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Heyde syndrome: a diagnosis to consider

Síndrome de Heyde: um diagnóstico a se considerar

Dolly Brandão Lages[1] Fernando Augusto Pacífico[1]
Maria Luiza Curi Paixão[1] Flavio Roberto Azevedo de Oliveira[2]
Mário Cruz Couto[1] Michelle Alves de Farias[1]
Eduardo Lins Paixão[1]

[1] Faculdade de Medicina de Olinda. Olinda, Pernambuco, Brazil.
[2] Hospital Memorial São José. Recife, Pernambuco, Brazil.

Abstract

Aortic valve stenosis is a frequent clinical condition, especially in older people. Also, these patients often have anemia.This hematological change may be caused by the Heyde syndrome, which presents anemia, intestinal angiodysplasia, and loss of high-molecular-weight multimers of von Willebrand factor, treated by correcting the aortic valve stenosis. In this sense, the Heyde syndrome should be part of the differential diagnosis in patients with anemia and severe aortic valve stenosis.

Keywords: Aortic valve stenosis; Angiodysplasia; Transcatheter aortic valve replacement; Type-2 von Willebrand disease; von Willebrand factor.

Corresponding author:
Dolly Brandão Lages
E-mail:
dollylages@hotmail.com
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Resumo

A estenose aórtica valvar (EAo) calcificada é uma entidade clínica frequente, particularmente em idosos. Muitos desses pacientes apresentam quadro clínico associado de anemia. Entre as possibilidades para essa alteração hematológica encontra-se a Síndrome de Heyde, que é uma anemia associada a angiodisplasia intestinal e perda de multímeros de alto peso molecular (MAPM) do fator de *von Willebrand* (FvW). A resolução da síndrome ocorre com a correção da estenose aórtica. A Síndrome de Heyde deve fazer parte do diagnóstico diferencial entre pacientes com anemia e portadores de estenose valvar aórtica severa.

Palavras-chaves: Estenose da valva aórtica; Angiodisplasia; Substituição da valva aórtica transcateter; Doença de von Willebrand Tipo 2; Fator de von Willebrand.

INTRODUCTION

Acquired von Willebrand syndrome (AvWS) is a rare bleeding disorder caused by a change in the structure, function, or concentration of von Willebrand factor (vWF) and associated with an increased risk of bleeding[1].

The most common causes of AvWS are congenital and acquired cardiac disorders (e.g., severe aortic stenosis or other valve diseases and congenital heart disease or mechanical heart devices in adults)[1,2]. Other causes include solid tumors, autoimmune disorders, certain medications, lymphoproliferative disorders, myeloproliferative neoplasms, hypothyroidism, hemoglobinopathies, and diabetes[2-4].

Symptomatic AvWS usually presents unexplained mucocutaneous bleeding, and its prevalence in patients with active bleeding is about 2% to 3%. Heyde syndrome includes gastrointestinal bleeding due to angiodysplasia in patients with AvWS caused by aortic valve stenosis (AS)[5-6]. The cardiac causes of this syndrome can be treated by correcting heart defects, including removing the left ventricular assist device and replacing the stenosed aortic valve[4].

Laboratory evidence of AvWS has been found in some patients with AS. Also, the aortic valve may become susceptible to serum proteases due to shear stress from the blood and changes in vWF, resulting in loss of high-molecular-weight multimers (HMWM) and AvWS type-2A, which regresses when the aortic valve is replaced[7].

In this sense, the study aimed to report a case of Heyde syndrome corrected by percutaneous transcatheter aortic valve implantation (TAVI).

CASE REPORT

An 84-year-old female patient sought medical care due to non-radiating oppressive precordial pain, sweating, paleness, and dyspnea on daily activity. The patient had no syncope, fainting, or melena. She presented a history of systemic arterial hypertension and dyslipidemia. The

patient was eupneic on physical examination, with mild paleness and no edema or jugular stasis. Her heart rate and blood pressure were 58 bpm and 140/70 mmHg, respectively. Cardiovascular examination suggested regular heart rhythm and intense ejection systolic murmur in the aorta irradiating to the furcula. The resting electrocardiogram revealed sinus rhythm, normal cardiac axis, left ventricular overload, and secondary changes in ventricular repolarization. Hemoglobin (Hb) was 10 g/dL, hematocrit was 30%, and creatinine was 1.7 mg/dL. The patient underwent pharmacological stress myocardial perfusion imaging, revealing a mild inferobasal ischemia (< 5%). The transthoracic echocardiogram showed mild dilation of the left ventricle, left atrial enlargement, and AS with a mean left ventricle-aorta (LV-AO) systolic gradient of 60 mmHg. She was referred for coronary angiography, revealing a severe bifurcation lesion of the right posterior descending coronary artery. Thus, a percutaneous coronary intervention (PCI) was performed using a stent implant, and a manometer confirmed the mean LV-AO systolic gradient of 60 mmHg. Although angina was reduced months after PCI, dyspnea on daily activity persisted, and anemia progressed (reaching an Hb of 8.3 g/dL), leading to more than one transfusion. The symptoms persisted without clinical signs of gastrointestinal bleeding. Fecal occult blood test for anemia was positive, and immunoelectrophoresis revealed monoclonal peaks in kappa and lambda. The patient was referred to hematology, which identified a monoclonal gammopathy of undetermined significance with no parameters for treatment. The colonoscopy showed regular results. A clinically significant anemia was recurrent (Hb reaching 7-8 g/dL), with hypotension and no clinical evidence of melena or enterorrhagia. The fecal occult blood test remained positive. Considering the severity of symptomatic AS, we performed TAVI due to the high surgical risk. The diagnostic hypothesis of Heyde Syndrome was formulated considering the clinically relevant and recurrent anemia with evidence of microscopic gastrointestinal bleeding in a patient with severe calcified AS.

