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A thrombopoietin receptor agonist to rescue an unusual platelet transfusion-induced reaction in a p.V1316M-associated von Willebrand disease type 2B patient

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Abstract: This report describes the first case of splenic injury in a patient with p.V1316M-associated von Willebrand disease type 2B (VWD2B) with chronic thrombocytopenia, successfully treated with nonoperative management including von Willebrand factor (VWF) replacement therapy, and platelet transfusions relayed by a thrombopoietin receptor agonist (TPO-RA, Eltrombopag). Eltrombopag was initially introduced to rescue an unusual post-platelet-transfusion reaction exacerbating the thrombocytopenia. In-depth analysis of the dramatic platelet count drop and VWF measurements timeline ruled out an allo-immune reaction and supported an alternative hypothesis of a sudden platelet clearance as a consequence of stress-induced release of abnormal VWF. One year later, a second life-threatening bleeding episode required urgent surgery successfully managed with VWF replacement therapy and platelet transfusions. Eltrombopag was further introduced in the post-surgery period to allow bleeding-free and platelet-transfusion-free successful recovery. Treatment decisions are particularly challenging in patients with VWD2B, and this case highlights how such decisions can benefit from understanding the molecular origin of platelet count fluctuations observed in these patients. Here, we successfully used a new therapeutic approach combining VWF-replacement therapy and initial platelet-transfusion relayed by TPO-RA to optimize patient management.

Plain language summary

A combination of von Willebrand factor replacement and thrombopoietin receptor agonist in thrombocytopenic patients with von Willebrand disease type 2B: a new therapy approach to optimize patient management?

- Therapeutic management of patients with von Willebrand disease type 2B are particularly challenging in case of severe thrombocytopenia.
- Treatment includes von Willebrands factor replacement therapy and iterative platelet transfusions.
- We describe the first case of splenic injury in a patient with p.V1316M-associated von Willebrand disease type 2B successfully treated with nonoperative management including von Willebrand factor replacement therapy and platelet transfusions relayed by a thrombopoietin receptor agonist.

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- We showed that the unusual post-platelet-transfusion reaction associated with a dramatic platelet count drop was a consequence of stress-induced release of abnormal von Willebrand factor.
- The combination of von Willebrand factor replacement therapy and thrombopoietin receptor agonist may offer a new therapeutic approach to optimize patient management.

Keywords: eltrombopag, thrombocytopenia, thrombopoietin receptor agonist, von Willebrand disease type 2B, von Willebrand factor

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Introduction

von Willebrand disease type 2B (VWD2B) is a rare inherited hemorrhagic disorder associating von Willebrand factor (VWF) and platelet abnormalities.[1] It is due to gain-of-function mutations clustered in exon 28 of *VWF* gene, increasing the affinity of the VWF-A1 domain for its platelet receptor glycoprotein Ibα. Platelet-bound VWF displays increased sensitivity to ADAMTS13-mediated proteolysis and induces platelet agglutination, leading to the loss of VWF high-molecular-weight multimers (HMWMs) and eventually thrombocytopenia. Platelet count (PC) is variable and can decrease concomitantly with increased VWF synthesis or release, such as, after desmopressin (DDAVP) administration or in stress situations, inflammation, or pregnancy. Although VWD2B is an heterogeneous disease, a genotype-phenotype correlation has been described.[2] Some mutations are associated with mild phenotypes, and others such as the p.V1316M substitution[3] are responsible for severe manifestations due to the absence of VWF HMWMs and persistent platelet abnormalities. The latter include 1/a chronic macro-thrombocytopenia with giant platelets, due to megakaryocyte dysfunctions[4,5] and increased platelet clearance[6] and 2/a specific thrombopathy with defective integrin αIIbβ3 activation.[7,8] Therapeutic management of patients carrying the p.V1316M variant can therefore be challenging, especially in case of life-threatening bleeding situations requiring exogenous VWF administration and iterative platelet transfusions.[9,10]

Here, we report the exceptional case of a 13-year-old girl with p.V1316M-associated VWD2B who developed an unusual post-platelet transfusion (PT) reaction and was successfully rescued with a thrombopoietin receptor agonist (TPO-RA) to overcome the thrombocytopenia during two serious bleeding episodes.

