CLINICAL VIGNETTE

Iron Deficiency Anemia in a Patient with Aortic Stenosis

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Introduction

Aortic valve stenosis (AS) is the most common cause of valvular heart disease, particularly in the aging population.[1] The association between AS and anemia due to gastrointestinal bleeding is and documented and was first described in 1958 by EC Heyde.[2] The triad of aortic stenosis, gastrointestinal bleeding due to angiodysplasia, and acquired type 2A von Willebrand disease is now referred to as Heyde syndrome. The diagnosis of Heyde syndrome requires a high degree of suspicion, and once recognized may be effectively treated with an aortic valve replacement.

Case

A 73-year-old female presented to the emergency room after a routine laboratory check by her primary care physician found a Hg of 4.5g/dL. Upon questioning, the patient did acknowledge one-month of increasing fatigue and dizziness. She denied any weight loss, abdominal pain, chest pain, shortness of breath, or dyspnea on exertion. She noted no vaginal bleeding, hematuria, hematochezia, or hematemesis but reported occasional episodes of melena.

Past medical history included hypertension and type II diabetes mellitus. She denied history of liver, gastrointestinal, or peptic ulcer disease and had never undergone colonoscopy. Home medications included amlodipine 5mg daily, aspirin 81 mg daily, and insulin basaglar 10 units QHS. She denied NSAID use, as well as tobacco, alcohol, or recreational drug use.

Presenting vital signs were T 37.0ºC, BP 154/66mmHg, HR 80 BPM, RR 20br/min, and oxygen saturation of 99% on room air. Notable physical exam findings included pale sclera, soft abdomen without tenderness to palpation, a grade 3/6 mid-systolic murmur best heard at the apex, and elevated jugular venous pressure of 10cm. Rectal exam showed dark stool without red blood. Laboratories were notable for a hemoglobin of 6.4g/dL, hematocrit of 20.7% with a mean corpuscle volume of 68.7fL. White blood cell count was 8.5kcumm with a normal differential and platelets were 397K/cumm. Iron studies included iron 12mcg/dL; iron binding capacity of 507mcg./dL, iron saturation of 2.4% and ferritin of 6ng/mL. Liver and renal function were normal.

By clinical evaluation, the anemia was best explained as iron deficiency anemia secondary to gastrointestinal bleed. Suggestive evidence included the patient's history of melena, iron studies, depressed MCV, and mild thrombocytosis. Normal indirect bilirubin made hemolysis less likely and myelodysplastic syndromes unlikely with normal cell count. Colonoscopy found three atriovenous malformations (AVM) in the cecum and ascending colon along with several sessile polyps (Figure 1). Endoscopy showed 4 AVM's in the stomach, duodenum, and jejunum (Figure 2). Transthoracic echocardiogram showed ejection fraction of 65%, and aortic valve annulus calcification, with valve area 0.88cm^2, mean gradient of 48mmHg, peak gradient 88mmHg, peak velocity of 4.7m/sec, and pulmonary arterial pressure of 33mmHg consistent with severe aortic stenosis.

The combination of severe aortic stenosis and multiple AVM's on EGD and colonoscopy raised concern for Heyde syndrome. She underwent aortic valve replacement with an Edwards 19mm bioprosthetic valve and on post-operative day 3 was discharged home. On follow up visits one year post aortic valve replacement the patient was doing well without any subsequent gastrointestinal bleeding or recurrence of iron deficiency anemia.

Discussion

The association between aortic stenosis and gastrointestinal bleeding was first described by EC Heyde in 1958.[2] In a letter to the editor of the New England Journal of Medicine, he described "at least 10 patients with calcific aortic stenosis who had massive gastrointestinal bleeding for which we could discover no cause." The same year, Goldman reviewed 37,423 cases of gastrointestinal bleeding and found that bleeding was three times higher than expected in patients with Aortic stenosis.[3] While certain aspects of this association remain controversial, the triad of aortic stenosis (AS), acquired coagulopathy due to Type 2A von Willebrand disease (2A-VWD), and gastrointestinal bleeding due to angiodysplasia has been commonly referred to as Heyde syndrome.

Several notable studies have provided evidence further strengthening the relationship between these findings.[4] King et al. described resolution of gastrointestinal bleeding in 14 patients with AS following valve replacement (AVR).[5] Nearly concurrently, two separate groups reported loss of high-molecular-weight von Willebrand multimers in patients with AS, which is the hallmark of Type 2A-VWD.[4] The combination of these findings led to the hypothesis that Heyde syndrome is

a form of acquired von Willebrand disease resulting in gastrointestinal bleeding and due to AS. Given that AS is the most common valvular heart disease affecting 2% and 4% of adults above the age of 65 and 85 years, respectively, familiarization and recognition of Heyde syndrome is of particular importance.[1]

The role of von Willebrand disease in AS and GI bleeding was first described in 1992 by Warkentin et al.[6] This group hypothesized that the cause of bleeding in patients with aortic stenosis may be due to the proteolysis of von Willebrand multimers under high sheer stress as it passes through the stenotic valve. This lysis reduces the amount of the largest and most active von Willebrand multimers.[6] The prevalence and cause of the association between aortic stenosis and vWS-2A was examined by Vincentelli et al, who reported skin or mucosal bleeding in 21 percent of the studied patients with severe aortic stenosis. Additionally, they found that platelet-function abnormalities, decreased von Willebrand factor collagen-binding activity, and/or the loss of the largest multimers was present in up to 92 percent of the studied patients. These findings correlated significantly with the severity of aortic valve stenosis.[7]

