Clinical Case Study

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Recurrent Gastrointestinal Bleeding from Dieulafoy's Lesions in a Patient with Type 1 von Willebrand Disease: A Rare Association

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Keywords
Von Willebrand disease · Von Willebrand factor · Dieulafoy's lesion · Small-bowel capsule endoscopy · Push enteroscopy

Abstract
Von Willebrand disease (vWD) is the most prevalent hereditary bleeding disorder, affecting 0.6–1.3% of the population. While gastrointestinal bleeding from angiodysplasia is a well-known complication of vWD, the same is not true for Dieulafoy's lesions (DLs). We report the case of a 21-year-old black male with type 1 vWD and 2 previous hospital admissions for severe anemia with no visible blood loss. In both episodes, DLs were identified and treated endoscopically, one in the stomach and another in the duodenum. The patient presented to the emergency department in September 2016 with dizziness, fatigue, and again no visible blood loss. He was hemodynamically stable, and laboratory workup showed a hemoglobin level of 3.4 g/dL. After transfusion of packed red blood cells, intravenous iron, and von Willebrand factor/factor VIII concentrate infusions, the patient underwent upper endoscopy and colonoscopy, which were normal. Small-bowel capsule endoscopy showed dark blood and a fresh clot in the proximal jejunum. At this site, push enteroscopy identified a pulsatile vessel with an overlying minimal mucosal defect, consistent with a DL, type 2b of the Yano-Yamamoto classification, which was successfully treated with adrenaline and 2 hemoclips. The patient remains stable after 18 months of follow-up, with a hemoglobin level of 13.2 g/dL. This is a case of recurrent severe occult gastrointestinal bleeding from multiple DL in a young patient with vWD who is otherwise healthy. Three other cases of DL bleeding in the setting of vWD have been reported in the literature, suggesting a possible association between these 2 entities.

Hemorragia Gastrointestinal Recorrente por Lesões de Dieulafoy num Doente com Doença de von Willebrand Tipo 1: Uma Associação Rara

Palavras Chave
Doença de von Willebrand · Fator de von Willebrand · Lesão de Dieulafoy · Enteroscopia por cápsula · Enteroscopia de pulsão

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Resumo

A doença de von Willebrand é a perturbação hemorrágica hereditária mais frequente, afetando 0.6 a 1.3% da população. A hemorragia por angiectasias do tubo digestivo é uma complicação bem estabelecida desta doença. Contudo, o mesmo não é verdade para as lesões de Dieulafoy. Apresentamos o caso de um doente de 21 anos, melanodérmico, com doença de von Willebrand tipo 1 e dois internamentos prévios por anemia grave sem perdas hemáticas visíveis. Em ambos os episódios foram identificadas lesões de Dieulafoy que foram tratadas endoscopicamente, uma das quais no estômago e outra no duodeno. O doente foi admitido no serviço de urgência em Setembro de 2016 por quadro de tonturas e cansaço, novamente sem perdas visíveis. Apresentava-se hemodinamicamente estável e a avaliação laboratorial mostrou hemoglobina de 3.4 g/dL. Após transfusão de concentrados eritrocitários, terapêutica com ferro endovenoso e concentrados de fator de von Willebrand/fator VIII, foram realizadas endoscopia digestiva alta e colonoscopia, sem alterações. A enteroscopia por cápsula detetou a presença de sangue digerido e um coágulo fresco no jejuno proximal. A enteroscopia de pulsão identificou nessa topografia uma solução de continuidade da mucosa milimétrica sobre lesão vascular pulsátil procidente, compatível com lesão de Dieulafoy tipo 2b da Classificação de Yano-Yamamoto, que foi tratada eficazmente com adrenalina e dois hemoclips. Após 18 meses, o doente mantém-se clinicamente estável e com Hb 13.2 g/dL. Este é um caso particular de hemorragia gastrointestinal oculta recorrente por múltiplas lesões de Dieulafoy num jovem com doença de von Willebrand, sem outras patologias. Há três casos semelhantes descritos na literatura, sugerindo uma possível associação entre estas duas entidades.

