Recurrent gastrointestinal bleeding in a patient with Heyde syndrome with elevated factor VIII levels: A case report

Omar Al-Radaideh¹, Iyad Farouji¹, Hossam Abed¹, Hamid Shaaban¹,²

ABSTRACT

Heyde syndrome is the association between gastrointestinal (GI) bleeding from intestinal angiodysplasia (IA) and aortic stenosis (AS). Although the course of disease progression that links AS and GI bleeding has not been determined, overlaps among AS, intestinal dysplasia, and acquired von Willebrand’s syndrome is thought to result in GI bleeding. Proper repair of the aortic valve can result in significant improvement of GI bleeding and its recurrence. Herein, we are reporting this rare case, in which a patient with moderate AS on echocardiogram presents with recurrent GI bleeding from multiple IA in the setting of elevated factor VIII levels, to propose a theory that angiodysplasia could potentially develop due to intermittent, recurrent low-grade obstruction of submucosal veins at the level of the muscularis propria secondary to venous thrombosis related to elevated factor VIII levels.

Key Words: Angiodysplasia, aortic stenosis, case report, hemorrhage, heyde syndrome

INTRODUCTION

Heyde syndrome is a clinical syndrome described as gastrointestinal (GI) bleeding from previously latent intestinal angiodysplasia (IA) associated with aortic stenosis (AS).¹ A deficiency of high molecular weight (HMW) multimers of von Willebrand factor (vWF) (Type 2A von Willebrand disease) has been described in some of these cases.¹ The prevalence of Heyde syndrome is higher among elderly persons than among other age groups, suggesting that a degenerative process may be a significant factor in disease progression.² The main treatment approach for this syndrome is to replace the aortic valve with the goal of correcting the vWF abnormalities and a long-term resolution of GI bleeding.³ The pathophysiology of angiodysplasia is not well understood. However, a proposed theory is that the condition develops due to intermittent, recurrent low-grade obstruction of submucosal veins at the level of the muscularis propria. We report this case of Heyde syndrome with elevated factor VIII levels to propose a theory that these patients develop a recurrent localized submucosal venous thrombosis related to elevated factor VIII levels and this, in turn, results in venous obstruction which subsequently results in dilatation and tortuosity of the draining areas (i.e., submucosal vessels, venules, and superficial capillaries).

CASE REPORT

An 85-year-old female with a medical history of hypertension, coronary artery disease, heart failure with preserved ejection fraction, and history of multiple vascular malformations in the colon on the previous endoscopic evaluations that were done 2 years before admission, presented to the hospital with lower GI bleeding and shortness of

© 2021 International Journal of Critical Illness and Injury Science | Published by Wolters Kluwer - Medknow 253
breath. She was on aspirin 81 mg daily for coronary artery disease. The patient described multiple episodes of maroon-colored rectal bleeding starting 1 day before her admission. Initially, vital signs were within the normal limits in the emergency department. On her physical examination, vital signs blood pressure 130/80 mmHg, heart rate 90/min, respiratory rate 18/min, SaO₂ 98% on room air, temperature 99.1 degrees F° and there was a systolic murmur with a grade of 4/6 at the second right intercostal space with clear lung fields. Her pulmonary, cardiac, and abdominal examinations were unremarkable. No purpura, petechiae, or bruises were evident on examination of her skin. No fresh blood was noted on the digital rectal examination. Laboratory tests showed hemoglobin of 7.6(normal 12-15.5)g/L, hematocrit 24%(normal 39.4%–44.5%), platelets 170 (normal 150–400) × 10⁹/L, serum electrolytes were normal, creatinine 1.7 and her baseline is 0.8(normal 0.7–1.1)μmol/L, troponins were within the normal range and coagulation parameters (prothrombin time 11 s, partial thromboplastin time 27 s, and international normalized ratio 1.1). Moreover, as part of the workup of the shortness of breath, electrocardiography shows a ventricular premature complex with left axis deviation. A chest X-ray was done and it did not reveal any acute pathology. Transthoracic echocardiography revealed a normal left ventricular systolic function with an ejection fraction of 60%–65%, left atrium is mildly dilated, moderate AS with peak aortic valve gradient is 23 mmHg, calculated aortic valve area by the continuity equation is 1.1 cm² and severe pulmonary hypertension [Figure 1a and b].

