CASE REPORT

Heyde's syndrome: exploring the link between aortic stenosis and an acquired bleeding disorder

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SUMMARY

Heyde's syndrome was first proposed in 1958. It refers to gastrointestinal haemorrhage resulting from a combination of aortic stenosis with angiodysplasia. This report explores the case of a 93-year-old lady who was admitted to hospital following a neck of femur fracture. She suffered from multiple comorbidities including renal failure and congestive heart failure secondary to critical aortic stenosis. As an inpatient she suffered an exacerbation of both her heart and renal failure postoperatively. A week later she suffered from heavy upper gastro-intestinal bleeding, which failed to respond to pharmacological and endoscopic therapies as well as angiographic embolisation. The pathophysiology of Heyde's syndrome: an acquired von Willebrand deficiency syndrome has a much wider impact than was commonly thought, both in terms of how common it is and in how the association may be extrapolated to a wide range of bleeding disorders, rather than simply angiodysplasia associated gastrointestinal haemorrhage.

BACKGROUND

This case is important as it facilitates exploration of a widely known but poorly understood association between aortic valve stenosis and gastrointestinal (GI) bleeding. It highlights that the mechanism of bleeding in Heyde's syndrome¹: an acquired von Willebrand Deficiency is likely to play a much wider role in mucosal surface bleeding, than just within the context of angiodysplasia. Clinicians should be aware of the association and its wider implications including when it should be considered and how it should be managed.

Aortic stenosis is the most common valvular disease with estimates as to its prevalence being as high as 5% in individuals aged over 65.² Critical aortic stenosis may afflict over 5% of individuals surviving to very old age.³ Risk factors for aortic valve disease are the same as for coronary artery disease and other atherosclerotic conditions. As these disorders and surviving in very old age becomes more common so does the likelihood that aortic valve disease will become more prevalent. Hence awareness and the ability to manage its complications are becoming increasingly important.

It also demonstrates a wide variety of complications that can arise from severe aortic stenosis: renal failure, congestive heart failure, chest pain, syncope, the dangers of anaesthesia as well as the risk of GI bleeding.

CASE PRESENTATION

A 93-year-old lady with a background of multiple comorbidities including aortic stenosis, congestive

heart failure, hypertension, atrial fibrillation, hypothyroidism, chronic kidney disease and dementia presented to the A&E department following a fall and subsequent inability to stand owing to severe right hip pain. She was rapidly diagnosed with fracture of the right neck of femur.

The day following her admission she underwent an emergency right hemiarthroplasty under spinal anaesthesia. During recovery her postoperative blood pressure dropped down to as low as 48/31 mm Hg. This was aggressively fluid resuscitated. The next day biochemical findings showed a rapid deterioration in her renal function. She subsequently developed marked pulmonary oedema with worsening breathlessness owing to the rapid fluid resuscitation.

She was reviewed by the renal team which felt that she had developed prerenal, acute kidney injury secondary to the episode of postoperative hypotension. Over the subsequent week the heart and renal failure proved difficult to control. She experienced episodes of breathlessness, daily central chest pain and occasional syncope on the ward. The cardiology team was subsequently involved and requested an Echo. It showed critical calcific aortic stenosis with an aortic valve area of 0.3 cm² and a peak gradient over the valve of 120–130 mm Hg, along with a severely hypertrophied left ventricle. Mild-to-moderate mitral regurgitation was also present but she had a remarkably preserved ejection fraction of 73%. The cardiology team felt that the patient's symptoms could be attributed to critical aortic stenosis, pulmonary hypertension and fluid overload. They started her on aspirin and discussed the feasibility of aortic valve replacement (AVR) or transcatheter aortic valve implantation (TAVI) within their team. They ultimately concluded that she was too frail for an AVR and that she would not be a candidate for TAVI on the basis of comorbidity and poor local service availability.

A week following the cardiology review and initiation of aspirin, the patient developed recurrent episodes of heavy melaena. Aspirin and alendronic acid were subsequently stopped and she was taken for upper GI endoscopy. The endoscopy showed gastritis with a small superficial ulcer in the first part of the duodenum (D1) but no evidence of a recent upper GI bleed. Unfortunately the bleeding did not stop following cessation of the likely precipitating medications and starting omeprazole. A few days after the first endoscopy, the second was performed. This time the blood was found oozing from the D1–D2 junction. The site was injected with adrenaline and an omeprazole infusion was given over the subsequent 72 h.

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Figure 1 Angiography: right gastroduodenal artery pre-embolisation.

In spite of two endoscopies the melaena continued. The interventional radiology team was consulted and a CT abdomen and pelvis, arterial phase demonstrated an image consistent with bleeding in D2. The patient was subsequently treated with radiologically guided embolisation of the gastroduodenal artery (GDA, see figures 1 and 2—before and after images of the coeliac axis with embolisation).

