

Heyde syndrome in a 71-year-old man who underwent chest radiotherapy at young age

Síndrome de Heyde en un hombre de 71 años que había recibido radioterapia en el pecho de joven

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ABSTRACT

We report the case of a 71-year-old man with diagnosis of aortic valve stenosis for ten years, who came to hospital because of breathlessness during the previous two months and recent low intestinal hemorrhage. On admission, laboratory tests and upper gastrointestinal endoscopy and colonoscopy revealed anemia and bleeding cecal angiodysplasia. The echocardiography study showed a severe aortic stenosis. Classical Heyde syndrome is described as the association of aortic stenosis, bleeding gastrointestinal angiodysplasia and secondary anemia. The antecedent of mediastinal radiotherapy for treatment of Hodgkin's disease during his youth, and eventual late cardiac adverse effects that may include aortic or mitral valve disturbances are highlighted. Electrocoagulation with argonium was performed on the sites of active bleeding during the colonoscopy. In sequence, surgical replacement by bioprosthesis was done on the aortic valve. The patient remains asymptomatic, under long-term outpatient surveillance, with normal control evaluations. The aim of this case study is to emphasize difficulties related to diagnosis, and to highlight the role of endoscopy and imaging studies to confirm a hypothesis of this underestimated condition.

Key words. Angiodysplasia, Aortic valve stenosis. Colon bleeding. Heyde syndrome. Mediastinal radiotherapy.

RESUMEN

Se presenta el caso de un varón de 71 años con estenosis aórtica diagnosticada diez años antes, que acude al hospital por disnea durante dos meses y reciente hemorragia digestiva baja. La analítica y la endoscopia oral y colonoscopia realizadas en el momento de la admisión revelaron anemia y angiodisplasia cecal con sangrado activo. El ecocardiograma mostró estenosis aórtica severa. El síndrome de Heyde clásico está descrito como asociación entre estenosis aórtica y sangrado por angiodisplasia gastrointestinal, con anemia secundaria. Se destaca el antecedente de radioterapia mediastinal para tratamiento de enfermedad de Hodgkin durante su juventud, y eventuales efectos adversos tardíos que pueden incluir trastornos de las válvulas aórtica y mitral. Durante la colonoscopia se realizó la electrocoagulación con argón del punto de sangrado activo. Posteriormente se realizó cirugía de sustitución valvular aórtica utilizando una bioprótesis. El paciente permanece asintomático, realizando un seguimiento ambulatorio a largo plazo, y con exámenes de control normales. El objetivo de este estudio es enfatizar las dificultades relacionadas al diagnóstico, y resaltar el papel de los estudios endoscópicos y de imágenes para confirmar una hipótesis de esta entidad subestimada.

Palabras clave. Angiodisplasia. Estenosis aórtica. Hemorragia digestiva baja. Síndrome de Heyde. Radioterapia mediastinal.

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INTRODUCTION

Heyde syndrome is a challenging condition first described by Heyde in 1958, which consisted of aortic valve stenosis, bleeding of gastrointestinal angiodysplasia and iron deficiency anemia^{1,3}. A secondary shear stress-enhanced proteolysis of high molecular weight multimers of von Willebrand factor during the blood flux through a severe aortic stenosis also play a role¹⁻⁶. Although angiodysplasia and degenerative aortic stenosis often occur in elderly people, the association between these entities in patients with Heyde syndrome was found significant^{1,3}. Moreover, valve replacement avoids recurrence of bleedings from angiodysplastic vessels^{2,6}. Additional factors include cholesterol emboli from the stenotic aortic valve, sympathetic-mediated vasodilation secondary to hypoxia and atherosclerotic changes in mesenteric vessels^{1,3}. Better awareness about this syn-

drome could contribute to early diagnosis and therapeutic decisions for management of patients with aortic valve stenosis and recurrent intestinal bleeding. This case study aims to increase the suspicious index about Heyde syndrome that is a challenging condition with not well-understood etiopathogenesis, involving multidisciplinary approaches.

