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Case Report

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Heyde's syndrome – a case report

Abstract

Heyde's Syndrome is composed by the association between aortic stenosis, acquired deficit of von Willebrand factor and gastrointestinal bleeding. The pathophysiology of the syndrome encompasses shearing of von Willebrand factor in the turbulent flow caused by aortic stenosis, leading to its alteration and favoring its proteolysis and dysfunction, which favors the bleeding of lesions such as intestinal angiodysplasia. The objective of this case is to bring to light aspects of this syndrome and its diagnostic and therapeutic challenges. The case was monitored at the Santa Casa de Caridade de Diamantina, and a literature review on the subject was carried out in the main databases. This is a woman, 85 years old, hospitalized with heart failure associated with lower digestive hemorrhage with iron deficiency anemia. Colonoscopy and upper digestive endoscopy inconclusive. Echocardiogram confirmed severe aortic stenosis. The hypothesis of Heyde's syndrome was raised, with indication of transcatheter implantation of the aortic valve, a procedure not available locally. Patient evolves to death without completing investigation or therapy due to new cardiac decompensation. Although the result of the endoscopies was inconclusive, there are situations inherent to the method and the examiner that make it difficult to identify certain lesions, and it is recommended to repeat the exams when there is clinical suspicion. The patient died before completing the investigation, which does not exclude the possibility of Heyde's syndrome. There are still difficulties in the diagnostic and therapeutic management of the syndrome, however, when indicated, diagnostic work-up must be performed in order to define the best long-term treatment and improve the prognosis of patients.

Keywords: Heyde's syndrome, aortic stenosis, intestinal angiodysplasia, von willebrand factor deficiency

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Background

Heyde's Syndrome was described for the first time in 1958, showing a relationship between aortic stenosis and gastrointestinal bleeding.[1–3] It was only in 1992 that a great loss of von Willebrand factor multimers was observed, characterizing its acquired type 2A deficiency, associated with the condition, and the possibility was raised that it was a link between the conditions of aortic stenosis and gastrointestinal bleeding.[1,4,5] The von Willebrand factor is a multimeric protein, responsible for platelet adhesion in primary hemostasis. Its deficiency in the syndrome stems from the shearing of the von Willebrand factor that occurs in the turbulent flow caused by aortic stenosis. As a result, there is a conformational change in von Willebrand factor, making it more vulnerable to proteolysis. The final effect is ineffective platelet adhesion, leading to bleeding from pre-existing lesions, such as intestinal angiodysplasia.[2,3] Normally, the main complaint of patients is digestive bleeding. It is common for patients not to be diagnosed and their approach is based on the treatment of acute episodes of digestive bleeding, which tend to recur with increasing frequency and severity, thus justifying the poor prognosis of this syndrome.[3,6] No entanto, uma vez diagnosticada, existem opções terapêuticas com potencial curativo a longo prazo, como é o caso da substituição valvar e valvuloplastia, e que melhoram o prognóstico reservado dos doentes com Síndrome de Heyde.[1,7]

Heyde's syndrome is still underdiagnosed due to lack of knowledge about it, and is described in only 1.7% of patients with significant aortic stenosis, and most publications related to this entity are case reports and small series.[3,6] This work presents the case report of a patient with a suggestive picture of Heyde's syndrome and its diagnostic and therapeutic challenges, with the objective of bringing to light the aspects of this syndrome so that it is more recognized and patients receive better therapy for the condition. The case study presented was accompanied by residents and preceptors of the medical clinic residency at Santa Casa de Caridade de Diamantina. A literature review on the subject was carried out in the main databases: UpToDate, Pubmed and Scielo.

Case report

It's about a woman, 85 years old, admitted to the Santa Casa de Caridade de Diamantina with a picture of decompensated heart failure, the etiology of which remains to be clarified. He was admitted complaining of tight chest pain, without irradiation, dyspnea and orthopnea. He also had a history of low digestive bleeding in small amounts, with no other bleeding sites. On physical examination, she was pale 3+/4+, heart rate 70bpm, respiratory rate 28 bpm, blood pressure 200x90. On cardiovascular examination, a systolic ejection murmur in the aortic focus, grade III/VI, radiating to the dorsum and sternal notch stood out. On pulmonary examination, he had diffuse coarse crackles and mild wheezing. Anasarcada 2+/4+. Good peripheral perfusion. Admission tests showed anemia, with hemoglobin 7.6, global leukocytes 7600, sodium 130, potassium 4.6, INR 1.2, urea 29, creatinine 1.22, albumin 3, CPK 99, CKMB 18, troponin negative. Additional investigation showed iron deficiency, with IST 17%.