The patient received two units of packed red blood cells, blood thinner (aspirin) was held, and she had a colonoscopy which revealed a few medium-sized localized angiodysplasia lesions that were actively bleeding in the cecum [Figure 2]. Hemostasis was achieved by successfully deploying clips on the bleeding vessel. In addition to that, multiple small-mouthed diverticula were found in the sigmoid and the descending colon with no evidence of bleeding. She did not require any anticoagulant reversal agents. A von Willebrand profile was ordered which revealed an elevated factor 8 activity 278% (Normal 56%–140%), elevated vWF Ag 286% (50%–200%), and normal VWF activity 193% (50%–200%). She remained hemodynamically stable for the next 2 days after the procedure and was discharged home with cardiology and gastroenterology follow-up.

**DISCUSSION**

We are reporting a rare case of a patient who presented with the clinical manifestations of Heyde syndrome, including GI bleeding associated with moderate AS and elevated factor VIII levels. This disease entity was first described in 1958 by Edward Heyde who was the first one to describe the association between chronic GI bleeding due to angiodysplasia and calcific AS.[1] In 1992, Warkentin et al. clarified the role of depletion of HMW multimers of vWF in the pathogenesis of Heyde syndrome.[5] Heyde syndrome is defined as a triad of AS, anemia due to bleeding from IA, and an acquired coagulopathy in a form of acquired Type IIA von Willebrand syndrome.[6] Refer to Table 1 for further characteristics of acquired VWD in comparison with hereditary VWD.

The acquired von Willebrand syndrome in patients with AS is explained by the mechanical disruption of von Willebrand multimers during turbulent passage through the narrowed valve and in addition to the interaction between the vWF with platelets that triggers platelet clearance. As it passes through the stenotic valve, vWF is subjected to high fluid shear stress that renders the multimers susceptible to cleavage by ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin Type 1 motif, member 13).[7,8] The severity of the vWF abnormality is related directly to the severity of the AS, which is measured by the mean transvalvular gradient.[9] One of the key features of Heyde syndrome is degenerative AS which represents the most prevalent valvular disease in Western countries.[10] It is more common in the elderly population and increases with age. While the prevalence is low in patients <60 years of age, it increases dramatically to approximately 10% in patients >80 years of age.[11,12] Angiodysplasia is also considered an age-related degenerative process, it is the most common vascular anomaly encountered in the GI tract and it is most often detected in patients older than 60 years.[13,14] It can occur anywhere in the GI tract but is most common in the ascending colon, particularly the cecum.[12] In a prospective study of colonoscopies of 1938 patients, typical angiodysplasia was found in 3% of cases, but 80% were asymptomatic. The sites of the highest prevalence of the lesions were the cecum (37%) and sigmoid colon (18%).[13]

The von Willebrand profile for our patient was not consistent with a diagnosis of acquired VWD. However, our patient did have elevated factor VIII levels. There are several studies reporting that high levels of factor VIII are associated with an increased risk of recurrences of thrombosis. Kraaijenhagen et al. found factor VIII levels ≥150 IU/dL in 57% of patients with recurrent venous thrombosis.[16] Kyrle et al. followed 360 patients

![Figure 1: (a and b) 2Decho images showing moderate aortic stenosis with peak aortic valve gradient 23 mm Hg, aortic valve area 1.1 cm²](image-url)
with venous thromboembolism and found a recurrence in 27% of patients with factor VIII levels >234% and in 9% of patients without elevated factor VIII levels. This led us to propose our theory that localized submucosal venous thrombosis secondary to elevated factor VIII levels may cause venous obstruction which subsequently results in dilatation and tortuosity of the draining areas (i.e., submucosal vessels, venules, and superficial capillaries). This would possibly explain why angiodysplasia often occurs in the right colon where wall tension is highest because this increased wall tension selectively compresses thin-walled veins compromised by the venous obstruction while allowing normal flow through the thicker-walled higher-pressure arterioles. Table 2 shows further characteristics and differences between acquired VWD and Heyde syndrome.

The most effective treatment for Heyde syndrome is aortic valve replacement (AVR) which usually improves clotting disorder and anemia. In one study, 91 patients were evaluated for AS and suspected chronic small bowel bleeding secondary to angiodysplasia, 16 of the patients underwent AVR for AS, during follow-up of 8–12 years, 15 had cessation of chronic GI blood loss. This fact supports the direct relationship between the severity of the angiodysplasia with the AS.

