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CASE REPORT

Colon cancer surgery in von Willebrand disease type 3 setting triggering vascular abnormalities on bowel anastomosis

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Abstract

Background: von Willebrand disease (VWD) is associated with vascular malformations in the gastrointestinal tract. This complication, more frequent in VWD types 2A and 3, may be due to abnormal angiogenesis, but the precise mechanism is still unclear. Angiogenesis and inflammation are closely linked and can potentiate each other.

Key Clinical Question: Can colon inflammation in the setting of cancer surgery potentiate angiogenesis in the VWD setting?

Clinical Approach: A woman with VWD type 3 underwent partial colectomy twice for an adenocarcinoma. After managing the first surgery with a plasma-derived von Willebrand factor (VWF) concentrate (Wilfactin; LFB), refractory gastrointestinal bleeding occurred from neovessels on bowel anastomosis. After a multidisciplinary discussion, a second surgery was undertaken with a recombinant VWF concentrate (Veyvondi; Takeda Pharmaceuticals). Pathologic neovessels were again observed on the new anastomosis.

Conclusion: Colectomy was complicated twice by pathologic neovessels on bowel anastomosis in 2 distinct procedures managed either with plasma-derived VWF or with recombinant VWF.

KEYWORDS

angiogenesis, GI bleeding, inflammation, von Willebrand disease, von Willebrand factor

Essentials

- von Willebrand disease (VWD) is associated with gastrointestinal vascular malformations (VMs).
- After surgery of a colon cancer in a woman with VWD type 3, VMs appeared on bowel anastomosis.
- Colectomy was complicated twice by VMs despite using 2 different Willebrand concentrates.
- Colon inflammation in the setting of surgical trauma could promote VMs in VWD type 3.

1 | INTRODUCTION

Clinical studies have demonstrated the validity of administering a high-purity von Willebrand factor (VWF) concentrate devoid of factor VIII

(FVIII) to correct both VWF and FVIII deficiencies through the ability of infused VWF to stabilize endogenous FVIII in patients with von Willebrand disease (VWD) [1]. This concept was first demonstrated for a plasma-derived VWF (pdVWF) product almost devoid of FVIII

(Wilfactin/Willfact; LFB), currently licensed in several European countries [2,3]. It was further confirmed for the first high-purity recombinant (rVWF) VWF product totally devoid of FVIII (vonicog alfa, Veyvondi; Takeda Pharmaceuticals), currently licensed in France in adults for episodic treatment of bleeding [4] and surgical prophylaxis [5].

In contrast to pdVWF, rVWF is not exposed to ADAMTS-13 during manufacturing and thus contains a full VWF multimeric profile, including ultralarge multimers [2,4]. It may contribute additional efficacy in the management of gastrointestinal (GI) bleeding from angiodysplasia, a complication more frequently observed in VWD types 2A and 3, which is notoriously difficult to treat [6]. Angiodysplasia in the VWD setting may result from abnormal angiogenesis, but the precise mechanism is still unclear and may be multifactorial. Angiogenesis and inflammation are closely linked and can potentiate each other [7].

In this case report, we provide the first description of a colon cancer surgery precipitating the appearance of vascular malformations (VMs) reminiscent of angiodysplasia on bowel anastomosis after 2 consecutive partial colectomies managed either with pdVWF or with rVWF.

2 | CASE

We report the case of a woman in her 40s with a VWD type 3 (see [Supplementary Material](#) for more details) who successively underwent 2 partial colectomies on a 28-month interval, the first one managed with pdVWF (Wilfactin) and the second one with rVWF (Veyvondi). The perioperative management of both surgeries, including the schedule of administration of VWF concentrates, is described in [Figure A](#) and [Supplementary Material](#).

This woman without any history of GI bleeding first presented with rectorrhagia revealing on colonoscopy a colonic adenocarcinoma (staged T1N0) with an indication of partial colectomy. At that time, colonoscopy was negative for VMs. The first surgery was performed with pdVWF ([Figure A](#)), as patient's usual on-demand treatment and previous evidence of effectiveness in the surgical setting.