Electrocardiogram: Sinus rhythm, HR 75bpm, 1st degree AV block, BRD. QS in D3 and aVF.

Chest X-ray: Increased cardiac area, bilateral diffuse infiltrate with flow cephalization, right meniscus sign.

The patient was hospitalized for treatment of decompensated heart failure in profile B, with anticongestive measures, showing improvement of the condition. He also had some episodes of digestive bleeding during hospitalization, accompanied by a drop

in hemoglobin and the need for blood transfusion. The transthoracic echocardiogram confirmed significant aortic stenosis, with a valve area of 0.8cm², a maximum gradient of 80 mmHg and a mean gradient of 44 mmHg. Ejection fraction 65%. Left ventricle with mild concentric hypertrophy and moderate enlargement of the left atrium, with moderate mitral regurgitation. In view of the severe aortic stenosis on the echocardiogram and the persistence of digestive bleeding, the hypothesis of Heyde's syndrome was raised. Upper digestive endoscopy and colonoscopy were performed, and the reports delivered were as follows:

Upper digestive endoscopy: small hiatal hernia. No signs of bleeding. H. pylori negative.

Colonoscopy: inconclusive.

Although the reports did not confirm the expected angiodysplasia for Heyde's syndrome, they lacked information, so that the hypothesis could not be completely refuted. The patient in question had the acute condition of heart failure treated, as well as optimization of the respiratory condition related to COPD, and was discharged with a request for Von Willebrand factor dosage and a new outpatient colonoscopy. Given the suspicion of Heyde's syndrome for the patient, the proposed treatment was valve correction surgery for aortic stenosis. Due to the patient's delicate clinical condition, percutaneous implantation of the aortic valve (TAVI) was indicated, a procedure not available in the Diamantina macro-region. The patient returned in less than a month to the emergency room with a significant worsening of the cardiac condition, associated with seizures and urinary tract sepsis, evolving to death during hospitalization without completing the investigation.

Discussion

The presence of intestinal bleeding, especially if associated with iron deficiency anemia, should be investigated endoscopically in search of sources of bleeding, such as ulcers, neoplasms, inflammatory diseases or diverticulosis. For this purpose, endoscopy and colonoscopy are recommended.[6,8] Of interest for Heyde's syndrome is angiodysplasia. Heyde's syndrome is characterized by the combination of aortic stenosis, iron deficiency anemia secondary to intestinal bleeding due to angiodysplasia, and acquired von Willebrand factor deficiency.[3,9] Usually, aortic stenosis and angiodysplasia are asymptomatic conditions, whose prevalence increases with age, justifying their higher incidence in elderly patients.[6,10,11] However, Vincentelli e cols[4] have already shown that about 21% of patients with severe aortic stenosis who would undergo valve surgery had skin or mucosal bleeding in the six months prior to the same.

Intestinal angiodysplasia is characterized by small (<5 mm), flat, cherry-red lesions located along the gastrointestinal mucosa. A "clear halo" around the lesion may also be visible. It corresponds to dilation of submucosal, tortuous vessels, distributed throughout the gastrointestinal tract, more frequently in the right colon and cecum (75%), where the thickness and tension of the wall seem to increase the predisposition to this type of injury. They may suffer spontaneous ruptures, being one of the main forms of digestive bleeding in the elderly.[8,10,12] Its diagnosis is made endoscopically, and the success of any endoscopic technique depends on several factors including operator experience, visibility, and the size and location of the lesion itself.[6,13] Due to these factors, it is recommended to repeat these exams, especially in cases of high clinical suspicion or when the initial exam is of poor quality, before investigating the small intestine.[13] The case in question presented inconclusive endoscopic reports. As the suspicion was high, it was decided to repeat the exam. Even so, if relevant lesions are not identified (such as GI tube neoplasia, or other GI pathology), or if angiodysplasia is identified, there are authors who argue that Heyde's syndrome should already be considered and the presence of aortic stenosis investigated.[6,8] In the case of the patient in question, who already had the diagnosis of aortic stenosis, the sensitivity to this hypothesis increased considerably. For the diagnosis of aortic stenosis, the gold standard test is the Doppler echocardiogram. Although Heyde's Syndrome is more common in moderate to severe aortic stenosis, it can be present in any degree of aortic stenosis.[6,11]