Case description

The patient was diagnosed at the age of 12, after a 10-year misdiagnosis of chronic refractory immune thrombocytopenia (ITP). She had persistent low PC ($30–50 \times 10^9$/L) with giant platelets, VWF:RCo of 0.15 IU/ml, VWF:Ag of 0.62 IU/ml, and FVIII:C > 0.5 IU/ml (Table 1). She was first referred to our hospital for a splenic trauma and hemoperitoneum occurring after hula-hooping (Figure 1). Because of her hemodynamically stable condition, nonoperative management was proposed, based on international consensus[11] and literature experience in hemophiliac patients.[12] Strict immobilization was prescribed and both VWF replacement therapy (30–60 IU/kg/bid, Voncento®) and platelet transfusions (PT) were initiated at day 1 (D1) aiming to maintain VWF:Ag > 1 IU/ml and PC > 50×10^9/L for the following 6–8 weeks (Table 1). Unfortunately, at the end of the fourth PT at D10, the patient developed hypotension, cephalalgia, and hyperthermic shivering (38–40°C). Paracetamol was administered and symptoms resolved 35 min later. Unexpectedly, PC dropped from 53 to 26 and 12×10^9/L at 1 and 2 h post-PT, respectively, and spontaneously returned to $50–57 \times 10^9$/L, 15–24 h post-PT, with no hemorrhagic manifestation (Table 1, Figure 2(a)). Further investigations showed no signs of hemolysis, normal hemoglobin level (Hb), and negative

Table 1. Patient's laboratory evaluation and treatments.

Days/Weeks/Months	Laboratory evaluation						Treatments			
	Platelets	VWF:Ag	VWF:RCo	FVIII:C	VWFpp	Hemoglobin	Replacement therapy	Platelet transfusion	TPO-RA (eltrombopag)	Tranexamic acid
	(×10⁹/L)	(IU/ml)	(IU/ml)	(IU/ml)	(IU/ml)	(g/dl)	(VWF, IU)	(SPD)	(mg)	(g)
First episode (splenic trauma, hemoperitoneum)										
Day 1 (before treatment)	33	0.65	0.34	0.76	1.29	10.1	2000			
Day 1 (1 h after treatment)	60	1.24	0.70	1.08	1.15	8.9		6.2		3 (1 tid)
Day 1 (12 h after treatment)	48	1.06	0.59	1.1	1.04	9.8	2000 bid			
Day 2	44	1.81	1.01	1.46	0.95	9.7	2000 bid			3 (1 tid)
Day 3	42	1.43	0.59	1.02	0.86	9.8	2000 bid	6.8 + 4.2		3 (1 tid)
Day 5	155					11.1	2000 bid			
Day 5	105	1.52	0.75	1.27	0.82		2000 bid			
Day 7	67	1.60	0.81	1.13	0.92	12.4	2000 bid			3 (1 tid)
Day 9	56	1.54	0.53	1.12	0.87	11.4	2000 bid			3 (1 tid)
Day 10 (before PT)	53					11.5	2400 qd			3 (1 tid)
Day 10 (1 h after PT)	26	2.24	1.26	1.75	3.95	11.5		8.2		
Day 10 (2 h after PT)	12					11.1				
Day 11	50	2.53	1.33	1.52	1.07	11.6	2400 qd		25 qd	3 (1 tid)
Day 12	57					12.1	2400 qd		25 qd	3 (1 tid)
Week 3	148	0.88	0.17	0.84	0.97	11.7	2400 tiw		25 tiw	3 (1 tid)
Week 4	84	1.32	0.66	1.00	0.89	11.3	2400 tiw		25 tiw	3 (1 tid)
Week 6	42	0.58	0.27	0.59	0.53	10.6	2400 tiw		25 qd	3 (1 tid)
Week 24	45	0.52	0.16	0.67						
Week 35	21	0.60	0.24	0.64		13.4				
Second episode (ovarian cyst rupture, intraperitoneal hemorrhage)										
Day 1 (admission)	18	0.52	0.26			9.4				
Day 1 (before surgery)	80	1.06	0.62	1.33		7.7	3000 qd	4.5 (+ 3 RBCT + 2 FFP)		
Day 2	56					8	3000 qd			3 (1 tid)