Despite a perioperative course free of bleeding and with no transfusion of packed red blood cells (PRBCs), the patient unexpectedly started 3 months later to present recurrent rectorrhagia with high transfusion needs (15 units of PRBC and 4 intravenous iron supplementations in the 31-month interval between the 2 surgeries). The first postoperative colonoscopy (fourth month after surgery) revealed on the bowel anastomosis the appearance of pathologic neovessels ([Figure B](#)) that were treated endoscopically by argon plasma coagulation. However, it failed to resolve GI bleeding. Afterward, GI bleeding remained refractory to several therapeutic strategies that were successively applied: i) a 6-month course of pdVWF prophylaxis (45 IU/kg thrice weekly), ii) a 4-month course of pdVWF prophylaxis (45 IU/kg thrice weekly) in association with octreotide (20 mg once a month), iii) a 2-month course of on-demand therapy with rVWF (which was introduced based on the results of the pivotal study suggesting a slightly higher half-life [8]) in association with octreotide, iv) a 9-month course of on-demand therapy

with rVWF, and v) a 3-month course of on-demand therapy with rVWF in association with bevacizumab, a humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor (VEGF) A (a total of 5 injections of 5 mg/kg administered every 2 weeks). Meanwhile, the endoscopic follow-up showed a progressive increase in the neovessel severity pattern ([Figure C, D](#); 9th and 18th month after surgery, respectively). In this setting of refractory GI bleeding without any concurrent bleeding lesion on video capsule endoscopy, a multidisciplinary decision to repeat the same surgery was taken in order to remove the pathologic wound with neovessels. At that time, we hypothesized that the use of rVWF could translate into improved clinical management compared with the use of pdVWF based on its slightly higher half-life and potentially the transient presence of ultralarge multimers after infusion. The second surgery was scheduled 3 months after the last infusion of bevacizumab. Similar VWF and FVIII trough levels were obtained after surgery with rVWF despite having a slightly lower concentration's consumption than that of pdVWF (total cumulative dose, 15 600 vs 23 500 IU, respectively; number of infusions, 5 vs 7 infusions, respectively) for the same type of surgical procedure ([Figure A](#)). However, after a second perioperative course free of bleeding and PRBC transfusion and despite resuming immediately after surgery rVWF prophylaxis (28 IU/kg thrice weekly) in association with octreotide (20 mg once a month), rectorrhagia recurred 4 months later prompting a new colonoscopy. The presence of neovessels was again observed on the new bowel anastomosis, with a slightly less severe pattern ([Figure E](#)) than that with the previous surgical anastomosis. Accordingly, GI bleeding was milder with resolution of PRBC transfusion dependency and 1 intravenous iron supplementation during an 18-month follow-up with ongoing rVWF prophylaxis (50 IU/kg thrice per week) in association with octreotide.

3 | DISCUSSION

We report here for the first time the appearance of pathologic neovessels on bowel anastomosis after surgery for an incidental colon cancer in the setting of VWD type 3. This unique complication was observed twice within the framework of sequential use of pdVWF and then rVWF for the management of a same type of major surgical procedure (partial colectomy) in a woman with VWD type 3. This observation suggests that inflammation in the setting of surgical trauma and cancer can precipitate GI VMs in VWD type 3 given the location of the pathologic neovessels at the anastomotic site.

Angiogenesis plays a crucial role in wound healing of damaged and inflammatory tissues. *In vitro* and *in vivo* studies indicate that VWF can regulate angiogenesis through multiple pathways, with most of them converging on VEGF signaling [9,10]. In a mouse model, VEGF was previously shown to play an important role in maintaining the integrity of the GI mucosa following bowel resection [11]. As VWF is expressed in a mosaic pattern in vascular beds [12], its contribution to angiogenesis and wound healing may be variable across tissues [13]. Whether our observation of impaired wound healing can apply to

