An unrecognized disease in routine clinical practice: the Heyde's syndrome

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Abstract

Heyde's syndrome (HS) is a triade constituted by aortic stenosis, gastrointestinal angiodysplasia and deficiency of high-molecular-weight von Willebrand factor multimers. Until now few cases of HS has been reported and we believe of interest to add a new patient having this disorder. We report a case of HS in an 86-year-old female patient admitted for the second episode of melena in the last 4 months. A colonoscopy revealed a bleeding due to angiodysplasia in the ascending colon and an endoscopic argon laser photocoagulation of the colonic angiodysplasia was successfully carried out. Physicians should be aware of the possibilities of acquired von Willebrand disease and gastrointestinal bleeding from angiodysplasia in patients with aortic valve stenosis because a right diagnosis affects the management of these patients, especially in emergency situations.

Introduction

The association between calcific aortic-valve stenosis and gastrointestinal (GI) bleeding was firstly described by Edward Heyde in the 1958 who reported ten elderly patients with calcific aortic stenosis and massive GI bleeding of obscure origin.[1] In 1986 submucosal angiodysplasia was identified as a possible source of GI bleeding in patients with aortic-valve stenosis.[2] One year later, King et al. reported the cessation of GI bleeding after aortic-valve replacement and confirmed the association between degenerative aortic-valve stenosis and GI bleeding due to angiodysplasia.[3] A key study in understanding of this disease was carried out by Warkentin *et al*. who suggested that HS was a form of type 2A von Willebrand disease (vWD), an acquired syndrome characterized by a deficiency of high-molecular-weight von Willebrand factor multimers (vWf).[4] VWf is a multimeric glycoprotein produced in endothelium and megacaryocites, playing a role in primary hemostasis because it permits the adhesion of platelets to the vascular subendothelium. The high molecular weight multimers are important for maintaining hemostasis during high shear stress, a condition that is found in patients with angiodysplastyc malformations.[4] Thus, the HS is a triade constituted by aortic-valve stenosis, GI angiodysplasia and deficiency of high-molecular-weight von Willebrand factor multimers. Until now few cases of Heyde's syndrome has been reported and we believe of interest to add a new case of patient having this syndrome.

Case Report

An 86-year-old female patient was hospitalized for the second episode of melena within 4 months. The patient had a history of scleroderma with calcinosis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly and telangiectasia (CREST) syndrome, hypothyroidism, chronic obstructive pulmonary disease, arterial hypertension and aortic-valve stenosis. Cardiac auscultation revealed a grade III/IV systolic murmur at the second right intercostal space radiating to the neck and digital rectal examination showed melena. Laboratory examination revealed a hypocromic microcytic anemia with haemoglobin concentrations of 7.2 g/dL, MCV 72 fL and MCH 22.5 pg; the platelet count was normal whereas an iron deficiency was detected (concentration of iron in blood serum was 30 mg/dL). A decrease of large molecular weight multimers of von Willebrand factor was finally detected. The transthoracic echocardiogram showed a severe aortic stenosis due to degenerative valve calcification with a mean transvalvular gradient of 41 mmHg and a valvular area of 0.9 cm^2. The endoscopic study of colon revealed a bleeding due to angiodysplasia in the ascending colon (Figure 1). The selective angiography of mesenteric arteries did not show an active bleeding. Other sites of bleeding in the digestive tract were also excluded by capsule endoscopy. The patient was supported with blood transfusions and iron supplement was also given intravenously. An endoscopic argon laser photocoagulation of the colonic angiodysplasia was successfully carried out (Figure 2).

Considering her age and comorbidities determining a significant surgical and anaesthesiological risk, surgical valve replacement was not performed. After six month of follow-up, the patient remained in good clinical conditions and no further GI bleeding occurred.

Discussion

The association between calcific aortic-valve stenosis and GI bleeding due to angiodysplasia has been confirmed by various studies and the prevalence varies among the studies so far published.[2,5] As in this reported case, both these disorders appear in elderly patients and are related to the degenerative process of aging.[6] As shown in Table 1, there is no gender preference, the age of patients having this syndrome is advanced (median 70 years) and all bowel segments may be involved by the angiodysplasia. The risk of mucosal bleeding is caused by the acquired type 2A von Willebrand syndrome that is a consequence of a high shear stress presented in narrowed valve.[41] During passing through stenotic aortic valves, the coiled von Willebrand multimer, which normally circulates in plasma, is converted into an elongated highly asymmetric protein exposing the A2 domain. The metalloproteinase ADAMTS-13 binds the A2 domain and causes the proteolysis of the high-molecular-weight multimers into smaller multimers that are less hemostatically competent.[42] In most cases the loss of high-molecular-weight multimers is associated with abnormalities in platelet adhesion and aggregation *in vitro*.[43] Vincentelli *et al*. reported that the 21% of 42 patients with severe aortic-valve stenosis had a history of mucosal bleeding with platelet function abnormalities and reduction of high-molecular-weight vWf multimers.[44] These data showed that the loss of largest multimers was inversely correlated with the transvalvular aortic gradient and the valve replacement halted the depletion of these multimers. In addition, von Willebrand factor is essential for

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Table 1. Clinical characteristics of patients having Heyde's syndrome in case reports and two retrospective studies.

