Disappearance of Atypical Gastric Mucosal Bleeding due to Heyde’s Syndrome after Transcatheter Aortic Valve Implantation

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Abstract
An 82-year-old man was admitted to our hospital due to dyspnea on exertion. Blood tests showed iron deficiency anemia, and echocardiography revealed severe aortic stenosis (AS). Considering the possibility of Heyde’s syndrome, esophagogastroduodenoscopy was performed to confirm the presence or absence of gastrointestinal angiodysplasia. Endoscopy revealed multiple sites of mucosal bleeding in the stomach without angiodysplasia or mucosal erosion. Although it was an atypical endoscopic finding, we diagnosed gastric mucosal bleeding associated with Heyde’s syndrome. Since no atypical blood vessels could be found, endoscopic treatment was not performed, and only transcatheter aortic valve implantation (TAVI) for aortic valve stenosis was performed. TAVI immediately improved the dyspnea on exertion, and follow-up endoscopy 4 months after TAVI showed the disappearance of the multifocal mucosal bleeding in the stomach. Heyde’s syndrome is characterized by AS, acquired deficiency or dysfunction of von Willebrand factor, and gastrointestinal angiodysplasia; however, the exact diagnostic criteria have not been established. This is a case of mucosal bleeding due to Heyde’s syndrome, without the typical endoscopic image of angiodysplasia. Cardiologists and gastroenterologists need to consider the possibility of Heyde’s syndrome in AS patients with atypical gastrointestinal bleeding on endoscopy.
Introduction

Aortic stenosis (AS) is sometimes associated with gastrointestinal bleeding; this condition is known as Heyde's syndrome [1, 2]. Heyde’s syndrome has been reported to occur in approximately 20% of patients with severe AS [3]. It is characterized by gastrointestinal bleeding from angiodysplasia and acquired von Willebrand factor (VWF) abnormalities. However, definitive diagnostic criteria have not yet been established. In addition, Tsuchiya et al. [4] have reported that there are cases that do not show loss of high-molecular-weight (HMW) multimers of VWF, which is one of the most important clinical features. Therefore, it can be difficult to definitively diagnose Heyde’s syndrome, and cardiologists and gastroenterologists are required to comprehensively interpret a variety of patient symptoms and medical test results in order to make the diagnosis. Transcatheter aortic valve implantation (TAVI) can be expected to improve gastrointestinal bleeding associated with Heyde’s syndrome [4–6]. Here, we present the case of an 82-year-old man with a history of severe AS who presented with iron deficiency anemia (IDA) and was found to have an atypical presentation of multifocal gastric bleeding cured by TAVI.

Case Report

An 82-year-old man was referred to our hospital due to dyspnea on exertion. Coronary angiography performed by a previous doctor was negative for angina pectoris associated with coronary artery stenosis and echocardiography suggested dyspnea on exertion due to AS. Therefore, the patient visited our hospital to receive TAVI. On admission, the patient had a normal sinus rhythm of 70 beats per minute with a blood pressure of 130/60 mm Hg. Physical examination revealed no peripheral stigmata of AS; however, he had been suffering for several weeks from dyspnea induced by light exertion, such as walking. He had been diagnosed with AS 3 years prior to hospitalization, and the severity of AS had progressed up to a maximum aortic valve pressure of 72 mm Hg (mean, 42 mm Hg), peak aortic flow of 4.23 m/s, and aortic valve area of 0.5 cm². An expert in the field of cardiology (TT) planned to perform TAVI for the patient’s AS; several screening tests were performed prior to TAVI. The screening blood tests showed IDA (hemoglobin level of 10.6 g/dL, serum iron level 25 μg/dL, total iron binding capacity 400 μg/dL, and serum ferritin level 21 ng/mL). Despite his IDA, he had never experienced hematemesis or melena in the past. The previous doctor was prescribed 100 mg of iron supplement per day and we decided to continue with it. Contrast-enhanced computed tomography and a total colonoscopy performed to investigate the cause of IDA did not reveal any lesions. As for the findings of total colonoscopy, no intestinal angiodysplasia was found, including Cecum and Ascending colon, which are considered to be hot spots. On the other hand, esophagogastroduodenoscopy showed multiple sites of gastric bleeding in the lower body (Fig. 1a), middle body (Fig. 1b), upper body (Fig. 1c), and near the cardia (Fig. 1d). Although multifocal gastric mucosal bleeding was observed, there were no obvious exposed blood vessels suspected of angiodysplasia, erosions, or Dieulafoy’s lesions. While performing endoscopic imaging near the bleeding point on the less curvature of the lower body of the stomach, irrigation of the blood did not reveal any obvious angiodysplasia (Fig. 2a, b). However, 6 s after irrigation, rebleeding from the seemingly normal gastric mucosa was observed (Fig. 2c). The patient was not taking any medications that could cause gastric mucosal bleeding, such as antithrombotic agents or nonsteroidal anti-inflammatory drugs, and his blood test was negative for Helicobacter pylori serum antibodies, excluding a current Helicobacter pylori infection. In this case, capsule endoscopy should have been considered to rule out angiodysplasia in the
small bowel. However, the patient had severe dyspnea on exertion associated with AS and had difficulty walking aggressively to encourage capsule ejection. Therefore, we did not perform capsule endoscopy on this patient. Based on the above results, we suspected gastrointestinal bleeding associated with Heyde’s syndrome and examined the VWF multimer analysis. The test revealed a normal result, showing that the plasma of the patient did not lack the HMW multimers of VWF (Fig. 2d). However, the VWF multimer analysis is not a measurable and quantified laboratory test, and an accurate assessment is difficult. By comprehensively assessing the symptoms, laboratory tests, and endoscopy results, we diagnosed gastric bleeding associated with Heyde’s syndrome. Endoscopic hemostasis was not performed because TAVI was expected to improve gastric bleeding. The patient started oral aspirin 100 mg and a proton pump inhibitor during the perioperative period and underwent TAVI. Following the TAVI procedure, his dyspnea on exertion immediately improved. Moreover, 20 days after TAVI, the patient showed improvement for IDA (hemoglobin level 12.1 g/dL, serum iron level 101 μg/dL, and total iron binding capacity 245 μg/dL) and he discontinued iron supplements. Three months after TAVI, he was completely cured of IDA (hemoglobin level of 14.5 g/dL, serum iron level 146 μg/dL, total iron binding capacity 284 μg/dL, and serum ferritin level 21 ng/mL). Notably, there was a clear disappearance of gastric bleeding in the lower body (Fig. 3a), middle body (Fig. 3b), upper body (Fig. 3c), and near the cardia (Fig. 3d) 4 months after TAVI. Moreover, while he continued single antiplatelet therapy with aspirin after TAVI, neither bleeding nor IDA episodes occurred. Retrospectively, this gastric bleeding was a result of Heyde’s syndrome, alleviated by TAVI.