(Continued)

Table 1. (Continued)

Days/Weeks/Months	Laboratory evaluation						Treatments			
	Platelets	VWF:Ag	VWF:RCo	FVIII:C	VWFpp	Hemoglobin	Replacement therapy	Platelet transfusion	TPO-RA (eltrombopag)	Tranexamic acid
	(×10⁹/L)	(IU/ml)	(IU/ml)	(IU/ml)	(IU/ml)	(g/dl)	(VWF, IU)	(SPD)	(mg)	(g)
Day 2	84	2.46	1.74	1.3		10.7		3.5		
Day 2	58					9.4				3 (1 tid)
Day 3	54					8.6	3000 qd	(1 RBCT)		
Day 3	57	2.18	1.18	1.53		10.4				
Day 3	51					10.7				
Day 4	58	1.72	0.83	1.25		10.5	3000 qd		25 qd	3 (1 tid)
Day 4	40					11.5				
Day 5	46	0.62	0.15	1.41		11.2	3000 qd		25 qd	3 (1 tid)
Day 5	46					12.1				
Day 6	39	1.47	0.56	1.31		11.7	3000 qd		25 qd	3 (1 tid)
Day 7	45					12.7	3000 qd		25 qd	3 (1 tid)
Day 8	46					13	3000 qd		25 qd	3 (1 tid)
Day 9	42	1.26	0.45	1.05		13.1	3000 qd		25 qd	3 (1 tid)
Day 10	31					13.5	3000 qd		25 qd	3 (1 tid)
Day 11	38	1.06	0.42	0.99		12.8	3000 qd		25 qd	3 (1 tid)
Day 12	72	0.60	0.25	0.84		12.6			25 qd	3 (1 tid)
Month 3	26					13.8				
Month 5	26	0.52	0.19	0.58		12.7				

bid, twice a day; FFP, fresh frozen plasma, 1 unit; IU, International Unit; PT, platelet transfusions; qd, once a day; RBCT, red blood cells transfusion, 1 unit; tid, three times a day; tiw; three times a week; TPO-RA, thrombopoietin receptor agonist; VWF, von Willebrand factor, SPD, single platelet donor.
Blood count was performed on blood anticoagulated with EDTA on a Sysmex XN®. Von Willebrand factor antigen (VWF: Ag) and factor VIII (FVIII:C) levels were measured on citrated platelet poor plasma (PPP) using STA®-Liatest-VWF-AG, STA®-ImmunoDefVIII and STA®-CKPrest on a STAR-Max®, Stago according to manufacturer's instructions. VWF activity (VWF: RCo) was measured on PPP using BCvonWillebrand Reagent® on a CS-5100®, Siemens according to manufacturer's instructions. VWF pro-peptide (VWFpp) was measured using an in-house ELISA as previously described.[14]