CASE REPORT

A 71-year-old man, with diagnosis of arterial hypertension and aortic valve stenosis for nearly ten years, claimed progressive breathlessness for the last two months, and rectal loss of bright blood. He was taking amlodipine, captopril, furosemide and enteric-coated aspirin. There was a history of chemotherapy and several courses of mediastinal radiotherapy to treat Hodgkin's lymphoma when he was a young man. He denied antecedent of pharyngotonsillitis, rheumatic diseases or hemorrhagic disorders. On physical examination he was pale, with an aortic systolic

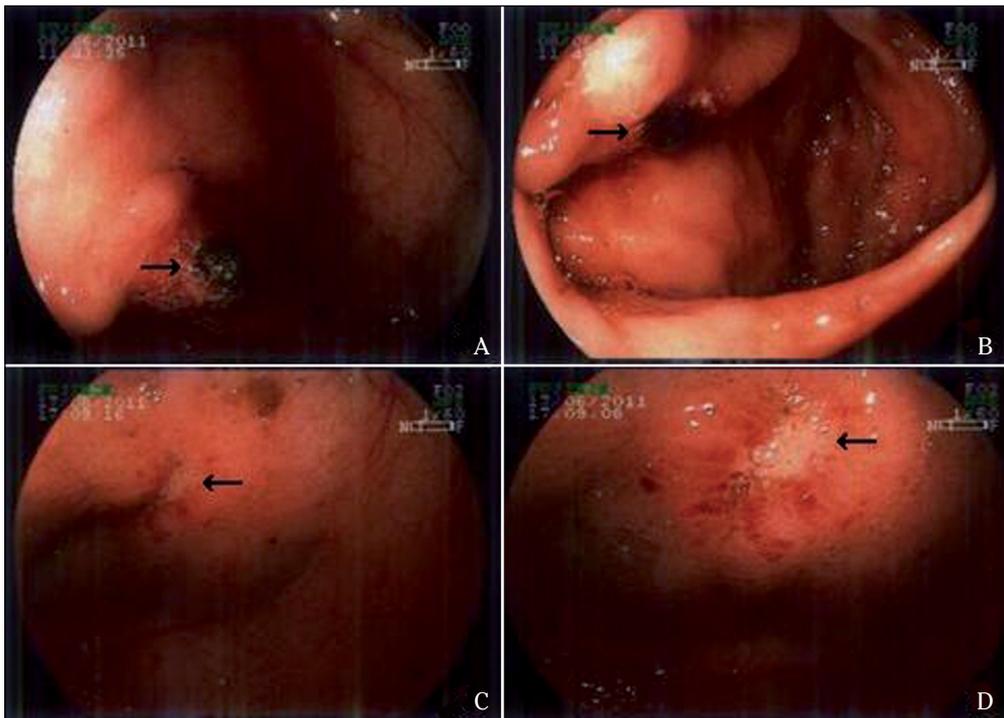


Figure 1. Colonoscopy features of the angiodysplasia and the clots of recent bleeding (1A and 1B); and aspect of the scars in the site of coagulation performed with argonium (1C and 1D).

murmur (3+) and a mitral diastolic murmur (2+); heart rhythm was regular with 70 bpm, and his blood pressure was 110/80 mmHg. Hematology data (Table 1) showed severe anemia, which was treated with a blood transfusion, in addition to iron supplementation. The lipidogram showed total cholesterol: 122 mg/dL, HDL-cholesterol: 34 mg/dL, LDL-cholesterol: 86 mg/dL, and triglycerides: 108 mg/dL. The results of other laboratory exams were unremarkable, including coagulation factors, tumor markers, hepatic and renal functions, as well as serologic tests. Upper digestive endoscopy was normal, but the colonoscopy study detected cecal angiodysplasia with signs of recent bleeding (Figs. 1A and 1B), and local hemostasy was performed by coagulation with argonium (Figs. 1C and 1D). Following his clinical management, he showed a gradual and slowly progressive improvement. The EKG revealed left ventricle (LV) hypertrophy and ST segment elevation (Fig. 2); while the heart catheterization study did not detect significant coronary artery obstructions. The images of cardiac

