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Heyde Syndrome: An Unusual Cause of Gastrointestinal Bleeding

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Abstract

Heyde syndrome is a multisystem disorder characterized by the classical triad of aortic stenosis, gastrointestinal (GI) angiodysplasias, and acquired von Willebrand syndrome. GI angiodysplasias, common in older patients, are tortuous, thin-walled blood vessels seen in the mucosa or submucosa of the GI tract and are highly prone to rupture resulting in GI bleeds. In this case report, we describe an elderly female with a past medical history of end-stage renal disease and chronic anemia who presented to the emergency department (ED) with complaints of dark-tarry stools and associated abdominal cramping. Patient reported a history of dark-tarry stools and multiple blood transfusions in the past, secondary to severe anemia. An inpatient echocardiogram was performed, revealing severe aortic stenosis. Additionally, gastroenterology was consulted for esophagogastroduodenoscopy and colonoscopy, which were negative for active bleeding. About a year ago, the patient underwent capsule endoscopy at an outlying facility, which was positive for angiodysplasia. Therefore, due to high clinical suspicion, presence of aortic stenosis, and GI angiodysplasia, a platelet function assay was ordered. It was found to be abnormal, pointing to the presence of acquired von Willebrand syndrome. Hence, a diagnosis of Heyde syndrome was established. The patient gradually improved and was discharged with a follow-up appointment with the cardiologist for a possible transcatheter aortic valve replacement procedure. The patient underwent the procedure without complications, after which she did not report episodes of GI bleeding. In this case report, we discuss the presentation, pathophysiology, diagnostic approach, and management of patients with Heyde syndrome.

Keywords

aortic stenosis, gastrointestinal bleeding, von Willebrand disorder

Introduction

First described by Edward Heyde in 1958, Heyde syndrome (HS) is a multisystem disorder characterized by the classical triad of aortic stenosis (AS), angiodysplasia of the gastrointestinal (GI) tract, and the presence of an acquired von Willebrand syndrome (AVWS).[1,2] The exact incidence and prevalence of HS is currently unknown; however, it is assumed to be higher than the rates reflected in literature due to lack of awareness contributing to significant underreporting of the disease entity.[1] It commonly affects the older demographic, and a diagnosis of HS is usually seen in individuals ≥65 years of age.[1] However, in elderly (≥65 years) individuals, there is a high prevalence of both AS and angiodysplasia of the GI tract, making it difficult and challenging to establish a definitive diagnosis of HS. There are no specified treatment protocols in place for the management of patients with HS, but studies do report significant control of GI bleeding and resolution of symptoms after correction of the AS.[1] As per literature, aortic valve replacement, when compared with other treatment modalities, such as medical management, endoscopic intervention, or colon surgery, has demonstrated higher rates of cessation of recurrent GI bleeding.[1] Therefore, there is a general consensus among physicians for aortic valve replacement as the first-line management of HS. In this case report, we detail a classical case of HS, discuss the potential pathophysiological mechanism leading to the disease entity,

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describe the diagnostic approach and treatment strategies for these patients.

Case Report

A 73-year-old woman with a past medical history of end-stage renal disease on hemodialysis, chronic anemia, diabetes mellitus, and hypertension presented to the emergency department (ED) with a chief complaint of dark-tarry stool and abdominal cramping for 1 day. One day prior to the ED visit, the patient reported multiple episodes of abdominal cramping and a change in the color of her stools from light brown to dark and tarry. She also noted new-onset mild shortness of breath on exertion and significant fatigue for the same duration. The patient reported high compliance with all her medications and hemodialysis (3 days/week). She did not have associated abdominal pain, change in stool consistency, change on bowel or bladder habits, painful defecation, recent diarrhea, or sick contacts. She denied using over-the-counter pain medications. She denied recent fevers, chills, night sweats, weight loss, cough, chest pain, or leg swellings. However, the patient did report multiple hospital admissions in the past with the most recent hospitalization about 2 months prior for similar complaints of dark tarry stools and severe anemia requiring blood transfusion. She was a nonsmoker and did not use alcohol, marijuana, or other substances.