In total, she required 10 units of red blood cells in just over a week, unfortunately even with these and the procedures previously described, the bleeding could not be stopped. The decision was ultimately made to focus on a palliative approach. She passed away a few days later.

INVESTIGATIONS

Echocardiogram

This showed a severely hypertrophied left ventricle. The systolic function was preserved with an ejection fraction of 73%. The right ventricle also demonstrated hypertrophy and dilation. Both atria were severely dilated. Doppler imaging showed critical calcific aortic stenosis with a peak gradient of about 120–130 mm Hg (variable secondary to AF). The aortic valve area was estimated to be only 0.3 cm².

In addition there was shown to be severe tricuspid, mild-to-moderate mitral and moderate pulmonary regurgitation.

Figure 2 Angiography: right coeliac trunk postembolisation.

First oesophagogastroduodenoscopy

This demonstrated gastritis and duodenitis with a small superficial ulcer in D1. There was, however, no evidence of a recent GI bleed. The campylobacter-like organism (CLO) test was later shown to be negative.

Second oesophagogastroduodenoscopy

The previous small duodenal ulcer had healed; some blood was seen to be oozing from the D1–D2 junction. Adrenaline was injected into D1–D2.

CT abdomen and pelvis

The arterial phase examination demonstrated linear high attenuation in D2 in keeping with active haemorrhage. The portal phase study subsequently confirmed the presence of contrast medium in D2–D3.

Angiography

No active bleeding was actually seen especially from the GDA which had seemed to be the likely bleeding point from the previous CT. It was felt that her continuing low systolic blood pressure (SBP) of 85 mm Hg may have meant there was not a high enough blood pressure to visualise the bleeding point. The GDA was embolised with four coils.

OUTCOME AND FOLLOW-UP

Unfortunately the patient continued to deteriorate. After discussion with her family it was felt that the invasive procedures were only serving to cause further distress. She was placed on a care pathway for the dying and passed away a few days later.

DISCUSSION

This case study raises many points for discussion and reflection. The two main themes I would like to focus on are (1) how the proposed pathophysiology of Heyde's syndrome may have played an important role in the severity of this lady's GI haemorrhage and (2) how the use of spinal anaesthesia rather than a general anaesthesia likely placed this lady at significant risk of postoperative ischaemic complications.

Heyde's syndrome

What is the proposed pathophysiology of Heyde's syndrome?

The current prevailing hypothesis was proposed by Warkentin *et al*⁴: Von Willebrand Factor (vWF) is a multimeric glycoprotein that circulates in the blood and binds to factor VIII. VWF has an important role in primary haemostasis. It is normally broken down at a steady rate by ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin motifs), a metalloproteinase. Over a stenosed aortic valve vWF multimers are subjected to high shear stresses that change their structure and render them more susceptible to proteolysis by ADAMTS13 resulting in depletion of vWF. This results in an acquired bleeding disorder: von Willebrand syndrome type 2A (vWS-2A). Corroborative studies have shown a strong correlation between the level of shear stress over the aortic valve and a lower level of serum vWF.⁵

While Warkentin's theory has strong evidence behind it and explains an increased rate of bleeding in aortic stenosis a causal link between angiodysplasia and aortic stenosis remains controversial. The main theory is that any association is likely coincidental, in that both angiodysplasia and aortic stenosis represent age-related degenerative processes, but there are several alternative hypotheses. It has been suggested that there may be a genetic predisposition to both angiodysplasia and aortic stenosis in the

context of a linking connective tissue disorder. In addition the hypoxaemic hypothesis proposes that hypoxaemia from aortic stenosis and heart failure predispose to angiodysplasia formation.

Warkentin's theory can be extended beyond the Heyde syndrome association. Shear stress can be found in other conditions such as hypertrophic cardiomyopathy (HCM), ventricular septal defects and patent ductus arteriosus which have also been shown to predispose to vWF deficiency type 2A and GI bleeding.^{6,7} In addition non-GI bleeding disorders have been linked with aortic stenosis for example, recurrent epistaxis.⁸ In one study of patients with critical aortic stenosis 20% suffered from cutaneous or mucosal bleeding with 70–90% of this group having haematological abnormalities correlating with the degree of aortic stenosis.³

Can acquired vWS-2A have been a factor in this patient's GI bleeding?

This lady had critical aortic stenosis with GI bleeding that although may have been initiated by aspirin, alendronic acid and the stress of a major surgical operation failed to cease in spite of maximal proton pump inhibitor therapy, two episodes of endoscopy and embolisation of the likely arterial source.

Unfortunately the presence of vWS-2A was never confirmed as she passed away prior to further investigation. From the information hereinbefore I feel that it is likely to have played a causal role in her decline.