echo Doppler study (Fig. 3) showed: a) mild left atrial (LA) dilation, moderate LV hypertrophy, calcifications in the mitral ring and in the mitro-aortic junction; b) maximum diastolic LA-LV gradient of 21 mmHg with a mean value of 12 mmHg, in addition to a discrete mitral valve insufficiency; c) trivalvular aortic valve with fibro calcifications, and commissural fusion; d) maximum diastolic LV-aorta gradient of 94 mmHg with a mean value of 58 mmHg and a valve area of 0.5 cm², and a relation between the aortic subvalvar and the valvar velocity of 0.17; e) moderate tricuspid insufficiency; f) normal pulmonary valve; and g) and estimated systolic pulmonary artery pressure of 68 mmHg. Association of severe aortic valve stenosis with bleeding from cecal angiodysplasia was consistent with the diagnosis of Heyde syndrome in this patient, and replacement of the abnormal valve by bioprosthesis was successfully performed, soon after correction of the blood parameters. The patient did not have new intestinal bleedings, and Table 1 shows the improved blood tests.

Table 1. Comparative laboratory data of a 71-year-old male with Heyde syndrome that was successfully controlled by aortic valve bioprosthesis*

Parameters (normal range)	**5/27/11	6/17/11	7/07/11	9/05/11	1/20/12
Erythrocytes (4.4-6.0 x10 ¹² /mm ³)	2.8	3.5	4.2	4.3	4.7
Hemoglobin (11.1-16.1 g/dL)	7.4	9.8	12.6	12.5	12.9
Hematocrit (39-53 %)	24	31	37	41	41
Mean corpuscular volume (80-100 fL)	86	89	88	95	87
Mean corpuscular hemoglobin (27-32 pg)	26	28	30	29	27
MCHC (32-37 g/dL)	31	32	34	30	31
Leukocytes (4.0-11.0 x10 ³ /mm ³)	12.3	12.5	12.8	15.3	11.4
Platelets (150-450x10 ³ /mm ³)	511	390	449	474	181
Prothrombin time (14.0 seconds)	14.5	15.3	15.2	-	-
Prothrombin activity (70-100%)	92.4	82.9	77.7	-	-
INR (0.9-1.2)	1.0	1.1	1.1	-	-
Thrombin time (12.0 seconds)	10.8	11.6	12.1	-	-
aPTT (30 seconds)	27.7	27.0	28.6	-	-

* The aortic valve bioprosthesis was replaced on August 9, 2011.

** Date of the episode of lower gastrointestinal bleeding; MCHC: mean corpuscular hemoglobin concentration; INR: international normalized ratio; aPTT: activated partial thromboplastin time.