On examination in the ED, the patient was found to have a temperature of 98 °F, respiratory rate of 18 breaths/min with an oxygen saturation of 98%, heart rate of 100 beats/min, and blood pressure 90/60 mm Hg. Overall, she looked pale with cold extremities and weak peripheral pulsations in all limbs. An arteriovenous fistula with thrill was present on the left upper extremity. No peripheral edema was noted. On examination of the chest, normal breath sounds were heard with good air entry bilaterally, and a crescendo-decrescendo systolic murmur with maximum intensity at the right sternal border and radiation to the carotids was also noted. Abdominal examination revealed a soft, nontender, and nondistended abdomen with normal bowel sounds. Laboratory investigations revealed a critically low hemoglobin level of 5.2 g/dL (12.1-15.1 g/dL), hematocrit 15.9% (35.5% to 44.9%), white blood cell count 10.1×10^9/L (4.5 to 11.0×10^9/L), platelet count 266×10^9/L (150 to 400×10^9/L), and a high reticulocyte count of 4.4% (0.5% to 1.5%). The peripheral smear revealed polychromasia and schistocytes. The blood urea nitrogen was found to be 53 mg/dL, creatinine 6.3 mg/dL (baseline creatinine 3 mg/dL), and B-type natriuretic peptide (BNP) was noted to be 1880 pg/mL. Serum electrolytes, prothrombin time, activated partial prothrombin time, and international normalized ratio (INR) were within normal limits. The serum troponin was found to be elevated at 0.089 ng/mL; however, the electrocardiogram (EKG) was unremarkable. Chest X-ray demonstrated cardiomegaly and mild congestion bilaterally in the chest.

Due to the patient's critically low hemoglobin level, she received 2 units of packed red blood cells in the ED that led to an elevation of her hemoglobin level to 8.9 g/dL. A decision was made to admit the patient to an inpatient setting for further investigation into the cause of bleeding. Additionally, serial troponin level measurements were performed every 6 hours, which eventually down trended. Serial EKGs performed every 6 hours were also found to be unremarkable. An inpatient echocardiogram was obtained, which revealed a left ventricular ejection fraction of 50% to 55%, grade 1 diastolic dysfunction, and severe AS with an aortic valve area of 0.8 cm^2. Furthermore, gastroenterology was consulted for source control of the GI bleed. An esophagogastroduodenoscopy and colonoscopy were performed, both of which were negative for active bleeding; however, there was high suspicion for angiodysplasia that may have led to the patient's presentation. The gastroenterologist consulted on the case had a detailed discussion with the patient about capsule endoscopy as the next intervention to locate the source of the bleed. The patient reported that a capsule endoscopy had been performed a year ago at an outlying facility, and the results were available with her primary care provider (PCP). We reached out to the PCP who informed us that the patient had angiodysplasias throughout her GI tract. With a history of significant and recurrent GI bleeding secondary to the angiodysplasias and the presence of AS, a platelet function assay (PFA) was ordered. It was found to be abnormal pointing toward the presence of AVWS. Hence, a diagnosis of HS was established. During the hospital stay, the patient showed significant improvement with complete resolution of her presenting symptoms; therefore, the decision was made to discharge her home. The patient was scheduled to follow-up with her cardiologist for evaluation for transcatheter aortic valve replacement (TAVR) procedure for the AS. Additionally, she was also advised to follow-up with her PCP within 2 weeks of discharge from the hospital. Eventually, the patient underwent TAVR without complications, after which she did not report episodes of GI bleeding.

Discussion

Heyde syndrome, described by Dr Edward Heyde in the 1950s, is a disorder that involves multiple systems and is characterized by the presence of a classical triad that includes AS, acquired coagulopathy, or AVWS, and the presence of angiodysplasia in the GI tract.[3] The pathogenesis of AVWS is believed to be secondary to the increased sheer stress forces on the blood as it flows through a stenotic valve. These sheer forces induce significant conformational change in the high-molecular-weight (HMW) von Willebrand factors (vWF) subsequently exposing the A2 domain of vWF, which can be cleaved by ADAMST13, a well-known plasma protease.[4] As a result, the HMW vWF multimers are significantly smaller in size and less competent for hemostasis when compared with the larger vWF multimers.[4] Due to increased interactions between the vWF multimers and the platelets, there is increased degradation and clearance of these vWF.[5]

Furthermore, angiodysplasia in the GI tract, part of the triad of HS, are described as tortuous, thin-walled blood vessels that are believed to occur secondary to vascular aging. Bleeding angiodysplasias strongly reflect the presence of a hemostatic defect superimposed on the vascular disease.[4] Additionally, there is evidence in literature to suggest that vWF plays a role in the maintenance of vascular integrity apart from its role in hemostasis; hence, these smaller size vWF molecules may also directly contribute to the development of angiodysplasia.[6]

The presence of AS and angiodysplasia in the GI tract are commonly seen in older individuals. Therefore, establishing a definitive diagnosis of HS may be challenging. The exact incidence and prevalence of HS is currently unknown, but it is believed that the disease may be underdiagnosed due to lack of awareness about the disease entity; hence, the actual prevalence of HS in the general population may be far greater than that reflected in current literature. In literature, the prevalence of concurrent AS and GI bleeding has been reported to be as high as 40%.[2] However, some studies report lower prevalence rates.[2] Overall, HS is commonly seen in the older individuals and is believed to be an aging-related degenerative processes. Furthermore, as per literature, there are no known gender variations, and it has been established that the angiodysplasias may involve any segment of the bowel.[7]

