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Heyde's syndrome: "It may stimulate some replies or statistical studies"

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Summary

We report the case of an 80-year-old woman with the clinical presentation of Heyde's syndrome, which is defined by the association of calcified aortic stenosis and gastrointestinal bleeding due to an acquired form of von Willebrand syndrome.

Transcatheter aortic valve implantation reverses von Willebrand factor abnormalities and reduces bleeding events. The clinical management is challenging and requires an interdisciplinary approach. Von Willebrand factor multimer analysis using protein electrophoresis remains the diagnostic gold standard. We suggest laboratory testing in patients with aortic valve stenosis prior to interventions with high risk of bleeding, patients with recurrent gastrointestinal bleeding who otherwise do not qualify for aortic valve replacement based on the cardiac defect alone and as an indicator for a dysfunctional cardiac device.

Keywords: Heyde's syndrome, gastrointestinal bleeding, aortic valve stenosis, acquired von Willebrand syndrome, Waring Blender syndrome

Case description

An 80-year-old woman with a history of severe aortic valve stenosis, atrial fibrillation and recurrent gastrointestinal bleeding was admitted to the emergency department with progressive weakness and exertional dyspnoea. Moreover, the patient had fainted twice in the previous 24 hours and had noticed black stool for a couple of days. Other signs of bleeding, chest pain, fever and other constitutional symptoms were denied.

Medications included aspirin 100 mg and amiodarone 200 mg once daily. Four weeks earlier, oral anticoagulation with apixaban was stopped after a left atrial appendage closure because of recurrent gastrointestinal bleeding. Echocardiographic assessment obtained 1 month before the current presentation showed severe aortic valve stenosis (dP mean/maximum 68/100 mm Hg, aortic valve area 0.6 cm^2).

Upon examination, the patient was alert and fully oriented. Vital signs were normal (temperature 35.9°C, heart rate 87/min, breathing rate 20/min with 99% oxygen saturation on air) except for a systolic blood pressure difference of 40 mm Hg (blood pressure right 122/50 mm Hg, blood pressure left 82/40 mm Hg). Physical examination revealed a 3/6 mid-systolic ejection murmur and skin pallor. There were no clinical signs of heart failure.

Blood analysis detected a reduced level of haemoglobin at 4.2 g/dl (reference range 12.0–15.4 g/dl) and a high lactate level of 5.0 mmol/l (reference <2.0 mmol/l). Levels of C-reactive protein, creatinine, estimated glomerular filtration rate and potassium were normal. The electrocardiogram showed ST-segment depression in leads I, II, III, aVF, V4–V6.

We focused on the exclusion of fatal conditions including hypovolaemic shock due to active gastrointestinal bleeding and aortic dissection indicated by the significant blood pressure difference. An aortic dissection and active lower gastrointestinal bleeding could not be seen in on computed tomographic angiography. Empiric therapy with proton pump inhibitors and a total of three red blood cell transfusions were administered, raising the haemoglobin level from 4.2 to 7.9 g/dl. Because of the severe aortic valve stenosis, the patient subsequently developed transfusion-associated circulatory overload with acute pulmonary oedema requiring intermittent noninvasive ventilation. Gastroscopy revealed oozing bleeding from a small angiodysplasia located in parts II/III of the duodenum. The bleeding source was treated by topical application of adrenalin and an endoscopic haemoclip. High dose treatment with proton pump inhibitors was prescribed for 4 weeks and platelet inhibition with aspirin was replaced by clopidogrel. One week after discharge, the patient was readmitted for elective transcatheter aortic valve implantation. The intervention and the further follow-up were uneventful; the haemoglobin level remained stable.

Discussion

Our case highlights the classic clinical presentation of Heyde's syndrome, which is defined by the association of calcified aortic stenosis and gastrointestinal bleeding due to angiodysplasia. The syndrome was named by general practitioner Edward C. Heyde, whose clinical observation was published in a brief letter to the editor of the *New Eng-*

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land Journal of Medicine in 1958. Heyde appreciated the printing of his letter and anticipated that "it may stimulate some replies or statistical studies". In the long period since Heyde's observation, several studies have been conducted to detect the explanatory pathophysiological missing links. Current data suggest that Heyde's syndrome is due to an acquired form of von Willebrand Syndrome (aVWS), with loss of high molecular weight multimers [1].

In the case of our patient, oral anticoagulation was stopped owing to recurrent gastrointestinal bleeding and replaced by aspirin. To prevent atrial thromboembolism, a left atrial appendage closure was performed. Since gastrointestinal bleeding persisted, antiplatelet therapy with aspirin was replaced by clopidogrel, as two studies showed a significant difference in the frequency of gastrointestinal bleeding favouring clopidogrel [2, 3]. In one of the studies, a daily intake of aspirin 325 mg was compared with 75 mg clopidogrel. However, nearly 1000 patients need to be treated with clopidogrel instead of aspirin (costing about 1 million dollars) to prevent one event of relevant gastrointestinal bleeding under aspirin. There was no difference in the frequency of bleeding in general.