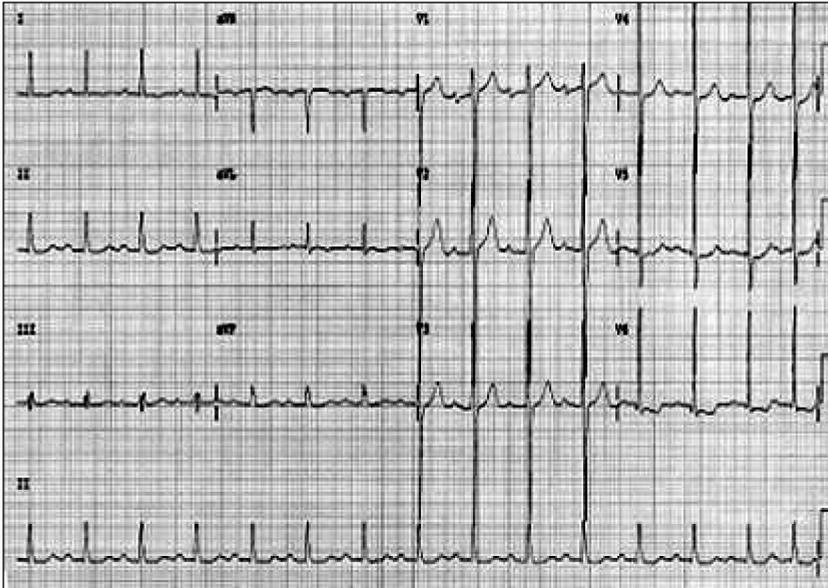


Figure 2. EKG showing characteristic features of a first-degree A-V block and left ventricle hypertrophy, in addition to secondary changes of ventricular repolarization.

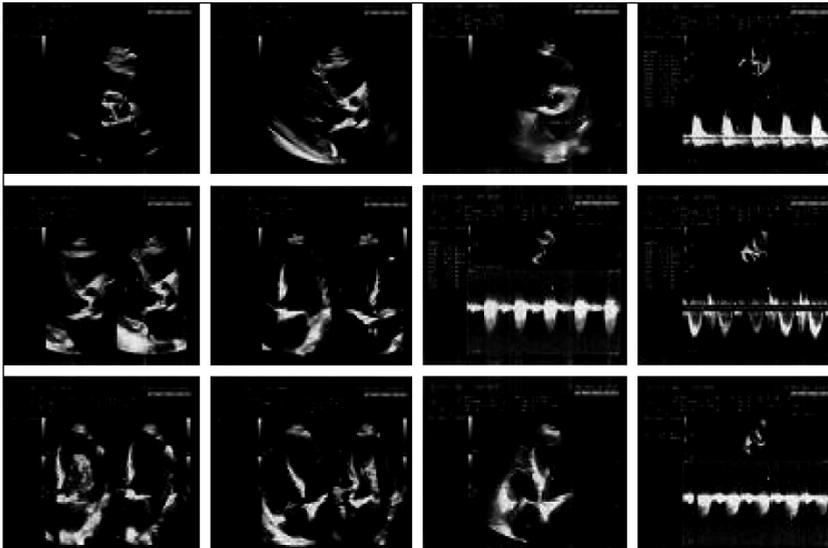


Figure 3. Images of the echo Doppler study that characterized severe aortic stenosis, moderate mitral and tricuspid insufficiency, in addition to pulmonary arterial hypertension.

DISCUSSION

A bleeding tendency found in Heyde syndrome was associated with the acquired type 2A von Willebrand disease³. Enlarged and fragile angiodysplastic vessels are more often found in the mucosa and submucosa of colon, stomach, small intestine, and nose, where recurrent episodes of bleeding may occur³. Batur et al found aortic stenosis in about 32% of patients with gastrointestinal arteriovenous malformations, while this valve change was detected in only 14% of the control population¹. Co-existent aortic stenosis has been described in 7-29% of patients with gastrointestinal angiodysplasia, and gastrointestinal bleedings may occur in 3% of those with severe stenosis^{3,6}. Furthermore, in the majority of patients with Heyde syndrome, the aortic valve replacement can prevent future recurrences of bleeding episodes of the gastrointestinal angiodysplastic vessels¹⁻¹². The degree of anemia secondary to intestinal blood losses is a major concern that should be clinically and endoscopically managed before the valve replacement¹. Preoperative hemolysis associated with the turbulence and shear stress produced by flow through the stenosed valve constitutes an important factor related to the mechanism of anemia¹³. Moreover, the aortic valve replacement by bioprosthesis contributes to control the occurrence of microangiopathic hemolysis. Mainstay of Heyde syndrome is aortic valve stenosis and bleeding angiodysplasia, but acquired von Willebrand coagulopathy type 2A (vWS-2A) was further considered part of the syndrome^{3,12}. This coagulopathy has multivariate origin³ and cardiovascular causes yield 12% of the cases^{3,6}. The heaviest multimers of von Willebrand factor (vWF) are needed to stop angiodysplastic bleedings, because they can mediate the platelet aggregation on the sites of vascular damage^{2,3,5,6}. Plasma proteases, activated in sites of turbulent blood flow, can clear these multimers^{2,3,12}. Unremarkable results of preoperative coagulation investigations constituted our initial concern; however, hematological abnormalities are

