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Gastroenterology I

Heyde Syndrome: An Underrecognized Cause of Gastrointestinal Bleeding in Patients with Aortic Stenosis: A Three-Case Series

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Abstract | **Case Series**

Heyde syndrome is a rare condition characterized by severe aortic stenosis and gastrointestinal bleeding from angiodysplasia, associated with an acquired type 2A von Willebrand syndrome. We report three cases: two men and one woman (mean age 70) with severe aortic stenosis (mean valve area 0.6 cm²; mean gradient 65 mmHg) presenting with recurrent gastrointestinal bleeding and iron-deficiency anemia. Endoscopy revealed colonic angiodysplasias in the men, while capsule endoscopy detected jejunal angiodysplasia in the woman. High-molecular-weight von Willebrand factor multimers were reduced in two patients. Despite argon plasma coagulation, bleeding persisted, and all underwent aortic valve replacement, which addressed the underlying hemodynamic abnormality. Heyde syndrome should be suspected in patients with aortic stenosis and unexplained gastrointestinal bleeding. Valve replacement usually resolves bleeding, but persistence may occur, highlighting the need for careful follow-up and a multidisciplinary approach.

Keywords: Heyde syndrome, aortic stenosis, gastrointestinal bleeding, angiodysplasia, von Willebrand factor.

INTRODUCTION

Heyde syndrome is a rare condition characterized by the association of severe aortic stenosis and gastrointestinal bleeding due to angiodysplasia. Its pathophysiology is primarily linked to an acquired type 2A von Willebrand syndrome, in which high shear stress across the stenotic valve leads to loss of high-molecular-weight von Willebrand factor multimers, impairing hemostasis. Clinically, patients often present with recurrent gastrointestinal bleeding and iron-deficiency anemia, which can complicate the management of aortic stenosis. Aortic valve replacement usually resolves bleeding, although persistent hemorrhage may occur in some cases. We report three cases of Heyde syndrome to highlight the diagnostic challenges and emphasize the importance of early recognition and appropriate management.

CASE SERIES

We report three cases of Heyde syndrome to enrich the current literature and enhance awareness among clinicians regarding this rare but clinically significant entity. For each patient, comprehensive data were collected, including epidemiological characteristics (age, sex), relevant comorbidities, the severity of aortic stenosis (measured valve area and mean transvalvular gradient), diagnostic approaches used to identify the source of gastrointestinal bleeding, and laboratory parameters, particularly hemoglobin levels and high-molecular-weight multimers of von Willebrand factor.

The study cohort consisted of two men and one woman, with a mean age of 70 years. All patients presented with severe aortic stenosis, with a mean valve area of 0.6 cm² and a mean transvalvular pressure gradient of 65 mmHg. Cardiovascular comorbidities were prevalent: all patients had systemic hypertension, two had a history of atrial fibrillation, and one had documented coronary artery disease. Clinically, all three patients experienced recurrent episodes of rectal bleeding, accompanied by severe iron-deficiency anemia necessitating multiple blood transfusions, highlighting the significant morbidity associated with this condition.

Endoscopic evaluation revealed angiodysplastic lesions in both male patients, localized in the cecum and ascending colon. In the female patient, initial conventional endoscopy failed to detect lesions; however, subsequent capsule endoscopy identified a jejunal angiodysplasia, underscoring the importance of advanced diagnostic modalities in detecting small bowel

sources of bleeding. Despite several sessions of argon plasma coagulation aimed at hemostasis, persistent bleeding was observed. Laboratory analysis demonstrated a reduction in high-molecular-weight von Willebrand factor multimers in two patients, consistent with the pathophysiological mechanism of acquired type 2A von Willebrand syndrome. All three patients ultimately underwent aortic valve replacement, addressing the underlying hemodynamic abnormality contributing to both bleeding and coagulation defects.