In patients older than 65 years, a history or presence of concurrent AS and GI bleeding should prompt the clinician to suspect HS as a differential diagnosis. Additionally, iron-deficiency anemia may also be seen in these patients, secondary to prolonged blood loss through the GI tract. Other potential causes of iron-deficiency anemia, such as nutritional deficiency, celiac disease, malabsorption syndromes, and malignancy, should always be ruled out. Endoscopic interventions such as sigmoidoscopy or colonoscopy are indicated in these patients to help control the source of active bleeding if present and visualize the angiodysplasia in the GI tract. However, like our patient, these studies may be often be negative but that does not prove the absence of angiodysplasias. Hence, in patients where the initial investigations do not yield a diagnosis, capsule endoscopy is the next step to help establish diagnosis.[8] Furthermore, it has been recommended in literature to have a lower threshold for echocardiogram in patients with known arteriovenous malformations or in patients with nondiagnostic colonoscopies.[8] In cases with a high degree of clinical suspicion for HS, a screening test such as the PFA may be employed. The gold standard diagnostic test for AVWS is the vWF multimer assay that uses gel electrophoresis to differentiate the vWF based on the size of the multimers. Although the vWF multimer assay is more sensitive and specific, PFA is commonly preferred in clinical practice as it is faster and results are reported within a few hours.[1] In comparison, the results for the multimer assay may typically take up to 7 to 10 days to be reported.[1] Other tests used to diagnose AVWS includes, from least sensitive to most sensitive, vWF antigen level, vWF ristocetin cofactor activity, skin bleeding time, PFA-100 closure time, and gel electrophoresis.[8]

Numerous treatment modalities are available for HS; however, there are no specific treatment protocols in place for management. As per current literature, there is consensus among physicians for aortic valve replacement as the first-line management strategy for HS. Like our case, studies report significant resolution of the acquired clotting disorder and anemia after a successful TAVR in patients with HS.[8] Aortic valve replacement, when compared with other treatment modalities, such as medical management, endoscopic intervention, or colon surgery, has demonstrated higher rates of cessation of recurrent GI bleeding in these patients.[1] Although in a specific subset of patients surgical intervention, including intestinal resection, may help in the resolution of symptoms, it is worth noting that surgical interventions have their own set of complications. Additionally, the GI bleeding may persist from other segments of the bowel postsurgery.

Although aortic valve replacement is the most preferred therapy for patients with HS, providers must be cautious and due consideration should be excised for the prescription of antiplatelet and oral anticoagulant agents as they may increase the risk of GI bleeding.[2] When compared with the conventional invasive surgical valve replacement, TAVR has demonstrated excellent results and is quickly becoming the most preferred method of valve replacement. For patients who are not surgical candidates or those with numerous comorbidities placing them at a high risk for surgical intervention, TAVR is always preferred.[9] Additionally, for patients who decline TAVR or those who are not candidates for valve replacement, medical management becomes the primary treatment approach.[8] It consists of oral iron supplementation and/or regular blood transfusions.[8] Moreover, a combination therapy with estrogen and progesterone may also be used to decrease bleeding from angiodysplasia.[5] The mechanism of this combination therapy is currently unknown.[5] Furthermore, endoscopic interventions with laser therapy may also be considered in cases with severe or recurrent hemorrhage.[8] Therapeutic options, such as VWF or factor VIII replacement, octreotide, and desmopressin, used in hereditary von Willebrand disease, are ineffective for HS.[10]

Conclusion

Heyde syndrome is a multisystem disorder characterized by aortic valve stenosis, angiodysplasia in the GI tract associated with blood loss anemia, and acquired von Willebrand disease. The exact incidence and prevalence of the disease is unknown, but it is commonly seen in older individuals. A history of recent or past GI bleeding and the presence of AS in patients typically older than 65 years should prompt the provider to consider HS as a potential differential diagnosis. Endoscopic interventions such as sigmoidoscopy or colonoscopy are indicated in these patients to identify the source of bleeding; however, a negative result does not rule out angiodysplasia.

Capsule endoscopy may be utilized in patients with negative colonoscopy. Although the gold standard testing to diagnose acquired von Willebrand disease is vWF multimer assay, PFA is usually preferred in clinical practice as the results are available within hours as compared with 7 to 10 days for vWF multimer assay. There are no specific guidelines on the management of HS, but consensus among physicians advocates for aortic valve replacement, preferably TAVR, as the first-line approach due to the significant decrease in GI bleeding after the procedure as reported in literature.

Health care providers need to be aware of the possibility of HS in older patients with AS, anemia, and/or angiodysplasia, as establishing the diagnosis of HS guides appropriate treatment. It is important to keep HS on the list of differentials in patients with GI bleeding after exclusion of other potential causes.

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Ethics Approval

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Informed Consent

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