

LETTER TO THE EDITOR

Gastrointestinal bleeding due to angiodysplasia in patients with type 1 von Willebrand disease: report on association and management

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The presence of gastrointestinal angiodysplasia (GI-A) can represent an urgent haematological problem as it produces serious bleeding, which is usually untreatable. It has been recognized that GI-A frequently occurs in patients with type 2–3 and acquired von Willebrand disease (VWD) but the strength of this association is unclear. One hypothesis relies on the lack of high molecular weight (HMW) molecules of von Willebrand factor (VWF) in the plasma [1]. Other findings suggest a potential role being played by the 3916T mutation of the esone 28 coding factor vW (domain A1) [2]. Angiodysplastic lesions can be found along the entire length of the GI tract, from the tongue to the colon. Although there are several diagnostic methods such as endoscopy, push enteroscopy, helical computed tomography (CT), mesenteric angiography and, more recently, video capsule endoscopy [3] available, the identification of angiodysplasia remains extremely difficult to document and most of the patients remain undiagnosed. Thereby, most patients are treated solely medically with several and mainly ineffective approaches [3].

Most previous publications on VWD and angiodysplasia have been reports of the association itself and there is little published data on the management and follow-up of affected patients. In addition, no such association has yet been documented in patients with type 1 VWD. We report our experiences in the management and follow-up of three patients suffer-

ing from angiodysplasia and type 1 VWD, according to the current classification [4]. Their baseline phenotypic characteristics are outlined in Table 1; investigation and management of individual patients are summarized in Table 2.

The first patient was a 49-year-old female with inherited type 1 VWD but no serious bleeding tendency. She presented with melena and iron-deficiency anaemia. Activity of both von Willebrand factor antigen (VWF:Ag) and von Willebrand factor Ristocetin co-factor activity (VWF:RCO) was reduced to <20%. GI endoscopy and colonoscopy proved normal at the time of her first hospital admission. The patient was treated with blood replacement, tranexamic acid and desmopressin (DDAVP) infusion, but these latter two approaches did not effectively reduce the bleeding. We therefore initiated VWF/factor VIII (FVIII) concentrate (Haemate P[®], CSL Behring) at the therapeutic dosage, 40–50 IU kg⁻¹ every day and then every two days for 4 weeks following hospital discharge. She did not display any bleeding symptoms for the next 5 months, when she then experienced a new incident of melena and serious anaemia (haemoglobin <7.0 g dL⁻¹). Mesenteric angiography and capsular endoscopy were thus performed: the latter procedure revealed two small angiodysplastic lesions in the ileum, clinically insignificant. We therefore initiated medical therapy with oestrogen and Haemate P[®] 30 IU kg⁻¹ every alternate day for 8 weeks. However, the patient experienced an adverse event to oestrogen therapy and serious bleeding when the VWF concentrate was withdrawn. Symptoms of anaemia continued for the next 22 months; GI bleeding was always reduced during prophylaxis with Haemate P[®] but commenced again whenever this was suspended. At that time, we repeated GI

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Table 1. Baseline patient characteristics.

Patient	Age (years)* /sex	Co-morbidity	VWD type	VWF:Ag (%)	VWF:RCo (%)	FVIII:C (%)
1	49/female	None	1	16	14	40.9
2	55/male	CLL	1	8	8	66
3	51/female	None	1	13	11	82

*At the time of gastrointestinal bleeding.

Abbreviations: CLL, chronic lymphatic leukaemia; VWD, von Willebrand's disease; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor Ristocetin co-factor activity; FVIII, factor VIII.

Table 2. Summary of investigations and management.