Introduction

Von Willebrand disease (vWD) is the most prevalent hereditary bleeding disorder, affecting 0.6–1.3% of the population [1, 2]. It results from defects in von Willebrand factor (vWF), a multimeric glycoprotein that is essential in platelet adhesion and aggregation and is also a carrier for coagulation factor VIII (FVIII). Type 1 vWD accounts for 70–80% of the cases and is characterized by a quantitative deficiency of vWF [3]. Type 2 vWD is caused by dysfunctional vWF, whereas type 3 vWD is characterized by the complete absence of vWF. Acquired forms of the disease are very rare and can be associated with a variety of conditions, including autoimmune diseases, lymphoproliferative disorders, plasma-cell dyscrasias [4], and high shear stress conditions such as aortic stenosis [5].

The most common clinical manifestations of vWD include epistaxis, bruising, hematomas, and menorrhagia [3]. While gastrointestinal bleeding from angiodysplasia is a well-known complication of vWD [3, 6], the same is not true for Dieulafoy's lesions (DLs). In fact, only 3 cases of gastrointestinal bleeding from DLs in patients with vWD have been described so far [7–9].

Clinical Case

We present the case of a 21-year-old black male with severe type 1 vWD diagnosed in 2010, after an investigation of chronic iron deficiency anemia with a hemoglobin level of 10 g/dL. He had a history of recurrent bruising, occasional bleeding gums, 1 bleeding episode after dental extraction, 2 episodes of severe epistaxis requiring nasal cauterization, and 2 hospital admissions (2009 and 2014) due to severe anemia (hemoglobin reaching 3 g/dL) with no visible blood loss. In both of these episodes, DLs were identified – 1 lesion in the lesser gastric curvature and 1 lesion in the second part of the duodenum – and treated endoscopically, the first with argon-plasma coagulation and the second with adrenaline monotherapy. The patient was followed in the immunohemotherapy outpatient clinic and was treated with oral and intravenous iron, when required. He was submitted to a trial of desmopressin treatment, which was, however, suspended due to insufficient response.

In September 2016, the patient presented to the emergency department with fatigue and dizziness, with otherwise no signs of gastrointestinal bleeding. On physical examination, he was hemodynamically stable, and his abdomen was soft and non-tender. Rectal examination showed no blood in the stool.

Laboratory workup showed a hemoglobin level of 3.4 g/dL, with a mean corpuscular volume of 67.1 fL and a mean corpuscular hemoglobin of 19.7 pg. The ferritin level was 5 ng/mL, and transferrin saturation was 7.3%. He had low vWF antigen (18.2%) and vWF ristocetin cofactor (16.2%) activity, with a normal FVIII (101%) concentration.

The patient received 5 units of packed red blood cells, intravenous iron, and several vWF/FVIII concentrate infusions, with an adequate rise in hemoglobin to 7.3 g/dL.

Upper gastrointestinal endoscopy and colonoscopy were normal. Random biopsies of the gastric and duodenal mucosa revealed no significant findings. Small-bowel capsule endoscopy identified, within a segment with dark blood in the proximal jejunum, a fresh clot apparently adhering to a mucosal fold (Fig. 1a, b). Push enteroscopy detected, in this location, a 3-mm mucosal defect over a protruding pulsatile vascular lesion, with no active bleeding (Fig. 2a). This was consistent with a DL, type 2b of the Yano-Yamamoto classification, which was treated endoscopically with an adrenalin injection (1:10,000) combined with 2 hemostatic clips (Fig. 2b, c). Endoscopic tattooing was performed both at the lesion level (Fig. 2d) and in the distal limit of progression.