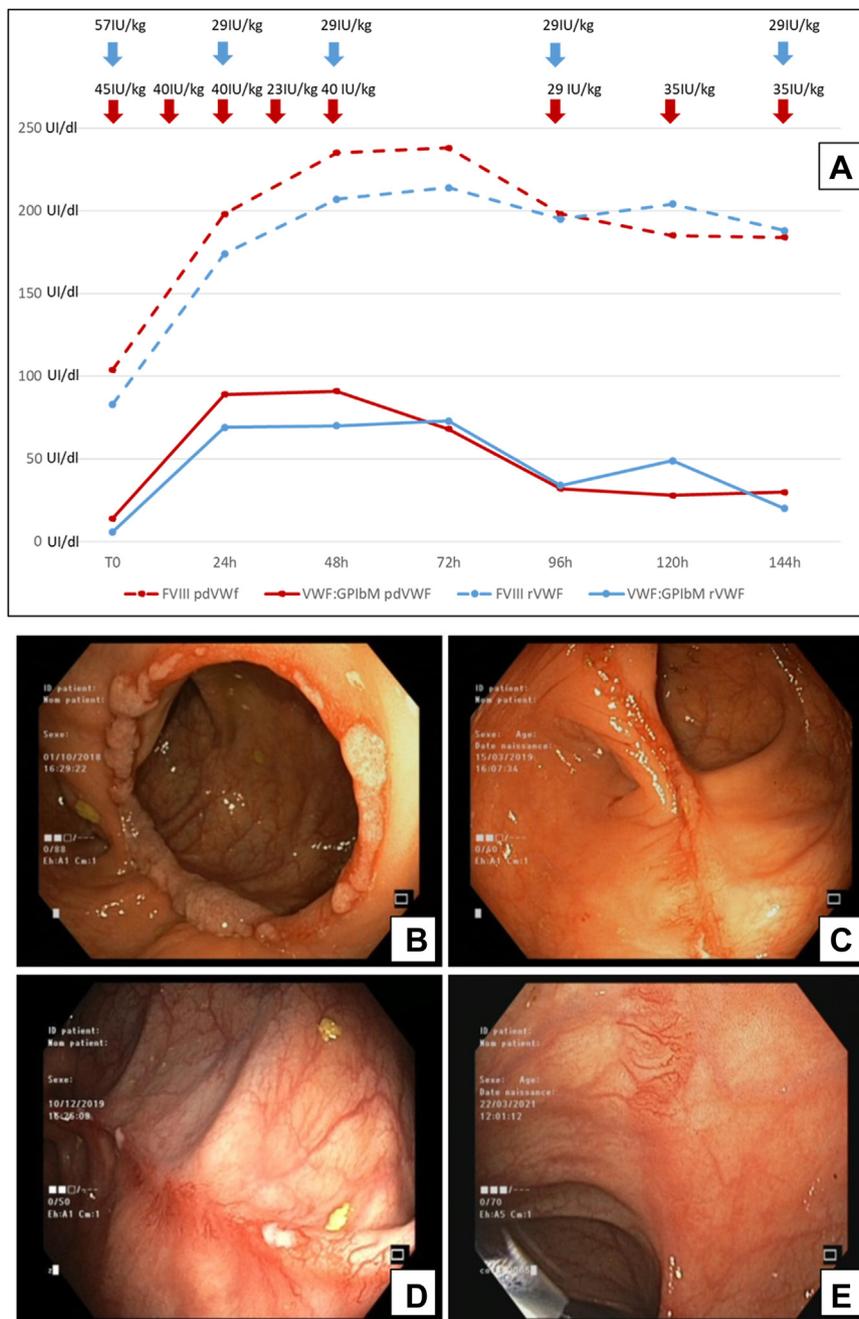


FIGURE Perioperative management with high-purity von Willebrand factor (VWF) products and long-term endoscopic follow-up of bowel surgical anastomoses. (A) Head-to-head comparison of the perioperative management applied for each surgery. Red and blue arrows represent weight-adjusted infusions of the high-purity plasma-derived VWF (pdVWF) (Wilfactin, administered for the first surgery) or recombinant VWF (rVWF) products (Veyvondi, administered for the second surgery), respectively. Dashed and plain lines represent the VWF platelet-binding activity to a gain-of-function mutant GPIb fragment (VWF:GPIbM) and factor VIII procoagulant activity (FVIII:C) trough levels. The first partial colectomy (pdVWF, dashed lines) took place 48 hours after the last infusion of pdVWF (47 IU/kg) in the setting of active gastrointestinal bleeding from the digestive neoplasia. The second partial colectomy (rVWF, solid lines) took place 72 hours after the last infusion of rVWF (57 IU/kg) administered in the prophylaxis setting. Endoscopic aspect of the surgical anastomosis at month 4 ([B]) presence of an inflammatory granulation tissue and angiodysplasia), month 9 ([C]) circumferential angiodysplasia pattern), and month 18 ([D]) diffuse angiodysplasia pattern) after the first partial colectomy managed with pdVWF. Endoscopic aspect of the surgical anastomosis at month 4 after the second partial colectomy managed with rVWF ([E]) limited noncircumferential angiodysplasia pattern).

other tissues than the GI tract deserves further clinical studies since microvascular abnormalities have been previously reported in the nail fold and the skin capillary beds of patients with VWD [14,15].