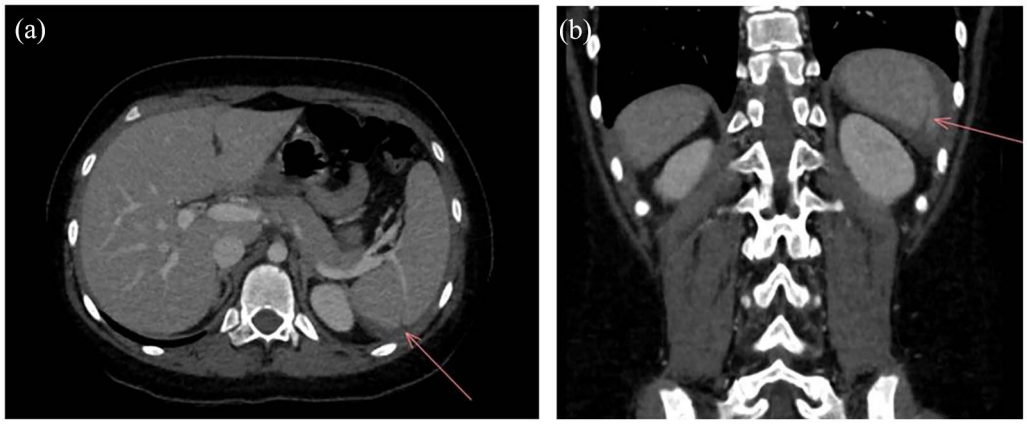


Figure 1. Computed tomography of the hemoperitoneum and splenic trauma: (a) hemoperitoneum seen as perisplenic blood collection (red arrow) and (b) splenic trauma seen as linear irregular hypodense area (red arrow).

blood cultures. Anti-HLA class I-II, anti-platelet-glycoprotein antibodies (anti-GPIaIIa, anti-GPIIbIIIa, anti-GPIb-IX) and ABO immune antibodies (IgG anti-A, anti-B) were measured after the PC drop to exclude an immune reaction. Neither anti-HLA class I-II nor specific anti-platelet-glycoprotein antibodies were evidenced. Instead, ABO immune antibodies were detected at high titers (IgG anti-A:1/512; anti-B:1/256), presumably consequent to the first ABO-incompatible PT (an A-pooled platelet unit was used while the patient is blood group O). PT was discontinued and oral TPO-RA (Eltrombopag, 25 mg/d) treatment was proposed and initiated at D11, after obtaining patient's parents informed consent. It resulted in an increase in PC, peaking at 148×10^9/L the next following week, and plateauing $50–80 \times 10^9$/L for the following 6 weeks during which the treatment was continued. One year later, the patient was again admitted for a voluminous intraperitoneal hemorrhage related to a left ovarian cyst rupture. PC (18×10^9/L) and Hb (9.4 g/dl) were low and Hb further dropped (7.7 g/dl) despite immediate initiation of VWF replacement therapy (50 IU/kg/bid, Voncento®) and a first ABO-identical PT (Table 1, Figure 2(b)). An exploratory laparotomy was required and uneventful, surrounded by 1 per- and 1 immediate post-surgery PT. Eltrombopag was again prescribed (D4) to avoid any further PT-induced reaction. PC peaked as expected D12 (72×10^9/L) and recovery was successful under the combination of Eltrombopag/VWF replacement up to D19 (Figure 2(b)). At 6-month follow-up, PC was consistently below 30×10^9/L and an estro-progestative pill was introduced to manage menorrhagia while preventing the recurrence of the ovarian cyst (Table 1).

Discussion

In our patient, the first ABO-minor incompatible platelet transfusion might have been responsible for the appearance of the ABO immune antibodies, an occurrence previously associated with hemolysis with/without hyperthermia.[15] However, in the absence of any subsequent signs of hemolysis or acute infection, and of any detectable alloimmunization, the dramatic drop in PC, which spontaneously resolved in 24 h, was unlikely attributable to a PT-related immune reaction. Conversely, post-transfusion PC kinetic was reminiscent of PC fluctuation post-DDAVP in patients with VWD2B,[16,17] with a nadir at 30–60 min post-treatment and spontaneous return to baseline at 24 h. Similar to what happens during stressful situations, DDAVP induces massive release of endothelial, hyper-functional VWF, which exacerbates biological abnormalities including VWF proteolysis and thrombocytopenia.[2,10,16,17] We hypothesized that the febrile post-transfusion reaction resulted in the stress situation provoking release of endogenous altered VWF and consequent sudden drop of the PC. Therefore, VWF propeptide (VWFpp) and VWF antigen (VWF:Ag) levels were measured to estimate endothelial VWF secretion and both endogenous/exogenous circulating VWF, respectively.