Patient	Presentation	Investigation	Treatment	Outcome
1	GI bleeding (melena)	GI endoscopy, capsular angiography, intraoperative enteroscopy (diagnostic)	Angiodysplasia treated with segmental jejunal resection, oestrogens, antifibrinolytics, FVIII/VWF concentrate	GI bleeding resolved
2	GI bleeding (melena)	GI endoscopy, microcapsular angiography, laparotomy (diagnostic)	Ileum resection, longastatin, antifibrinolytics, FVIII/VWF concentrate	GI bleeding resolved
3	Rectal bleeding	GI endoscopy, colonoscopy (diagnostic)	Diathermy, hemicolectomy, intraoperative enteroscopy, antifibrinolytics, FVIII/VWF concentrate	GI bleeding resolved only together with prophylaxis with FVIII/VWF concentrate

Abbreviations: GI, gastrointestinal; VWF, von Willebrand factor; FVIII, factor VIII.

imaging with mesenteric and capsular endoscopy but the exact locus of ileum bleeding could not be found. In agreement with the patient, we decided to undergo intraoperative enteroscopy (conducted under Haemate P[®] at 50 IU kg⁻¹), which showed an angiodysplastic lesion of 3-cm diameter at the jejunum. Segmental jejunal resection was then performed; histological findings were not significant (absence of neoplasia). The patient continued anti-haemorrhagic prophylaxis for 4 weeks following discharge (Haemate P[®] 30 IU kg⁻¹ any other day). At a follow-up 2 years later, she had not experienced any bleeding symptoms and her haemoglobin levels remained stable.

The second patient, a 55-year-old male, had VWF:Ag and VWF:RCo (VWF:RCo) activity reduced to <10%. The bleeding episodes started in 1999 when he experienced several episodes of melena. The first episode was concomitant with the diagnosis of a lymphoproliferative disorder [chronic lymphatic leukaemia (CLL) type B, stage A]; at that time the VWF had values of 10% for activity and 12% for antigen. No antibodies against VWF were found at the time of the diagnosis and subsequently during 3 years of follow-up. The patient experienced several episodes of GI bleeding without any endoscopic evidence of haemorrhagic foci in the upper

and lower GI tract. The CLL was treated with chemotherapy (cyclophosphamide, vincristina and prednisone) and Rituximab (Mabthera[®], 372 mg/m²) for eight cycles. Two years after the CLL diagnosis (concomitant with the first episode of bleeding), he underwent a laparotomy that revealed multiple angiodysplastic lesions in the ileum. These lesions were removed by abdominal surgical approach under prophylaxis with Haemate P[®] at a dosage of 50 IU kg⁻¹; after surgery, the patient commenced longastatin (octecroide) at a dosage of 0.2 mg, three times daily for 2 weeks. Anti-hemorrhagic prophylaxis was then carried out for 4 weeks with Haemate P[®] at a dosage of 20 IU kg⁻¹ every alternate day in order to maintain VWF:RCo/FVIII:C >50%. At the end of this period all medical treatment was stopped; the patient did not experience any further bleeding episodes for the next 18 months.

The third patient was a 51-year-old female, with VWF:Ag and VWF:RCo activity both reduced to <15%. She presented, aged 29 years, with rectal bleeding and iron-deficiency anaemia. Upper GI endoscopy was normal. Colonoscopy demonstrated angiodysplasia of the left side of the colon. Diathermy of the colonic lesions, conducted under Haemate P[®] at 40 IU kg⁻¹, proved ineffective over the long-term and she eventually underwent a left

hemicolectomy because of severe multiple bleeding episodes. Despite long-term treatment with tranexamic acid, bleeding recurred 2 months later and was persistent and produced iron-deficiency anemia. Colonoscopy proved normal as did mesenteric angiography. Anti-hemorrhagic prophylaxis was then initiated with VWF/FVIII concentrate (Haemate P[®]) in order to maintain VWF/FVIII above 30%. A new episode of melena, occurring 12 months later, was investigated with sigmoidoscopy, but no bleeding source was identified. Because of the persistent bleeding, intraoperative enteroscopy was performed. The examination revealed multiple angiodysplastic lesions in the ileum which were partially removed; histological findings were negative for cancer. As GI blood loss and iron deficiency continued, anti-haemorrhagic prophylaxis was initiated to reach and maintain VWF/FVIII levels >50%. A new endoscopic investigation was performed but without evidence of any identifiable source of bleeding. At present she is managed with iron supplementation and prophylactic Haemate P[®] (20 IU kg⁻¹ three times weekly); this regimen has consistently reduced the need for blood transfusion.