Most authors have argued that the GI bleeding associated with Heyde syndrome is due to an acquired von Willebrand disease in the setting of angiodysplasia, which is commonly seen in the aging patient. However, some evidence exists for an intrinsic vascular diathesis in younger patients with von Willebrand disease. This correlation is thought to be due to platelet dysfunction, which negatively affects the role of platelets in maintaining capillary integrity. Therefore, it is possible that the Type 2A-VWD seen in Heyde syndrome might not only cause bleeding due to existing gastrointestinal AVMs, but may have an active role in creating them.[4]

The diagnosis of Heyde syndrome requires a high degree of suspicion. In elderly patients with aortic stenosis and evidence of blood loss including hematochezia, melena, or new iron deficiency anemia, Heyde syndrome should be suspected. The presence of angiodysplasia or an absence of readily apparent cause of gastrointestinal bleeding on colonoscopy will also support the diagnosis of Heyde syndrome. Alternatively, patients presenting with gastrointestinal bleeding warrant a careful cardiovascular exam for findings consistent with AS, and there should be a low threshold for obtaining an echocardiogram in these patients. Gel electrophoresis may be used to establish an absence of large vWF multimers consistent with Type 2A-VWD and Heyde syndrome.[6,8]

The treatment of Heyde syndrome is replacement of the aortic valve. Aortic valve replacement (AVR) has been shown to be 93% effective in a retrospective study of 91 patients with presumed Heyde syndrome.[5] By comparison, patients who underwent surgical resection of AVM's, including some with bowel resection, had cessation of bleeding in only 5% of cases. While surgical AVR is considered the "gold standard" for treatment of AS, one single-center retrospective study showed that transcatheter aortic valve implantation (TAVI) may also be effective for treatment of Heyde's syndrome in patients with high risk for surgical AVR.[9] While this small study lacked a control group or measurements of vWF multimer levels, all 37 patients who underwent successful TAVI had no recurrence of bleeding. Blood transfusions, intravenous fluids, and DDAVP may be needed perioperatively.[10] Patients either unwilling or unable to undergo AVR may be managed conservatively with iron supplementation and blood transfusions when necessary.[3]

Conclusion

The relationship between aortic stenosis, gastrointestinal bleed, and acquired von Willebrand syndrome type 2A is well documented and is commonly known as Heyde syndrome. Patients of advanced age with either unexplained gastrointestinal bleed or aortic stenosis should be evaluated for the possible existence of this triad. Correction of the disorder is through aortic valve replacement and typically leads to long term resolution of bleeding.

Figures

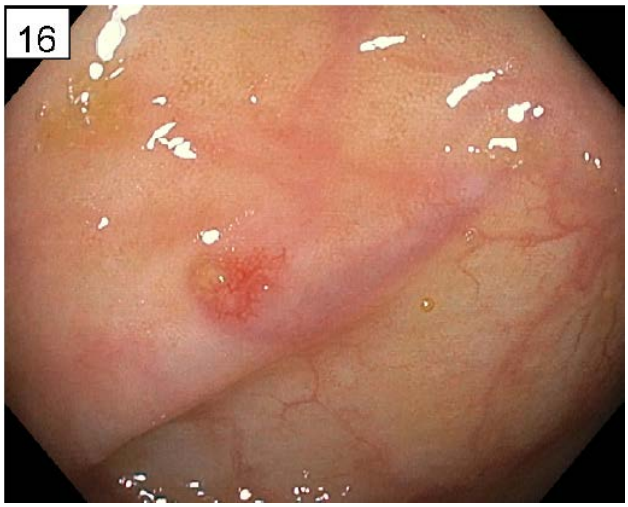

Figure 1. Atriovenous malformation in the ascending colon

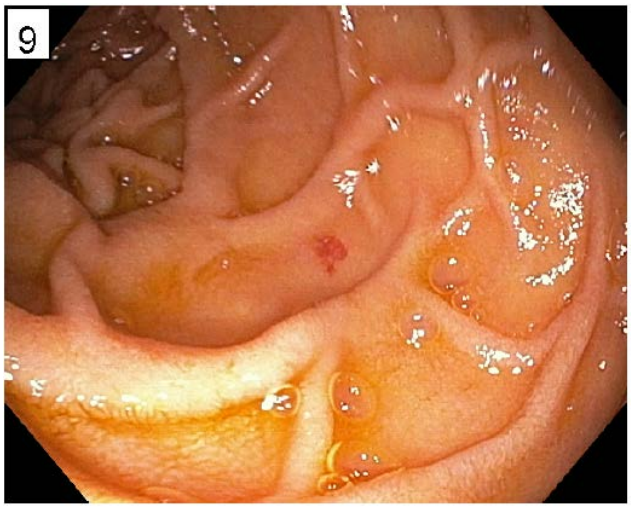

Figure 2. Gastric atriovenous malformation

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