Table 2: Differences between Heyde syndrome versus von Willebrand disease

| Parameter                          | Acquired VWD | Inherited VWD |
|------------------------------------|--------------|---------------|
| Aortic stenosis                    | −/+          | +             |
| Angiodysplasia of the GI tract     | Normal/prolonged | Prolonged     |
| Activated partial thromboplastin time | Normal        | Normal        |
| PT                                 | Normal       | Normal        |
| WBC                                | Normal       | Normal        |
| Platelet count                     | Normal/except type 2 | Normal |
| Factor VIII: C                     | Normal       | Normal/low    |
| VWF: propeptide to VWF: Ag         | High         | High/normal/low |
| VWF: collagen binding              | Decreased    | Decreased     |
| VWF: collagen factor               | Decreased    | Decreased     |

VWD: Von Willebrand’s disease; GI: Gastrointestinal; PT: Prothrombin time; WBC: White blood cell; IDA: Iron deficiency anemia; PFA: Platelet function analyzer: VWF: Von Willebrand factor; VWF: Ag: VWF antigen; VWF: RC0: VWF ristocetin cofactor activity

Specifically the CARE guideline, during the conduct of this research project.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Pate GE, Mulligan A. An epidemiological study of Heyde’s syndrome: An association between aortic stenosis and gastrointestinal bleeding. J Heart Valve Dis 2004;13:713–6.
2. Chukwudum CA, Vera S, Sharma M, Varon J, Surani S. Heyde syndrome: A case report and literature review. Cureus 2020;12:e7896.
3. Alshuwaykh O, Krier MJ. A case of Heyde syndrome with resolution of gastrointestinal bleeding two weeks after aortic valve replacement. Am J...
Heyde syndrome and elevated Factor VIII level

4. Hudzik B, Wilczek K, Gasior M. Heyde syndrome: Gastrointestinal bleeding and aortic stenosis. CMAJ 2016;188:135-8.
5. Warkentin TE, Moore JC, Morgan DG. Aortic stenosis and bleeding gastrointestinal angiodysplasia: Is acquired von Willebrand's disease the link? Lancet 1992;340:35-7.
6. Massyn MW, Khan SA. Heyde syndrome: A common diagnosis in older patients with severe aortic stenosis. Age Ageing 2009;38:267-70.
7. Vincentelli A, Susen S, Le Tourneau T, Six I, Fabre O, Juthier F, et al. Acquired von Willebrand syndrome in aortic stenosis. N Engl J Med 2003;349:343-9.
8. Pareti FL, Lattuada A, Bressi C, Zanobini M, Sala A, Steffan A, et al. Proteolysis of von Willebrand factor and shear stress-induced platelet aggregation in patients with aortic valve stenosis. Circulation 2000;102:1290-5.
9. Blackshear JL, Wysokinska EM, Safford RE, Thomas CS, Stark ME, Shapiro BP, et al. Indexes of von Willebrand factor as biomarkers of aortic stenosis severity (from the Biomarkers of Aortic Stenosis Severity [BASS] study). Am J Cardiol 2013;111:374-81.
10. Iung B, Vahanian A. Epidemiology of valvular heart disease in the adult. Nat Rev Cardiol 2011;8:162-72.
11. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvar aortic stenosis. The Tromso study. Heart 2013;99:396-400.
12. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: A population-based study. Lancet 2006;368:1005-11.
13. Gunnaugsson O. Angiodysplasia of the stomach and duodenum. Gastrointest Endosc 1985;31:251-4.
14. Clouse RE, Costigan DJ, Mills BA, Zuckerman GR. Angiodysplasia as a cause of upper gastrointestinal bleeding. Arch Intern Med 1985;145:458-61.
15. Höchter W, Weingart J, Kühner W, Frimberger E, Ottenjann R. Angiodysplasia in the colon and rectum. Endoscopic morphology, localisation and frequency. Endoscopy 1985;17:182-5.
16. Kraaijenhagen RA, In't Anker PS, Koopman MM, Reitsma PH, Prins MH, van den Ende A, et al. High plasma concentration of factor VIIIc is a major risk factor for venous thromboembolism. Thromb Haemost 2000;83:5-9.
17. Kyrle PA, Minar E, Hirschl M, Bialonczyck C, Stain M, Schneider B, et al. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. N Engl J Med 2000;343:457-62.
18. King RM, Pluth JR, Giuliani ER. The association of unexplained gastrointestinal bleeding with calcific aortic stenosis. Ann Thorac Surg 1987;44:514-6.
19. Cappell MS, Lebwohl O. Cessation of recurrent bleeding from gastrointestinal angiodysplasias after aortic valve replacement. Ann Intern Med 1986;105:54-7.
20. Scheffer SM, Leatherman LL. Resolution of Heyde's syndrome of aortic stenosis and gastrointestinal bleeding after aortic valve replacement. Ann Thorac Surg 1986;42:477-80.