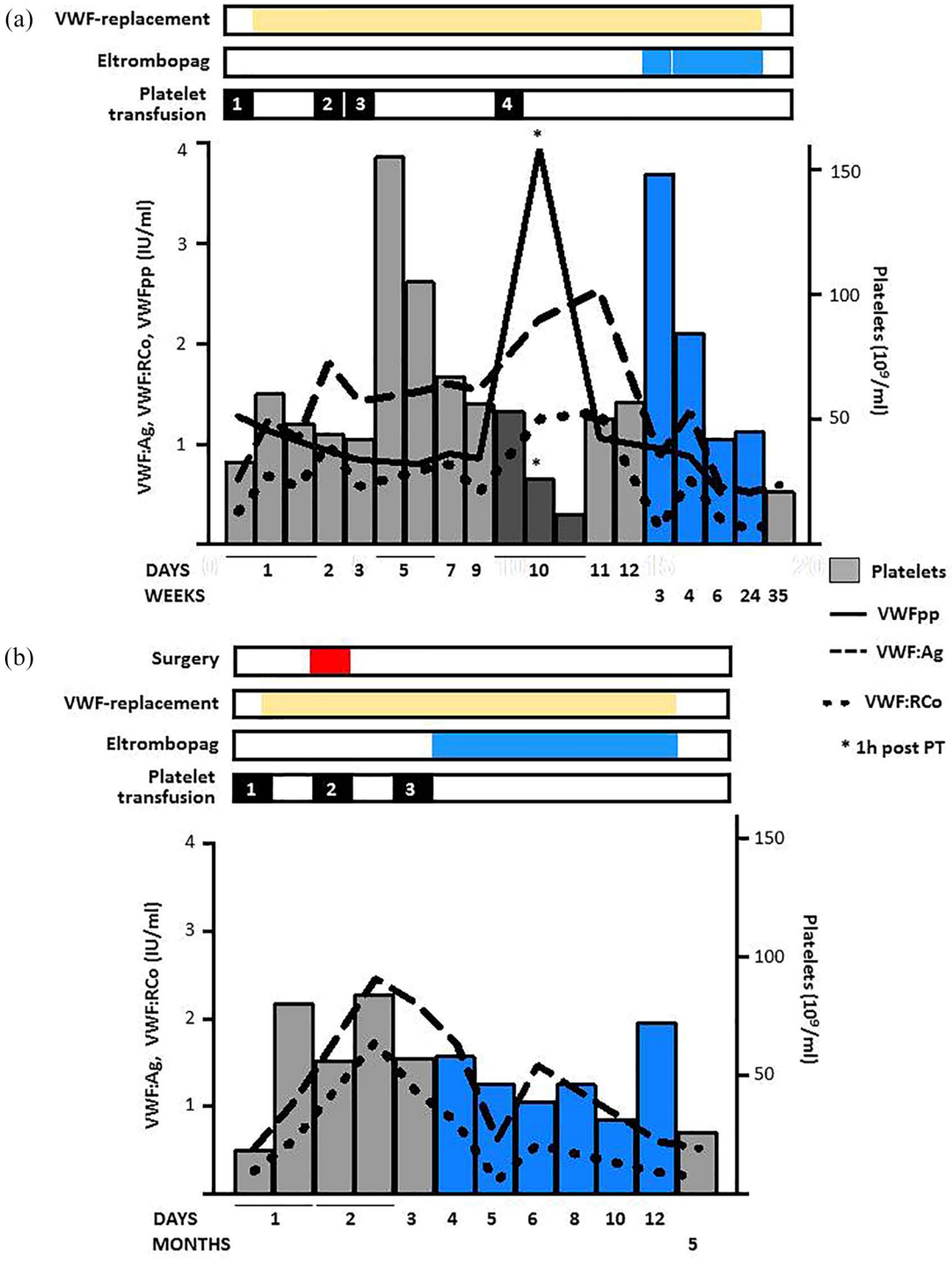
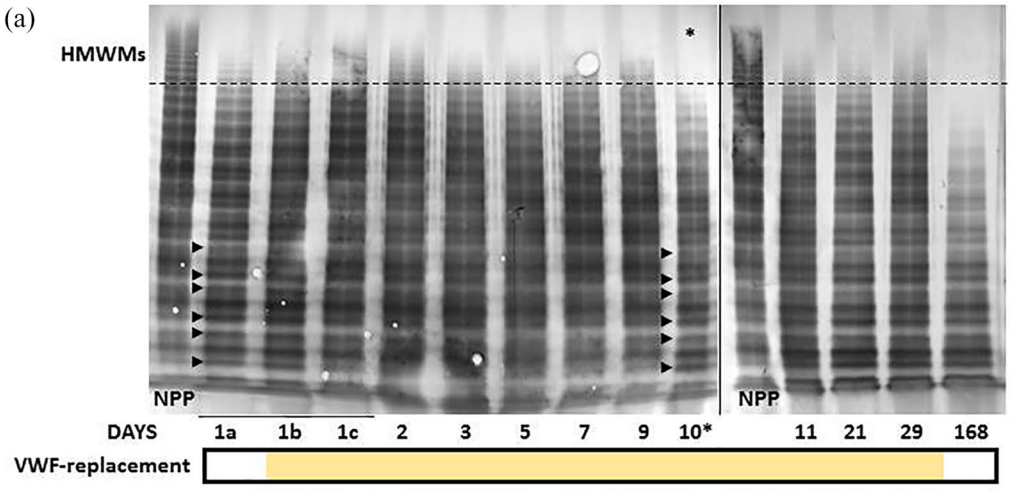