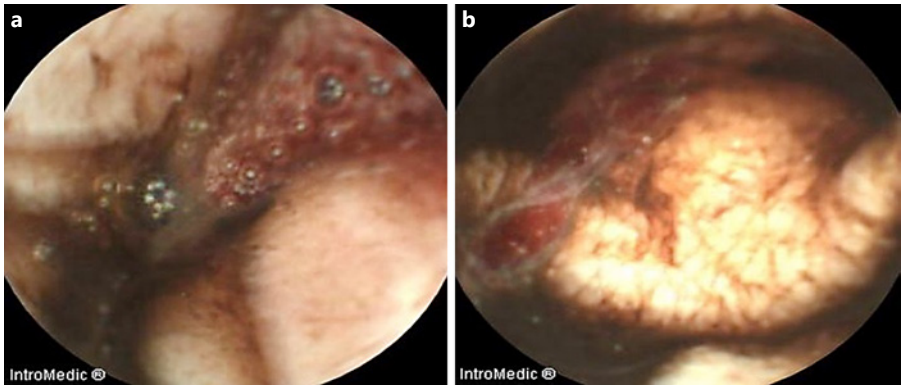

Fig. 1. Images from small-bowel capsule endoscopy showing a segment with dark blood in the proximal jejunum (**a**) and a fresh clot apparently adhering to a mucosal fold (**b**).

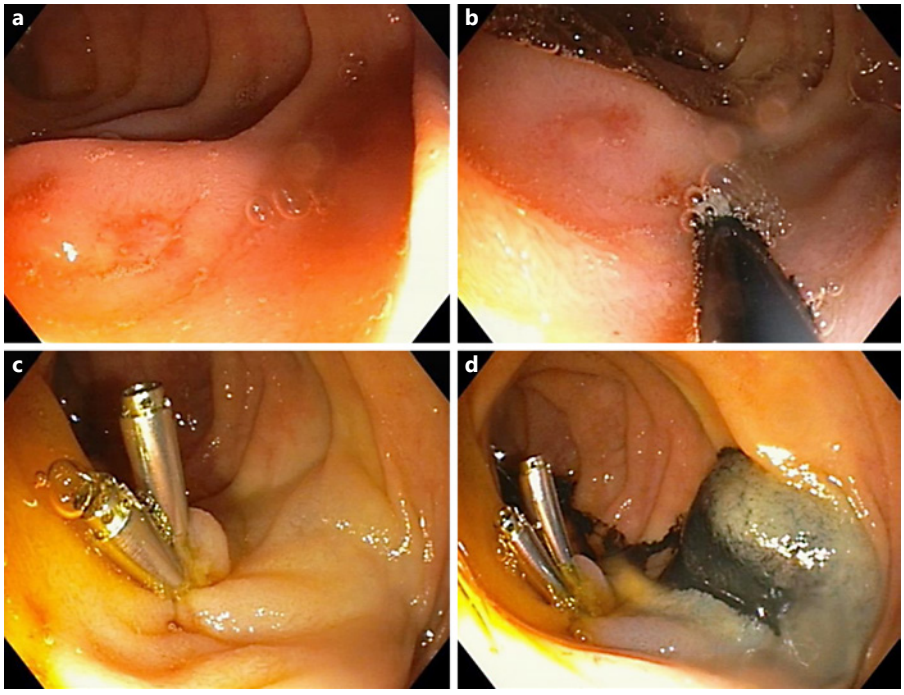

Fig. 2. Push enteroscopy images from the proximal jejunum showing a 3-mm mucosal defect over a protruding pulsatile vascular lesion, with no active bleeding; i.e., DL, type 2b of the Yano-Yamamoto classification (**a**). The lesion was treated endoscopically with an adrenalin injection (1:10,000) (**b**) combined with 2 hemostatic clips (**c**). Endoscopic tattooing was performed both at the lesion level (**d**) and in the distal limit of progression.

The patient was discharged after 4 days and experienced a steady increase in his hemoglobin level up to 13.2 g/dL, which is maintained after 18 months of follow-up.

Discussion

A DL is a vascular abnormality corresponding to a dilated and tortuous submucosal artery that retains a large caliber as it reaches the mucosa [10]. It is an otherwise structurally normal vessel, with no associated atherosclerosis or inflammation [11], and it is surrounded by histologically normal mucosa [10]. It has been proposed that the pulsations of the artery disrupt the overlying epithelium, ultimately resulting in erosion and bleeding [10, 11]. Little is known, however, about the genesis of this malformation, and no direct disease associations have been clearly recognized. DLs are generally thought to be an acquired condition, mainly because they seem to be more common in the elderly. However, they can affect any age group and have even been reported in newborns [12], raising the possibility that they can also be congenital [11]. These lesions occur more frequently in males and in the setting of comorbidities such as cardiopulmonary dysfunction and chronic kidney disease. The use of aspirin, warfarin, or nonsteroidal anti-inflammatory drugs has been reported in half of patients bleeding from DLs [13], although no causal link has been established.