Although GI-A has been reported only in patients with type 2 and 3 VWD, we found such association in three patients with type 1 VWD, having a joint VWF:Ag and VWF:RCo reduction to <20%. However, we did not perform gene analysis and/or determination of VW multimers, so we cannot exclude that some of our patients may have mixed VW phenotypes [4]. All our patients suffered of recurrent and potentially life-threatening bleeding from the GI tract, yet in none of them, despite an extensive investigation, could a source responsible for such significant bleeding be found. Mesenteric and capsular endoscopy revealed angiodysplasia, but failed to demonstrate the exact site of bleeding. Initial management of acute GI bleeding was conservative in all patients and required clotting factor concentrates because of the inefficacy of tranexamic acid and desmopressin. Even in the long-term follow-up iron supplementation and tranexamic acid were not successful and all patients required some form of specific intervention. In one patient diathermy was ineffective with the lesions rapidly recurring. Surgical resection was successful at its first attempt in two of the three patients. The third patient required extensive surgery of the ileum without long-term resolution of bleeding. Oestrogen-progesterone has been shown to be effective, controlling severe recurrent bleeding from GI vascular malformations [1] and such approach is reserved for patients who either continue to bleed following endoscopic or surgical

management, or who are not candidates for invasive management. However, such an approach was not tolerated and proved unsuccessful in one of our patients. The successful use of the somatostatin analogue, octreotide, has been recently reported [1] in two patients with VWD and GI bleeding from angiodysplasia. The mode of action is unclear, but it may be significant that increases in factor VIII:C and VWF:RCo were observed in one patient while receiving octreotide. In our experience, octreotide therapy did not significantly affect the course of bleeding.

In summary, in our experience no single investigative modality was successful; even currently available medical therapy was unable to control severe bleeding. In these cases, hormonal and octreotide therapy can be applied, but their safety and efficacy remain to be established in GI-A patients with coagulation disorders. In our and others' experiences [5], the use of long-term prophylaxis with VWF/FVIII concentrates effectively reduced the need for transfusion, this being shown in the one patient in whom a surgical approach did not provide a satisfactory result. The increasing use of capsular endoscopy and push enteroscopy will permit to increase the surgical approaches that should be always taken into consideration in such patients because of the high risk of uncontrolled bleeding in case of medical therapy only.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

References

- 1 Makris M. Gastrointestinal bleeding in von Willebrand disease. *Thromb Res* 2006; **118**: 13–7.
- 2 Satoh Y, Kita H, Kihira K *et al.* Gastrointestinal angiodysplasia in a patient with type 2 von Willebrand's disease and analysis of exon 28 of the von Willebrand factor gene. *Am J Gastroenterol* 2004; **99**: 2495–8.
- 3 Berntorp E. The von Willebrand Disease Prophylaxis Network (VWD PN): exploring a treatment concept. *Thromb Res* 2006; **118**: S19–22.
- 4 Sadler JE, Budde U, Eikenboom JC *et al.* Working Party on von Willebrand Disease Classification. Update on the pathophysiology and classification of von Willebrand disease: a report of the subcommittee on von Willebrand Factor. *J Thromb Haemost* 2006; **4**: 2103–14.
- 5 Coppola A, Cimino E, Conca P *et al.* Long-term prophylaxis with intermediate-purity factor VIII concentrate (Haemate P) in a patient with type 3 von Willebrand disease and recurrent gastrointestinal bleeding. *Haemophilia* 2006; **12**: 1–113.