The first surgery managed with pdVWF, which does not contain ultralarge multimers, was complicated by the occurrence of VMs on bowel anastomosis. When repeating later the same type of surgery

with rVWF, less infusions and lower doses were needed to achieve similar factor trough levels than of pdVWF, as previously reported [5,8,16]. Interestingly, the second surgery was also complicated by the occurrence of VMs on the new bowel anastomosis, suggesting that GI angiogenesis at the anastomotic site was still abnormal when using rVWF after surgery and then in the prophylaxis setting. The increased prevalence of GI bleeding from angiodysplasia in VWD type 2A and in aortic stenosis suggests a specific role for plasma VWF multimers in angiogenesis [17,18]. Whether the use of rVWF could translate into improved clinical outcomes in patients with VWD and GI bleeding from angiodysplasia has been suggested in type 2A case reports [19]. The ultralarge VWF multimers present in rVWF have an increased hemostatic and proangiogenic potential compared with smaller multimers [10]. However, they are rapidly cleared from the bloodstream after rVWF infusion [8]. Moreover, exogenous VWF is not able to correct VWF endothelial deficiency, thus presumably being unable to totally correct impaired angiogenesis in the VWD type 3 setting. In the phase 3 study investigating the efficacy and safety of vonicog alpha prophylaxis, patients switching from prophylaxis with pdVWF to rVWF experienced a similar level of control of bleeding, but the numbers were too limited to assess specifically the GI bleeding outcome [20].

This report has a major limitation confounding the assessment of the efficacy of both VWF high-purity concentrates on GI bleeding. Concurrently to VWF replacement therapy (with either pdVWF or rVWF) administered during surgery and in the prophylaxis setting, the patient received several antiangiogenic drugs. It is therefore difficult to ascertain what intervention was truly beneficial on the reduction of transfusion needs observed after the second surgery.

4 | CONCLUSION

We report for the first time the onset of VMs translating in refractory GI bleeding after bowel surgery in a patient with VWD type 3. This complication was observed twice when managing the same type of surgical procedure either with pdVWF or with rVWF. GI inflammation in the setting of surgical trauma and VWD type 3 could promote VMs on the anastomotic site.

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AUTHOR CONTRIBUTIONS

A.R. drafted the manuscript. C.P., M.D., and J.B. collected the data and/or drafted the manuscript. J.G. and S.S. collected the data and critically revised the manuscript.

RELATIONSHIP DISCLOSURE

A.R. received research support for his institution from CSL Behring and Roche/Chugai; received support for attending scientific meetings from Biomarin, CSL Behring, LFB, Novo Nordisk, Roche-Chugai, and Sobi; performed consultancy for Biomarin, CSL Behring, LFB, Octapharma, Roche, and Sobi (fees go to the institution); and has been an investigator in studies sponsored by Biomarin, Bioverativ, CSL Behring, LFB, Shire/Takeda, Roche, and Sobi. S.S. received research support for her institution from LFB and CSL Behring and performed consultancy for LFB, Roche, Sobi, and Takeda (fees go to the institution). S.S. is a co-founder and owner of Laelaps Therapeutics. J.G. received support for attending scientific meetings and honoraria from Baxalta-Shire, Bayer Healthcare, CSL Behring, LFB, Novo Nordisk, Roche-Chugai, and Sobi. Other authors have no competing interests to disclose.