The von Willebrand factor (VWF) is a multifunctional, large glycoprotein with important functions in primary haemostasis. In patients with aortic valve stenosis, elevated shear stress leads to a structural change of VWF multimers, which allows proteolytic cleavage by the plasma protease ADAMTS13. Consequently, the multimers decrease in size and lose their important role in maintaining optimal haemostasis. A VWF deficiency therefore leads to elevated bleeding tendencies [1]. The assumption that high shear stress is a cause of aVWS, suggests that other cardiovascular disorders with elevated shear forces from a left ventricular assist device and a broad range of congenital and acquired cardiac defects can also possibly lead to augmented bleeding complications [4]. Intravascular haemolysis has been described in patients with prosthetic and dysfunctional native aortic valves and it has been suggested that the severity of intravascular haemolysis is associated with the transvalvular flow velocity [5]. In our patient, intravascular haemolysis was unlikely to be the main cause of the anaemia since total bilirubin and the absolute reticulocyte count on admission were within reference range (3 µmol/l, reference range <21 µmol/l and 87.8 10^9/l, reference range 25.0–105 10^9/l, respectively) and lactate dehydrogenase measured before elective transcatheter aortic valve implantation was not elevated (205 U/l, reference range <214 U/l).

It is as yet unknown why the typical bleeding occurs within gastrointestinal angiodysplasias. Some authors assume a high prevalence of angiodysplasia in elderly people due to vascular aging (irrespective of aVWS), whereas other authors have suggested that VWF plays a role in the suppression of angiogenesis [6]. A case report was published which described persistent gastrointestinal angiodysplasia 6 months after aortic valve replacement and normalised high molecular weight VWF levels. The authors suggested that there could be unknown factors, other than decreased VWF multimers, linked to the aetiology of gastrointestinal angiodysplasia [7]. Although such discussions are of pathophysiological interest, we would like to emphasise that the only permanent treatment is a correction of the mechanical defect [8].

Laboratory assessment to diagnose aVWS includes the measurement of VWF activity, VWF antigen and factor VIII. Since these assays are frequently normal in patients with aortic stenosis and aVWS, VWF multimer analysis using protein electrophoresis remains the diagnostic gold standard [9]. When performing laboratory testing it should be noted that VWF is an acute phase protein (VWF is found to be elevated in inflammatory condition or stress) [10]. Interestingly, laboratory testing was performed in our patient due to suspected Heyde's syndrome 1 year prior to the current presentation. Due to normal levels of VWF and a normal VWF functional/antigenetic ratio, Heyde's syndrome was formally ruled out. However, since VWF multimeric analysis was not performed by protein electrophoresis, the diagnosis was – at least in retrospect – possibly missed. In such cases, we recommend a multidisciplinary team approach with the involvement of a haematologist with expertise in haemostasis and coagulation.

We do not advocate laboratory testing for aVWS in all patients with aortic stenosis. However, it should be recommended for patients with suspected aVWS prior to major surgery, other interventions with elevated risk of bleeding, or if they have a clear clinical bleeding tendency. Furthermore, we recommend laboratory testing in selected patients with recurrent gastrointestinal bleeding who otherwise do not qualify for aortic valve replacement based on the cardiac defect alone. In selected cases, severe bleeding due to aVWS may represent a sufficient indication for aortic valve replacement independent of cardiopulmonary symptoms [11]. Based on the investigations from Blackshear and colleagues, we further recommend measuring VWF multimers in patients with recurrent gastrointestinal bleeding who have already undergone aortic valve replacement [12]. It should be remembered that elevated shear forces due to prosthetic valve dysfunction produce enough stress to lead to a proteolytic loss of high molecular weight VWF multimers. This association is known as Waring Blender syndrome [13]. As such, testing for aVWS might indicate a dysfunctional device. In patients with severe aortic stenosis, transcatheter aortic valve implantation leads to a reversal of VWF abnormalities and reduction in bleeding [14]. The presence of unexplained anaemia, occult bleeding and recurrent gastrointestinal bleeding without an obvious source should raise the suspicion of Heyde's syndrome.

The clinical management of patients with aortic valve stenosis and acute gastrointestinal bleeding due to aVWS is challenging and requires an interdisciplinary approach. Gastrointestinal bleeding should be treated with local endoscopic or interventional radiologic procedures. The isolated administration of packed red blood cells and other blood components (fresh frozen plasma, fibrinogen, etc.) according to the blood results is often insufficient to control active bleeding. The antifibrinolytic agent tranexamic acid may provide an additional benefit. Other options are VWF concentrates alone or in combination with other modalities (e.g., desmopressin, immune globulin, recombinant activated factor VII, antiangiogenetic drugs in the case of angiodysplasias, etc.). As soon as the bleeding has

stopped, it is crucial to discuss definitive treatment options to repair the mechanical defect [11].

Disclosure statement

No potential conflict of interest relevant to this article was reported.

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