The patient underwent percutaneous aortic endoprosthesis implantation. Although the procedure had no intercurrence, a stent was implanted in the right iliac artery due to dissection caused by removing the sheaths at the end of the procedure, which was successfully performed. The hematological parameters were monitored during the immediate postoperative period and in the sixth month, with regular Hb (11.6 g/dL) and no signs of bleeding. She has no symptoms, angina, or dyspnea complaints. The transthoracic echocardiogram on the fifth postoperative month showed regular functioning of the prosthesis, with a mild periprosthetic leak without hemodynamic repercussions and a maximum transprosthetic gradient of 14 mmHg (mean of 7 mmHg).

DISCUSSION

In 1958, E. C. Heyde, a general practitioner from Washington (United States), sent a letter to the New England Journal of Medicine to report the possible association of calcified AS with gastrointestinal bleeding[8]:

> "(...) In the past ten years, I have seen at least 10 patients with calcific aortic stenosis who had massive gastrointestinal bleeding for which we could discover no cause. They were nearly all elderly people, ranging from sixty to eighty, and most of them had classic signs of calcified aortic stenosis, with harsh systolic murmurs transmitted widely into neck or back and palpable systolic thrills. I have not found any reference to this association in the literature, and thought that a letter to a prominent journal might elicit some response about the matter. I suppose these people bleed from sclerotic vessels, but I would certainly be interested in hearing from some of your readers concerning their observations. It seems to me that people with this disease have gastrointestinal hemorrhage considerably more often than comparable age groups without it. I would appreciate your printing this letter, and hope it may stimulate some replies or statistical studies."[8].

Many years later, submucosal angiodysplasia was identified as the source of gastrointestinal bleeding in these patients[9]. King et al.[10] conducted a critical study to clarify this association, demonstrating a cease of bleeding in 14 patients with AS after valve replacement. Also, other groups have reported the loss of HMWM of vWF in patients with AS[11]. Considering these factors, Warkentin et al.[12] hypothesized that the syndrome described by Heyde was a type-2A von Willebrand syndrome with an acquired HMWM deficiency. These HMWM are essential to maintain platelet-mediated hemostasis and suffer proteolysis under high shear stress when passing through the stenotic valve. Recent studies have shown that patients with severe AS had decreased HMWM, which was normalized in all patients after valve replacement on the first postoperative day[13].

Regarding the prevalence of angiodysplasia in these patients, severe AS may be associated with decreased gastrointestinal perfusion, resulting in hypoxia-induced fixed vasodilation and angiodysplasia[14]. vWF disease is rare and has been described in patients with multiple myeloma or monoclonal gammopathy of undetermined significance, which has been associated with gastrointestinal angiodysplasia and bleeding. Also, lambda light chain-induced monoclonal gammopathy with deficiency of HMWM of vWF has been reported[15].

In this clinical case, although angiodysplasia was not observed using colonoscopy, fecal occult blood test was positive and persistent, and recurrent anemia was reported. The patient had monoclonal gammopathy and severe calcified AS with a systolic gradient of 60 mmHg. More than 60 years have passed since the original letter of Heyde to the editor appeared in the New England Journal of Medicine. His direct clinical report of an association between AS and gastrointestinal bleeding helped us understand a fundamental biological mechanism underlying a complex aspect of hemostasis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

DBL (main investigator): research and schedule elaboration, literature review, data col-

lection and analysis, manuscript writing, review, and final approval, and submission procedures. **FAP** (co-supervisor): research and schedule elaboration, manuscript writing, review, and final approval. **MLCP** (collaborating researcher): manuscript writing, review, and final approval. **FRON** (collaborating researcher): manuscript writing, review, and final approval. **MCC** (collaborating researcher): manuscript writing, review, and final approval. **MAF** (collaborating researcher): manuscript writing, review, and final approval. **ELP** (supervisor): manuscript review and final approval.

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