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REFERENCES

- [1] Mannucci PM. New therapies for von Willebrand disease. *Hematology Am Soc Hematol Educ Program*. 2019;2019:590–5.
- [2] Goudemand J, Scharrer I, Berntorp E, Lee CA, Borel-Derlon A, Stieltjes N, et al. Pharmacokinetic studies on Wilfactin, a von Willebrand factor concentrate with a low factor VIII content treated with three virus-inactivation/removal methods. *J Thromb Haemost*. 2005;3:2219–27.
- [3] Borel-Derlon A, Federici AB, Roussel-Robert V, Goudemand J, Lee CA, Scharrer I, et al. Treatment of severe von Willebrand disease with a high-purity von Willebrand factor concentrate (Wilfactin): a prospective study of 50 patients. *J Thromb Haemost*. 2007;5:1115–24.
- [4] Gill JC, Castaman G, Windyga J, Kouides P, Ragni M, Leebeek FW, et al. Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. *Blood*. 2015;126:2038–46.
- [5] Peyvandi F, Mamaev A, Wang JD, Stasyshyn O, Timofeeva M, Curry N, et al. Phase 3 study of recombinant von Willebrand factor in patients with severe von Willebrand disease who are undergoing elective surgery. *J Thromb Haemost*. 2019;17:52–62.
- [6] Chornenki NLJ, Ocran E, James PD. Special considerations in GI bleeding in VWD patients. *Hematology Am Soc Hematol Educ Program*. 2022;2022:624–30.
- [7] Carmeliet P, Jain RK. Molecular mechanisms and clinical applications of angiogenesis. *Nature*. 2011;473:298–307.
- [8] Mannucci PM, Kempton C, Millar C, Romond E, Shapiro A, Birschmann I, et al. Pharmacokinetics and safety of a novel recombinant human von Willebrand factor manufactured with a plasma-free method: a prospective clinical trial. *Blood*. 2013;122:648–57.
- [9] Starke RD, Ferraro F, Paschalaki KE, Dryden NH, McKinnon TA, Sutton RE, et al. Endothelial von Willebrand factor regulates angiogenesis. *Blood*. 2011;117:1071–80.
- [10] Randi AM, Smith KE, Castaman G. von Willebrand factor regulation of blood vessel formation. *Blood*. 2018;132:132–40.
- [11] Parvadia JK, Keswani SG, Vaikunth S, Maldonado AR, Marwan A, Stehr W, et al. Role of VEGF in small bowel adaptation after

- resection: the adaptive response is angiogenesis dependent. *Am J Physiol Gastrointest Liver Physiol*. 2007;293:G591–8.
- [12] Yuan L, Chan GC, Beeler D, Janes L, Spokes KC, Dharaneeswaran H, et al. A role of stochastic phenotype switching in generating mosaic endothelial cell heterogeneity. *Nat Commun*. 2016;7:10160.
- [13] Ishihara J, Ishihara A, Starke RD, Peghaire CR, Smith KE, McKinnon TAJ, et al. The heparin binding domain of von Willebrand factor binds to growth factors and promotes angiogenesis in wound healing. *Blood*. 2019;133:2559–69.
- [14] Chornenki NLJ, Shanjer M, James PD. Vascular abnormalities in patients with von Willebrand disease: a scoping review. *J Thromb Haemost*. 2021;19:2151–60.
- [15] Koscielny JK, Latza R, Mürsdorf S, Mrowietz C, Kiesewetter H, Wenzel E, et al. Capillary microscopic and rheological dimensions for the diagnosis of von Willebrand disease in comparison to other haemorrhagic diatheses. *Thromb Haemost*. 2000;84:981–8.
- [16] Desprez D, Drillaud N, Flaujac C, Volot F, Pan-Petes B, Beurrier P, et al. Efficacy and safety of a recombinant von Willebrand factor treatment in patients with inherited von Willebrand disease requiring surgical procedures. *Haemophilia*. 2021;27:270–6.
- [17] Rauch A, Paris C, Repesse Y, Branche J, D'Oiron R, Harroche A, et al. Gastrointestinal bleeding from angiodysplasia in von Willebrand disease: improved diagnosis and outcome prediction using video-capsule on top of conventional endoscopy. *J Thromb Haemost*. 2021;19:380–6.
- [18] Loscalzo J. From clinical observation to mechanism—Heyde's syndrome. *N Engl J Med*. 2012;367:1954–6.
- [19] Brown R. Recombinant von Willebrand factor for severe gastrointestinal bleeding unresponsive to other treatments in a patient with type 2A von Willebrand disease: a case report. *Blood Coagul Fibrinolysis*. 2017;28:570–5.
- [20] Leebeek FWG, Peyvandi F, Escobar M, Tiede A, Castaman G, Wang M, et al. Recombinant von Willebrand factor prophylaxis in patients with severe von Willebrand disease: phase 3 study results. *Blood*. 2022;140:89–98.

SUPPLEMENTARY MATERIAL

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