Figure 2. Timeline of patient's platelet count and von Willebrand factor antigen, activity and propeptide levels. Platelet count was measured in EDTA-anticoagulated blood on a Sysmex XN® (bars). VWF: Ag (dashed line) was measured in citrated-platelet poor plasma (PPP) using STA®-Liatest-VWF-AG® on a STAR-Max®, Stago, according to manufacturers' instructions. VWF: RCo (dotted line) was measured in PPP using BCvonWillebrand Reagent® on a CS-5100®, Siemens, according to manufacturers' instructions. VWFpp (solid line) was measured using an in-house ELISA as previously described.[13] (a) Evolution of platelet count, VWF: Ag, VWF:RCo and VWFpp levels from Day 1 to Week 35 after the first bleeding episode. (b) Evolution of platelet count and VWF levels from Day 1 to Month 5 after the second bleeding episode.



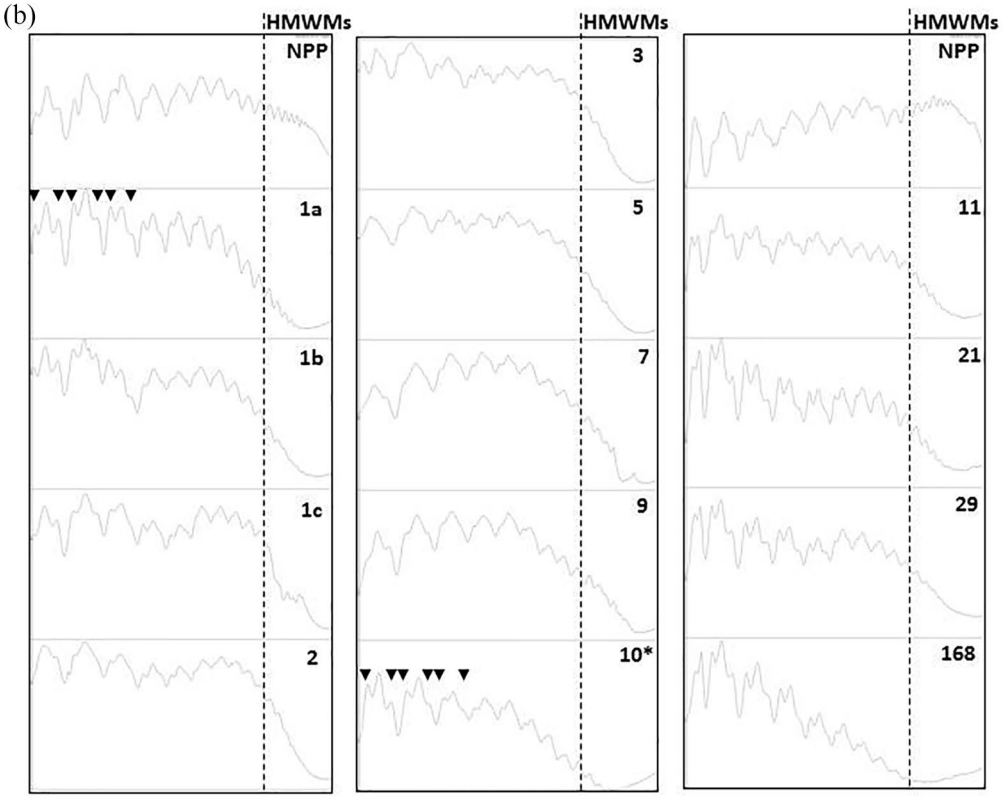


Figure 3. Multimer profile of patient's von Willebrand factor after the first bleeding episode. (a) The multimeric profile of VWF was analyzed in citrated-platelet poor plasma in 2% agarose gel essentially as previously described[13] using an in-house alkaline phosphatase-conjugated anti-human VWF polyclonal antibody. Pictures were acquired using a G:BOX Chemi XT16 Image Systems and a Gene Tools version 4.0.0.0 (Syngene) software. The solid line separates two gels. The dashed line indicates VWF high molecular weight multimers (HMWMs). Arrowheads indicate satellite bands, such as VWF fragments derived from ADAMTS13-mediated proteolysis. (b) Profiles plots of multimers shown in (a). Multimer plots have been generated with ImageJ 2.1.0 software using the Gel Analyzer tool.
NPP, normal pooled plasma.