Fig. 1. Preoperative images of the multifocal gastric bleeding. a Gastric bleeding at lower body. b Gastric bleeding at middle body. c Gastric bleeding at upper body. d Gastric bleeding near the cardia.
Heyde’s syndrome has been reported in a case series and is a well-known condition for cardiologists and gastroenterologists. However, definitive diagnostic criteria have not yet been established. Therefore, cardiologists and gastroenterologists are required to comprehensively interpret and diagnose Heyde’s syndrome based on various patient symptoms and medical test results. The acquired VWF abnormalities associated with AS were noted in approximately 67% of patients with severe AS [7]. This means that about 33% of patients did not have acquired VWF abnormalities, which was also the case in our patient. There have been several reports of cases of Heyde’s syndrome that did not show loss of HMW multimers of VWF [4, 8].

Angiodysplasia is characterized by focal or diffuse venous or capillary lesions presenting as bright red ectatic vessels or pulsatile red protrusions, with surrounding venous dilatation or patchy erythema, with or without oozing. The classification system recognizes the location, size, and number of angiodysplasias [9]. Oozing bleeding without angiodysplasia sometimes occurs due to water jet irrigation of friable gastric mucosa. Not just for this case, rough irrigation of the stomach reduces the quality of the esophagastroduodenoscopy; therefore, we usually use a syringe to manually inject water containing a mucus remover and an antifoaming agent to clean the gastric mucosa. Fortunately, little gastric mucus was

Fig. 2. Preoperative images of the gastric bleeding at the less curvature of the lower body and the result of VWF multimer analysis. a Image close to the bleeding point of the less curvature of the lower body. b Image close to the bleeding point on the less curvature of the lower body and irrigation of the blood: no dilated blood vessels were found. c Six seconds after irrigation of the bleeding point: oozing from the mucosal surface is observed, and vascular rupture which cannot be identified by endoscopy is suspected. d The test yielded a normal result; the plasma of the patient did not lack the HMW multimers of VWF.
seen in this patient, and the mucosa was well observable with a small amount of gentle manual irrigation. Moreover, gastric mucosal bleeding was observed before irrigation, and this multifocal gastric bleeding is not the result of irrigation. In the present case, we could not visualize venous dilatation after irrigating the bleeding site (Fig. 2a, b). However, 6 s after irrigation, rebleeding from the seemingly normal gastric mucosa was observed (Fig. 2c). Boley et al. [10] proposed a mechanism for the development of angiodysplasia. They suggested that after a period of many years of intermittent obstruction, submucosal veins may become dilated and tortuous and also involve additional veins and venules draining into the system. In our case, the fragile blood vessels may have ruptured before they were fully dilated. Furthermore, bleeding from the mucosal surface may indicate that the blood vessels in that area were ruptured, even though they were minute blood vessels that could not be identified by endoscopy. It was difficult to definitively diagnose Heyde’s syndrome in the present case. However, there was a clear disappearance of gastric bleeding 4 months after TAVI. Moreover, while he continued single antiplatelet therapy with aspirin after TAVI, neither bleeding nor IDA episodes occurred. Retrospectively, this gastric bleeding was a result of Heyde’s syndrome, alleviated by TAVI.

This is a noteworthy case report that should be read by cardiologists who perform TAVI for AS and gastroenterologists who perform esophagogastroduodenoscopy. The possibility of Heyde’s syndrome still needs to be considered in patients with AS who present with normal VWF HMW multimer results and in patients with atypical gastrointestinal bleeding without the typical endoscopy finding of angiodysplasia.
Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Institutional Review Boards of Ise Red Cross Hospital do not require Institutional Review Boards review for a single case report.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

Shinya Sugimoto wrote the initial draft of the manuscript. Takeshi Takamura critically reviewed and approved the final version of the manuscript. All authors have read and approved the final version of the manuscript.

Data Availability Statement

All data generated during this study are included in this article. Further inquiries can be directed to the corresponding author.

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