related to severity and may lack in 8-33% of cases^{3,8,12}. Moreover, some case studies about Heyde syndrome have been published without confirmation by the gold standard gel electrophoresis that the heaviest vWF multimers were decreased^{2,5,12,14}. This may be due to unavailability of the required high cost assays in developing regions, and vWS-2A coagulopathy may be absent in patients with aortic gradients below 50 mmHg^{6,12}. Additional concern in the management of this group of patients is about the use of medicines that can enhance the hemorrhagic tendency, like aspirin, clopidogrel, ticlopidine, and warfarin^{3,10}. Avoiding unnecessary colectomy after valve replacement, one must distinguish adverse-effects of these drugs from recurrent bleeding of angiodysplasia. The main features of Heyde syndrome, in addition to a possible relationship with chest radiation in the present case are showed in Table 2. This 71-year-old patient with clinical diagnosis of Heyde syndrome underwent mediastinal radiotherapy to treat a Hodgkin's lymphoma nearly 40 years earlier. Cardiovascular injuries induced by radiation are the second main cause of late mortality in survivors of Hodgkin's lymphoma submitted to mediastinal radiotherapy¹⁵. Survival patients with lymphoma treated by mediastinal radiation at a young age may develop asymptomatic or symptomatic effects, which include accelerated coronary disease, aortic calcification, myocardial fibrosis, pericarditis, and aortic or mitral valve dysfunction¹⁵⁻¹⁹. Mechanisms of these abnormalities are not elucidated, and the changes usually evolve for very long periods of time after mediastinal radiotherapy¹⁵⁻¹⁹. Aortic and/or mitral replacement may be required to correct the late effect of radiation-associated valvular disease, which can be characterized from 5 to 30 years after the radiotherapy^{15,17-19}. Although degenerative calcified changes are often found in elderly people, and result in variable aortic valve dysfunction, an additional role of mediastinal radiation was not ruled out in this case. Technological advances in radiotherapy, developed in the last two decades, have contributed to increase the tumor control

without provoking further toxicity. These improvements include three-dimensional conformal radiotherapy, intensity modulated radiotherapy for maximum conformation, and high precision in radiation

delivery and better preservation of healthy tissue²⁰. Therefore, ancient hazards of late cardiovascular toxicity were actually reduced to a minimum.

Table 2. Highlighted features of Heyde syndrome

1. Prevention and the earliest possible surgical correction of severe aortic valve stenosis play a major role in the quality of life of the individuals with Heyde syndrome.
2. Association between systolic murmur in aortic focus and iron deficiency anemia may be merely casual, but these data represent the cornerstone for the diagnosis suspicion.
3. Hypoxemia of gastrointestinal mucosa, cholesterol embolism to gastrointestinal vessels, acquired type 2A von Willebrand coagulopathy, intravascular hemolysis, drug-adverse effects, and platelet dysfunctions are involved in the etiopathogenesis of anemia.
4. Because of difficulties in establishing an early diagnosis, complete digestive imaging studies are necessary to confirm the clinical suspicion of gastrointestinal angiodysplasia.
5. Aortic valve replacement usually stops the gastrointestinal blood losses, but some patients may present postoperative recurrent bleedings in the angiodysplastic vessels. Possible adverse effect of anticoagulant drugs should be ruled out in this setting.
6. Although ancient hazards of late cardiovascular toxicity were actually reduced to a minimum, antecedent of mediastinal radiotherapy at a young age may have played an additional role on the development of severe degenerative aortic valve stenosis detected in this 71-year-old patient.

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