It becomes necessary for the investigation to study the von Willebrand factor. The location of intestinal bleeding and the confirmation of von Willebrand disease remain the major challenge in diagnosing this syndrome.[6] The association of the syndrome with Von Willebrand disease, type 2A acquired deficiency, is justified by the pathophysiology proposed by Veyradier *et al*: it is characterized by the loss of the largest multimers of von Willebrand factor, whose proteolysis occurs when passing through the stenosed aortic valve. Frictional forces can induce conformational changes in the shape of the von Willebrand molecule, leading to exposure of the bond between amino acids 842 and 843, which is more sensitive to the action of its specific protease and favors its proteolysis.[5] This results in proteolysis of the higher molecular weight multimers of von Willebrand factor, which is the most efficient platelet mediator in primary hemostasis. This theory is corroborated when it is verified that bleeding is substantially reduced with valve replacement.[3,14] Given the complexity of the pathophysiology of von Willebrand factor itself, there is not yet a single sufficient test for the diagnosis of von Willebrand disease. A set of tests is therefore still needed for different aspects of the structure and function of the von Willebrand factor. Furthermore, no test has sufficient sensitivity to exclude the diagnosis of the disease in question.[8]

Initially, a coagulogram and PFA-100 (which measures platelet function) should be performed. Despite its limits in anemic patients, PFA-100 is prolonged in 92% of patients with severe aortic stenosis and 50% of patients with moderate aortic stenosis. In the face of suspected von Willebrand disease, there are more specific tests for a more definitive diagnosis. There is already evidence that abnormalities of von Willebrand factor or deficiency in platelet action are proportional to the severity of aortic stenosis.[5] However, even if the combination of all tests is negative, it is not sufficient to exclude Von Willebrand disease.[6] Faced with the reality of most patients in the Jequitinhonha Valley, which is characterized by predominant social and financial vulnerability,[15] dependent on the unified health system and primarily on primary care, it becomes difficult, if not impossible, to investigate Von Willebrand disease. In the above case, the patient was unable to take the exam in the time available.

Regarding the treatment of this condition, it is important to have a treatment that encompasses both the short term, with anemia and digestive bleeding, as well as the long term, with the correction of aortic stenosis.[3] Endoscopic and pharmacological techniques, such as transfusion of blood concentrates and desmopressin (increases the function of von Willebrand factor up to four times) are ineffective for the chronic condition, but can be used as a bridge to definitive treatment: valve replacement, or in patients with high surgical risk, transcatheter aortic valve implantation (TAVI).[1,3,5] It is important to emphasize that the correction of valve stenosis with replacement or TAVI solves problems related to increased bleeding and anemia in approximately 90%, and that patients who do not undergo this correction have a greater risk of major bleeding, even in non-operative surgeries. cardiac. For the reason presented, it was observed that the

risk of major bleeding in the first hour after the correction of aortic stenosis is quite limited.[5,16]

As for TAVI, several studies demonstrate comparable and even superior results compared to surgical replacement of the aortic valve in individuals with contraindications for this or high surgical risk (advanced age, multiple comorbidities, and under dual antiplatelet therapy).[3,6] Due to the high surgical risk, the TAVI technique was indicated for the patient in question. Unfortunately, the patient died before having access to treatment. Although this is a case presented in a hospital environment, patients with iron deficiency anemia and aortic stenosis are frequent in the day-to-day of primary care, especially in the case of normally elderly patients, since generative aortic stenosis is the most common valvular disease in the elderly and is one of the major causes of morbidity and mortality in this age group. Its prevalence increases with age, reaching rates of 2-7% after 65 years of age. In turn, angiodysplasia is also an age-related disease.[6,17] It is understood, then, that the prevalence of the condition may be more present in day-to-day life than is then expected. Family medicine then has the opportunity to identify and suspect cases even before the patient reaches tertiary care, being able, after adequate investigation, to indicate the best treatment for the patient.

Final considerations

Heyde's syndrome is an underrecognized syndrome, which is not to say that it is rare. The presentation of elderly people with angiodysplasia and digestive bleeding is common, and in these cases, it is interesting to perform an echocardiogram. There are still difficulties in the diagnostic and therapeutic management of the syndrome. Even so, it is necessary to investigate the syndrome, when indicated, in order to define the best long-term treatment and improve the prognosis of patients. In this context, primary care has the advantage of being able to identify patients and suspect Heyde's syndrome before unfavorable outcomes such as the one presented occur.

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Conflcits of interest

The author declares there is no confclit of interest.

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