease (VWD), is usually prolonged because of reduced levels of factor VIII, which typically accompany a reduction in VWF levels. However, a highly significant finding in aVWS is the possibility of a normal or only slightly elevated APTT, which makes severe cases of aVWS easily missed prior to surgery. Hence, a bleeding time test is a useful, easily available test to screen for the presence of aVWS.[10]

Conventional aVWS treatment is usually aimed at replacing VWF or stimulating its secretion from storage in endothelial cells through the administration of DDVAP, which increases plasma levels of factor VIII and VWF. DDVAP has been successfully used for the treatment of the milder, congenital forms of hemophilia A and VWD. However, DDVAP is not uniformly effective in correcting the abnormal hemostasis of aVWS patients. When DDVAP fails to correct VWF Ag and VWF Act, the usual treatment involves replacing the VWF levels, including the administration of cryoprecipitate, VWF concentrate, and IVIG when an autoimmune disorder is suspected to be associated with aVWS.[11]

In the present case, the DIM treatment was directed against both the humoral and cell-mediated immune mechanisms by virtue of dexamethasone having powerful anti-inflammatory and immunosuppressive effects,[12] IVIG down-regulating antibody production,[13] and MMF exerting immunosuppressive effects on both B and T lymphocytes.[14] The patient had shown only a short, partial response to treatment with IVIG and VWF concentrate, and the increases in VWF Ag and VWF Act levels were not sustained, either due to a high titer of the inhibitors to VWF activity or because of high grade interference with the VWF antigen. When dexamethasone was added to the IVIG treatment, the combination was more effective at maintaining normal VWF Ag and VWF Act levels for 5 days. When MMF was further added, the VWF Ag and VWF Act levels were maintained at an acceptable level for approximately 2 months, sufficient to allow complete wound healing. The VWF Ag and Act returned to the pre-treatment, baseline level only when MMF was discontinued.

In this case, the underlying immune cause was treated by immunosuppressive drug therapy, rather than by replacing the deficient factors. DIM shoed a much more significant response than did rituximab when the latter was used to treat aVWS secondary to an autoimmune antibody response.[15] Replacing the deficient factor is more effective in patients with congenital VWD, but less so for those with acquired bleeding disorders. In patients with acquired immune factor deficiencies, replacing the deficient factors makes the immune disorder more refractory to treatment, similar to what occurs in immune thrombocytopenia[16] and immune hemolytic anemia.[17] In this case, the APTT was not excessively prolonged, then became within normal limits while the VWF Ag and Act were both very low. Additionally, the IgG level did not correlate with the VWF Ag and Act, which suggests the possibility of a specific primary autoimmune antibody directed against VWF, in association with MGUS.

From this experience, both the coagulation profile and bleeding times are important parameters to be checked before surgical procedures, even in the absence of a personal or family history of bleeding disorders. Normal or minor impairments in a patient's coagulation profile can hide a major, severe acquired disorder. DIM was a more successful treatment for refractory aVWS than conventional treatments, especially since surgery was required in a high-risk aVWS patient. The suitability of DIM for other acquired bleeding disorders should be investigated through randomized controlled studies.

This patient leading normal life without hemostatic treatment but for surgery he require DIM treatment to avoid catastrophic bleeding because of his sever refractory aVWS. Dexamethason and IVIG alone have only short effect and MMF alone did not keep the levels to normal so DIM combination has the best and more sustain effect. This patient presentation is rare in the possibility of catastrophic hemorrhage during surgery and the presence of mild to normal coagulation profile derangement.

Conflict of interest statement

None declared.

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None declared.

Ethical approval

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Author contributions

Hassan Al-Jafar conceived of the study, gave the DIM treatment and drafted the manuscript. H. Al-Barjas performed the surgical procedure, revised the manuscript and added to it. Raed A. Hashem reviewed the article and added valuable references. Thanaa M.K. Refaii revised the study from clinical biochemistry point of view and helped to draft the manuscript. Ahmad M. AlSaeed revised the manuscript and added suggestions and pharmacology references. All authors read and approved the final manuscript.

Key learning points

- Mild INR or APTT could have serious underling coagulation disorder.
- Bleeding time is important prior to surgery in cases of deranged coagulopathy.
- The combination of dexamethasone, intravenous immunoglobulin, and mycophenolate mofetil could be useful in acquired cases of coagulopathy requiring insisting surgery when the underling cause of coagulopathy is an immune based, more clinical trails required to prove he efficacy of this combination.

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