VWF multimer profiles were measured to estimate secretion of endogenous altered VWF, administration of exogenous wild-type multimers, and their proteolytic state. While antigen levels were compatible with replacement regimen, VWFpp dramatically increased 1 h after the fourth PT (D10), concomitant with PC drop (Figure 2(a)). When analyzing multimer profiles (Figure 3), HMWMs were restored post-VWF replacement but punctually disappeared again at D10, 1 h post-PT. Satellite bands, the intensity of which reflects VWF proteolysis, appeared as smears in control plasma and as sharp, intense bands before treatment and again at D10, 1 h post-PT (Figure 3(a) and (b)), confirming enhanced proteolysis at these times. Together with the VWFpp peak and the brutal PC drop, these results support the hypothesis of a sudden release of altered VWF from the endothelial reservoirs triggered by the post-PT stress. The abnormal VWF is preferentially proteolyzed by ADAMTS13, consistent with sharp satellite bands, and punctually exacerbates thrombocytopenia. Conversely, while VWFpp returned to baseline at D11, HMWMs reappeared, and PC rose to the pre-PT level. This chronology further supports the deleterious role of the dramatic release of the abnormal p.V1316M-VWF in PC fluctuation in our case. Following initial PT required for the management of the first acute bleeding and the next vital surgery to maintain PC above $50–80 \times 10^9$/L, a TPO-RA was introduced to durably correct PC the next following weeks in this patient. Eltrombopag was initially introduced to prevent PT-induced stress reaction and avoid iterative PT required for the nonoperative management of the splenic injury. During the second life-threatening episode, Eltrombopag was started after surgery to successfully correct PC during the postoperative period without any further PT. To the best of our knowledge, this is the first case of splenic injury successfully treated with nonoperative management in a patient with p.V1316M-associated VWD2B and thrombocytopenia. Along with replacement therapy, initial PT were efficiently relayed by TPO-RA treatment to rise PC while avoiding iterative PT the next following weeks and allowed PT-free successful recovery.