Endoscopically, a DL is defined by the presence of either (1) arterial spurting or micropulsatile streaming, (2) a protruding vessel, or (3) a fresh clot, associated with a normal surrounding mucosa or a minimal mucosal defect [11]. The large majority of DLs are found in the stomach, typically 6–10 cm from the gastroesophageal junction along the lesser gastric curvature [14]. Approximately one-third of all DLs are extragastric, most frequently located in the duodenum and colon [14]. Jejunal location was traditionally considered very rare (<1%) [11], but some recent reports suggest that it may be more common than previously estimated, particularly the proximal jejunum [15]. DLs usually present as severe overt gastrointestinal bleeding, frequently with hemodynamic instability [16].

Endoscopic treatment is effective in around 90% of the cases, and evidence suggests that combined therapy should be preferred to monotherapy [13, 14, 16], with some studies favoring mechanical therapies such as band ligation or clipping to other methods [14].

We present a particular case of recurrent severe occult gastrointestinal bleeding from multiple DLs in a young patient with vWD who is otherwise healthy. This is a rare case in several aspects, including the recurrent nature, the jejunal location in the most recent episode, and particularly the fact that the bleeding was repeatedly occult, albeit severe. The fact that a lesion could be identified through push enteroscopy without being actively bleeding is also unusual, although the exploration was guided by the finding of a fresh clot in the same location by small-bowel capsule endoscopy.

This case raises the question of whether there is a causal association between vWD and bleeding from DLs. To date, 2 similar cases have been described in the literature, including a 72-year-old male with type 1 vWD and bleeding duodenal DLs [7] and a 65-year-old male with a known history of type 2A vWD, liver cirrhosis, partial gastrectomy, and angiodysplasia, with bleeding gastric and duodenal DLs [9]. A third patient was reported with colonic DL and acquired vWD related to aortic stenosis [8].

It could be argued that vWD simply promotes bleeding from a DL as it happens with other types of mucosal defects, without this necessarily implying a causal link or a shared pathophysiology. However, previous reports of similar cases and the severe and recurrent course of bleeding in our patient evoke the possibility of a direct association. Indeed, there is some evidence supporting a link between vWD and angiodysplasia [3, 6, 17], a different kind of vascular abnormality. These conditions were proposed to form a triad along with aortic stenosis in the pathophysiology of Heyde's syndrome, with the initial event being selective destruction of the largest vWF multimers by the stenosed aortic valve, resulting in acquired vWD [18, 19]. The loss of these multimers would then promote bleeding in the particular setting of a local high-shear condition found in angiodysplasias [18]. Whether a similar mechanism could be involved in bleeding DLs in vWD is currently unknown.

Another possible pathophysiological mechanism for this association could reside in the recently described antiangiogenic properties of vWF [19]. Indeed, a recent study reported that the inhibition of vWF expression in endothelial cells in vitro resulted in increased angiogenesis mediated by vascular endothelial growth factor [20]. The same authors observed increased vascularization in vWF-deficient mice. In another study, vascular endothelial growth factor expression was found to be increased in endothelial cells lining a DL [21]. A better understanding of this link between hemostasis and angiogenesis could have therapeutic implications in patients with vascular disorders.

In conclusion, we report a clinical case that suggests a potential link between vWD and DL and propose possible pathophysiological mechanisms for this association, although further investigation is needed to confirm this hypothesis.

Statement of Ethics

This study did not require informed consent or review/approval by the appropriate ethics committee.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Drafting the article: Mariana Ferreira Cardoso; critical revision of the article: Luís Carvalho Lourenço, Margarida Antunes; final approval of the version to be published: Mariana Ferreira Cardoso, Luís Carvalho Lourenço, Margarida Antunes, Joana Carvalho e Branco, Liliana Santos, Alexandra Martins, and Jorge A. Reis.

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