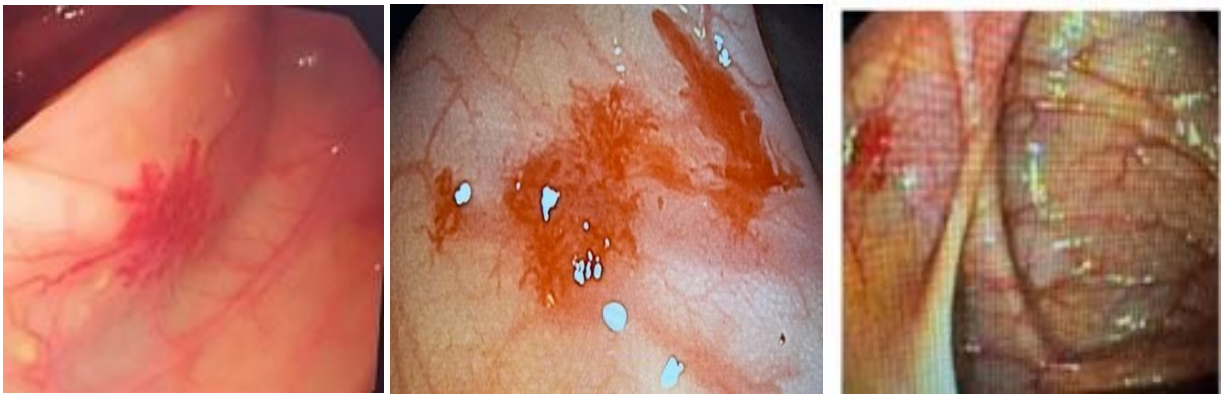

Figure 1: Angiodysplasia of the colon

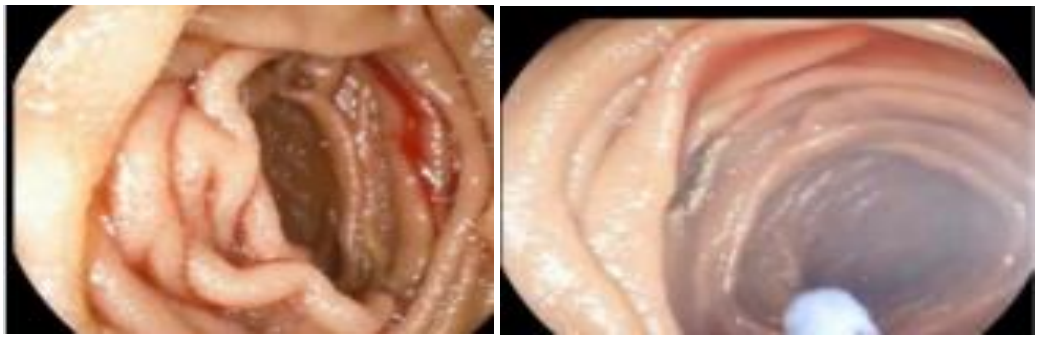

Figure 2: Argon plasma coagulation made for jejunal angiodysplasia

DISCUSSION

Heyde syndrome is a complex clinico-pathological entity characterized by the association of aortic stenosis (AS), gastrointestinal bleeding due to angiodysplasia, and acquired von Willebrand syndrome (AVWS). Since its first description by Edward C. Heyde in 1958, this association has been widely debated regarding its pathophysiological basis and optimal management.

1. Epidemiology and Clinical Association

Heyde syndrome primarily affects elderly patients, reflecting the increasing prevalence of degenerative AS and gastrointestinal angiodysplasia with advancing age. The prevalence of gastrointestinal bleeding in patients with AS ranges from 7% to 21%, while angiodysplasias are reported in 20% to 40% of cases [2,3].

In our series, the mean age of 70 years and the presence of cardiovascular comorbidities (hypertension, atrial fibrillation, and coronary artery disease) are consistent with the literature. These comorbidities may further increase bleeding risk, particularly in patients receiving anticoagulant or antiplatelet therapy.

2. Pathophysiology: Central Role of von Willebrand Factor

The main pathophysiological mechanism underlying Heyde syndrome is an acquired type 2A von Willebrand syndrome. High shear stress across the stenotic aortic valve induces conformational changes in von Willebrand factor (vWF), making it more susceptible to proteolysis by ADAMTS13. This results in a loss of high-molecular-weight multimers, which are essential for normal platelet adhesion and primary hemostasis [4,5].

This hemostatic defect explains the increased tendency for bleeding, particularly from fragile vascular lesions such as angiodysplasias. Additionally, experimental studies suggest that vWF plays a regulatory role in angiogenesis; its deficiency may promote the development of angiodysplastic lesions, creating a vicious cycle between vascular proliferation and bleeding [6].

In our study, the reduction of high-molecular-weight vWF multimers in two patients supports this mechanism, although this abnormality is not consistently observed in all cases, as also reported in the literature.

3. Localization and Characteristics of Angiodysplasia

Angiodysplasias associated with Heyde syndrome are most commonly located in the right colon (cecum and ascending colon) and the small intestine [7]. This distribution may be explained by local hemodynamic factors, including higher wall tension and relative hypoxia, which favor vascular dilation.

In our series, two patients had right-sided colonic lesions, while one patient had jejunal angiodysplasia detected only by capsule endoscopy, highlighting the importance of this modality in evaluating obscure gastrointestinal bleeding.

4. Diagnostic Approach

The diagnosis of Heyde syndrome relies on a combination of clinical, biological, and imaging findings. The classical triad includes:

- Severe aortic stenosis
- Recurrent gastrointestinal bleeding
- Abnormalities in von Willebrand factor

However, this triad is not always complete, making diagnosis challenging in some cases. Specific laboratory testing, particularly multimer analysis of vWF, remains limited in routine clinical practice.

Upper and lower gastrointestinal endoscopy are first-line investigations but may fail to identify the bleeding source, especially in small bowel lesions. In such cases, capsule endoscopy and device-assisted enteroscopy significantly improve diagnostic yield [8].

5. Therapeutic Management

5.1 Endoscopic Treatment

Endoscopic therapies, particularly argon plasma coagulation (APC), are commonly used as first-line treatment to control bleeding. However, they are associated with a high rate of recurrence, as observed in our patients [9].

5.2 Aortic Valve Replacement

Aortic valve replacement (AVR) remains the cornerstone of treatment, as it corrects the underlying hemodynamic abnormality responsible for vWF degradation. Several studies have demonstrated rapid normalization of vWF multimers following valve replacement, with cessation of bleeding in 70% to 90% of cases [10,11].

Transcatheter aortic valve implantation (TAVI) has emerged as an effective alternative in high-risk surgical patients, showing comparable outcomes in terms of bleeding control [12].

5.3 Persistence of Bleeding After Valve Replacement

Despite these favorable outcomes, persistent or recurrent bleeding occurs in approximately 10% to 30% of cases. Several mechanisms may explain this phenomenon:

- Persistence of pre-existing angiodysplastic lesions
- Development of new vascular lesions
- Incomplete correction of vWF abnormalities
- Concomitant factors (anticoagulation, comorbidities)

Our findings are consistent with these observations, as bleeding persisted despite valve replacement, emphasizing the need for long-term follow-up and multidisciplinary management.

CONCLUSION

Heyde syndrome should be considered in patients presenting with both aortic stenosis and gastrointestinal angiodysplasia. Although valve replacement typically resolves bleeding, persistence can occur. Increased awareness and further research are needed to better understand the pathophysiology, improve early diagnosis, and guide optimal management.

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