TPO-RA, such as romiplostim and Eltrombopag, increase platelet production by activating JAK2/STAT5 pathway downstream of TPO-R, which results in megakaryocytes proliferation and differentiation. Romiplostim competes directly with TPO for receptor-binding at its extra-cytoplasmic domain while eltrombopag binds at a distinct transmembrane site (residue H499).[18] They have been first licensed for the treatment of chronic ITP and, the latter, for patients with severe aplastic anemia or interferon-ribavidin-treated hepatitis C. Clinical data suggest that TPO-RAs are comparably efficient in correcting PC in some hereditary thrombocytopenia such as myosin heavy chain 9-related disease (MYH9-RD) or Wiskott-Aldrich Syndrome (WAS).[19] Eltrombopag has been efficiently used on a short-term basis to temporarily increase PC when needed prior surgery or invasive procedure in macrothrombocytopenia such as MYH9-RD, including in children.[19–21] In a previous report, Eltrombopag was successfully used to correct a severe thrombocytopenia responsible for an intracranial hemorrhage in a p.V1316M-VWD2B patient.[22] However, the question of whether the newly formed platelets remain dysfunctional is unanswered. In patients with WAS and ITP, eltrombopag treatment was not associated with platelet functional improvement.[23,24] In VWD2B, platelet dysfunction derives from the interaction of hyper-active VWF with GPIbα and abnormal activation of the PKC/P2Y12/Rap1 signaling pathway.[8] The replacement therapy shifts the equilibrium toward high concentration of normal VWF, potentially protecting newly formed platelet from the PKC-dependent pre-activation. We therefore speculate that the combination of TPO-RA and VWF-replacement therapy over several weeks could favor the production of an increased number of normal platelets although future studies are required to prove this hypothesis.

Conclusion

In conclusion, we report the first case of VWD2B patient with splenic injury successfully treated with nonoperative management including VWF replacement therapy and TPO-RA. Eltrombopag was initially introduced to counteract the exacerbated thrombocytopenia post PT-stress reaction and successfully applied to prevent postoperative hemorrhage. The present case supports the safety and efficacy of eltrombopag administration in combination with VWF replacement therapy to improve the hemostatic management of nonurgent situations in thrombocytopenic VWD2B patients.

Author contributions

Caterina Casari: Conceptualization; Formal analysis; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Alexandre Kauskot: Formal analysis; Methodology; Validation; Visualization; Writing – review & editing.

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Cecile V. Denis: Conceptualization; Formal analysis; Methodology; Supervision; Validation; Writing – review & editing.

Valerie Proulle: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: This research was supported by a research grant from CSL Behring to Valerie Proulle. The research grant from CSL Behring provided supports for VWF testing. The publication fees were paid by AEMSSI, Association pour l'Etude des Maladies du Sang et du Systeme Immunitaire, Le Kremlin-Bicetre, France. The other authors have no conflicts of interest to declare.

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Statement of ethics

This case report complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The case report is reported according to the CARE guidelines. The patient's parents gave their informed consent to publish the case.

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