How is vWS-2A investigated?

The gold standard investigation is electrophoresis of vWF multimers,⁹ there may also be a prolonged bleeding time and decreased ristocetin cofactor activity. The APTT and factor VIII levels are not normally affected. Unfortunately the patient EH passed away before these tests could be performed, the basic coagulation tests were normal except for an increased prothrombin time.

How is Heyde's syndrome treated?

There are several potential treatment targets in Heyde's syndrome. Treating the aortic stenosis is regarded as the gold standard and has been shown to normalise vWS-2A syndrome. It has been used as an alternative strategy to GI surgery for uncontrollable GI bleeding. One small study looked at the outcomes in 91 patients with Heyde's syndrome—95% of patients who underwent surgical resection of angiodysplasia had an episode of rebleeding later. In contrast 93% of patients who had AVR (only a small minority of whom also had an intestinal resection) developed any episodes of further rebleeding in the subsequent 10 years.¹⁰ Other treatment targets include the angiodysplasia which can be endoscopically cauterised, angiographically embolised or surgically resected. VWS-2A deficiency can be targeted—coagulation factor replacement can be used but typically does not work well in the management of the acquired vWF deficiencies. Antifibrinolytics are another option. The final option in those not fit for more interventional procedures is a symptomatic approach with regular transfusions and iron replacement therapy.

Use of spinal anaesthesia in patients with severe aortic stenosis

As the aortic valve area decreases in size, the left ventricle needs to work harder in order to maintain cardiac output. The left ventricle hypertrophies in response, requiring a greater blood supply by the coronary arteries. Patients with aortic stenosis commonly suffer from angina as a result of increased demand provided by hypertrophied myocardial tissue in combination with likely atherosclerotic coronary vasculature.

Spinal anaesthesia produces profound peripheral sympathetic blockade, which markedly decreases systemic vascular resistance, reducing venous return to the heart and subsequently reducing cardiac output and myocardial perfusion. In addition, a compensatory tachycardia reduces the time the heart spends in diastole, thereby minimising coronary perfusion time and further impairing myocardial supply of oxygenated blood. Resulting ischaemia of myocardium and ventricular subendocardium contributes to impaired cardiac output. Reduced cardiac output leads to systemic hypotension and markedly reduced tissue perfusion of critical organs such as the kidneys and brain.

Spinal anaesthesia is the most likely cause of the profound postoperative hypotension in this patient. The resulting myocardial damage compounded with chronic heart failure contributed to refractory pulmonary oedema. The marked renal hypoperfusion in the context of chronic kidney disease and likely atherosclerotic renal vasculature resulted in acute tubular necrosis.

In the general population, multiple meta-analyses have been unable to determine a significant difference in morbidity or mortality comparing regional versus general anaesthesia in the context of adult hip fracture surgery.¹¹ Regional anaesthesia may reduce postoperative confusion and deep vein thrombosis, and general anaesthesia may reduce operative time, but there is insufficient evidence to suggest whether this is significant or not. Spinal anaesthesia, however, presents a clear risk to individuals with severe aortic sclerosis. Individuals with known aortic sclerosis, or clear clinical signs of an ejection systolic murmur, an absent second heart sound, and ECG signs of left ventricular hypertrophy and left heart strain should be highlighted to the anaesthetic team and spinal anaesthesia avoided.

Review of previous case reports

Multiple previous case reports have described Heyde's syndrome linking angiodysplasia with aortic stenosis, only a few have identified the potential for wider implications of von Willebrand 2A deficiency. Most recently Blackshear *et al*¹² demonstrated the presence of an acquired von Willebrand deficiency in association with HCM and Schödel *et al*¹³ demonstrated von Willebrand 2A deficiency presenting with epistaxis.

Learning points

- ▶ Critical aortic stenosis is very common in the elderly.
- ▶ Acquired von Willebrand syndrome: vWS-2A should be considered as a potential predisposing and perpetuating factor in gastrointestinal bleeding in people with severe aortic stenosis.
- ▶ In light of the high prevalence of the condition clinical management of GI bleeding secondary to angiodysplasia or other sources should consider vWS-2A and its causes when structuring further investigation and treatments. The gold-standard investigation of vWS-2A deficiency is vWF multimer electrophoresis—with the standard coagulation tests unlikely to show any abnormalities.
- ▶ VWS-2A deficiency should be considered in other instances of mucosal bleeding, for example epistaxis when there is a comorbid condition associated with high intravascular shear stress for example, aortic stenosis and hypertrophic cardiomyopathy.
- ▶ Spinal anaesthesia can cause profound hypotension in individuals with severe aortic stenosis. Patients with previously known aortic sclerosis, or clinical and ECG features of aortic stenosis should be highlighted preoperatively to anaesthetists and general anaesthesia used instead.

Competing interests None.

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