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Letter to the editor

Von Willebrand disease and extra-intestinal angiodysplasia

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Von Willebrand disease (VWD) is characterised by a qualitative or quantitative defect in von Willebrand factor (VWF) resulting in a bleeding tendency such as mucocutaneous bleeding. It is the most common inherited bleeding disorder [1]. VWF has a pivotal role in both primary and secondary haemostasis as it captures platelets at sites of endothelial damage and has a carrier function for factor VIII (FVIII). Recently, a role for VWF in regulating blood vessel formation has been demonstrated [2], with a loss of endothelial VWF resulting in dysregulated angiogenesis.

Angiodysplastic lesions in VWD are mostly reported in the gastrointestinal tract with frequencies of 2% in type 2 VWD, 4.5% in type 3 VWD, and 11.5% in acquired VWD [3]. Despite this well-recognised gastrointestinal angiodysplasia, vascular malformation in other tissues are rarely reported, and it is unknown if the reason is poor reporting or that the lesions do not occur outside the gastrointestinal tract. Here we present three cases of VWD and abnormal angiogenesis outside the gastro-intestinal tract.

The first case is a 32-year-old man diagnosed with type 2M VWD due to a c.4120C>T mutation and leading to lifelong easy bruising and epistaxis. His baseline VWF activity is 8% (normal range 50-172%), VWF antigen 21% (46-146%), FVIII 54% (52-184%) and he has a qualitatively normal multimer pattern. On physical examination he was found to have a large venous malformation around his left ankle and a varicose vein on his left calf, both present since birth.

His grandfather was also diagnosed with type 2M VWD with a VWF activity of 1%, VWF antigen of 24%, FVIII 37%, and similar to his grandson a normal multimer pattern. At the age of 70, he developed a prominent cluster of angiomas on his glans penis with a few on the scrotum, histologically confirmed to be angiokeratomas. Later in life they became more prominent and troublesome, requiring laser therapy.

The third case is a man with type 2A VWD (familial mutation c.4493A>T) who suffered from severe bleeding due to intestinal angiodysplasia. He received over 300 units of blood before responding to high dose atorvastatin in 2008 [4]. He died two years later due to a myocardial infarction. On autopsy he had multiple angiomatoid littoral cell hamartomas in the spleen, alongside his known gastrointestinal angiodysplasia.

Recurrent gastrointestinal bleeding is a serious complication in VWD, and an increased prevalence of gastrointestinal angiodysplasia in VWD is assumed. This might be an overestimation reflecting the increased likelihood of becoming clinically evident due to the bleeding tendency. Nonetheless, recent preclinical data suggest that a lack of VWF results in dysregulated angiogenesis [2], and there is no reason why this should be restricted to the gut.

Reports of non-gastrointestinal angiodysplasia associated with VWD are limited. Clinically, when refractory epistaxis is observed, nasal arteriovenous malformations are considered but these cases are hardly reported. In f a woman with type 2B VWD and significant angiodysplasia of the gastrointestinal tract, significant epistaxis due to a large number of telangiectases in the nasal cavity is described [5]. The second report is of a young woman with VWD and angiodysplasia in the lung, but this could have been due to coinheritance of VWD and hereditary haemorrhagic telangiectasia (HHT) as both her father and grandfather also suffered from pulmonary angiodysplasia in the absence of a bleeding disorder [6]. The VWF gene is located on chromosome 12, as is the ACVRL1 gene coding for activin receptor-like kinase 1 with mutations causing HHT type 2.A third male patient had symptoms of recurrent haematuria and haemospermia with prostatic telangiectasia and VWD [7]. Recently a case of type 1 VWD and haematuria with haemospermia was reported without evidence of prostatic or cystic angiodysplasia, possibly because it can be difficult to document angiodysplastic lesions [8].

In two of the three cases we describe the multimer pattern is normal, whereas previously it was thought that angiodysplasia was associated with VWD subtypes lacking high-molecular weight multimers (HMWM). In an older, large international survey conducted in 4503 VWD patients, angiodysplasia was reported only in patients with type 2 and type 3 VWD [3]. More recently, the VWD Prophylaxis Network reported angiodysplasia in nine patients with type 1 VWD [9], in addition to three other cases reported by a group from Italy [10]. Based on the antiangiogenic properties ascribed to VWF, it is possible that the level of functional VWF is also of importance as well as the loss of HMWM specifically.

As both VWD and vascular malformations are relatively common, case-control studies are needed to elucidate whether VWF also has a role in the development of extra-intestinal vascular malformations. In future cases of VWD with extra-intestinal angiodysplasias, it would be worthwhile genotyping for endoglin and ACVRL1 mutations for possible coinheritance of HHT. Likewise, it would be interesting to conduct a study examining the prevalence of nasal angiodysplasias in VWD patients with refractory epistaxis. These efforts could elucidate whether what we are reporting is a coincidence or a related pathogenic process

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