Case reports	Cases (n.)	Gender	Age at diagnosis	Site angiodysplasia	Bleeding recurrence	Treatment
Galloway *et al.*[7]	3	3 F	53, 71, 70	Ascending colon		Blood transfusions, right colectomy
Gelfand *et al.*[8]	5	2 M, 3 F	65	4 ascending colon, 1 small bowel		5 Blood transfusions, 4 right colectomy, 1 resection of jejunum
Boyle *et al.*[9]	1	1 F	64	Not identified		Aortic valve replacement
Cappell and Lebwohl[10]	2	2 F	66, 69	1 gastroduodenal, 1 stomach, colon		Aortic valve replacement, blood transfusion, iron supplementation
Baciewicz and Davis[11]	1	1M	48	Descending colon	Yes	Colectomy with ileoproctostomy
Casson and McKenzie[12]	1	1 F	68	Stomach		Endoscopic sclerosis
Apostolakis *et al.*[13]	2	1 M, 1 F	67, 68	2 Colon		Aortic valve replacement, blood transfusion
Kraft and Hahn[14]	4	3 M, 1 F	67, 87, 74, 73	3 small bowel 1 colon		Resection, blood transfusion
Natowitz *et al.*[15]	2	1 M, 1 F	72, 74	2 small bowel		Replacement of the aortic valve
Knobloch *et al.*[16]	2	1 M, 1 F	61, 75	1 not identified 1 small bowel		Aortic valve replacement, blood transfusion
Granel *et al.*[17]	1	1 M	61	Small bowel		Aortic valve replacement, blood transfusion
Luckraz *et al.*[18]	1	1 F	80	Small bowel	Yes	Aortic valve replacement, endoscopic argon plasma coagulation
Lee *et al.*[19]	1	1 F	68	Colon	Yes	Hemicolectomy, argon plasma coagulation
Pennacchietti and Capone[20]	1	1 F	72	Not identified		Medical treatment
Corrêa *et al.*[21]	1	1	89	Small bowel		Medical treatment
Giovannini *et al.*[22]	1	1 M	70	Small bowel	Yes	Right hemicolectomy and resection of terminal ileum
Ogano *et al.*[23]	1	1 M	64	Colon		Colectomy
De Palma *et al.*[24]	1	1 M	58	Small bowel		Octreotide 20 mg, at monthly interval
Morishima *et al*[25]	1	1 F	78	Small bowel		Aortic valve replacement, supplementation of von Willebrand factor and factor VIII
Henne *et al.*[26]	1	1 M	60	Stomach	Yes	Endoscopic argon plasma coagulation
Schmid *et al.*[27]	1	1 M	79	Colon		Medical treatment
Hokama *et al.*[28]	1	1 F	90	Ascending colon		Hemoclipping
Hui *et al.*[29]	1	1 F	68	Small bowel		Blood transfusion, iron supplements, endoscopic treatment
Rahhal and Chamberlain[30]	1	1 F	64	Cecum		Endoscopic laser coagulation
Gandhi *et al.*[31]	1	1 F	82	Ascending colon		Medical treatment
Takahashi *et al.*[32]	1	1 F	82	Colon		Endoscopic clipping before the successful aortic valve replacement
Vaz *et al.*[33]	1	1 M	69	Stomach		Blood transfusion, iron supplements, endoscopic argon, laser photocoagulation, valve replacement
García-Martín *et al.*[34]	1	1 F	89	Small bowel		Intestinal resection
Figuinha *et al.*[35]	1	1 M	76	Ascending colon		Medical treatment
Abi-Akar *et al.*[36]	1	1 M	68	Duodenum and colon	Yes	Blood transfusions, endoscopic treatment
Gül *et al.*[37]	1	1 F	75	Cecum and distal ileum	Yes	Valve replacement, endoscopic argon plasma coagulation, blood transfusion
Godino *et al.*[38]	1	1 F	83	Duodenum	Yes	Endoscopic argon plasma coagulation
Present case	1	1 F	86	Ascending colon		Blood transfusion, iron supplements, endoscopic laser coagulation
Overall	46	18 M (39.1%), 28 F (60.9%)	Median age 71 yrs		10 (21.7%)	
Retrospective studies						
Thompson *et al.*[39]	57	39 M (68.4%), 18 F (31.6%)	Median age 75 yrs	Duodenum-ascending colon	12 (21.1%)	Aortic valve replacement
Godino *et al.*[40]	7	NR	Mean age 78±10 yrs	NR	2 (28.6%)	NR

M, male; F, female; NR, not reported.

the role of platelets in maintaining vascular integrity independent of their essential function in hemostasis;in fact, in young patients with von Willebrand's disease capillary dilatation, tortuosity, and blood extravasation are observed on nail-bed capillaroscopy and angiodysplasia may be a consequence of von Willebrand factor alteration.[45] As shown in Table 1, various treatments have been proposed for the gastrointestinal bleeding due to angiodysplasia varying from conservative medical treatment to surgery.

The main disagreements regarding the HS are not on the association between aortic stenosis and angiodysplasia, but on the pathogenesis of Heyde's syndrome, ranging from vWf deficiency and age-related degeneration to mucosal ischemia and cholesterol embolization.[46] However, after a revision of literature data, it has been claimed that HS exists and this assumption is based on two factors: the gastrointestinal bleeding caused by angiodysplasia ceases in the major part of patients after valve replacement even if angiodysplasia remains and the cause of the association between aortic stenosis and bleeding from angiodysplasia is still uncertain, but impaired aggregability of thrombocytes does not seem to be a simple explanation.[47]

Nowadays endoscopic laser photocoagulation seems to be the choice when the intestinal angiodysplasia can be reached by endoscopy. Rebleeding is reported in one-third of cases.[39] In patients with severe symptomatic aortic-valve stenosis, the valve replacement is indicated as a *gold standard* for the definitive resolution of GI bleeding.[48]

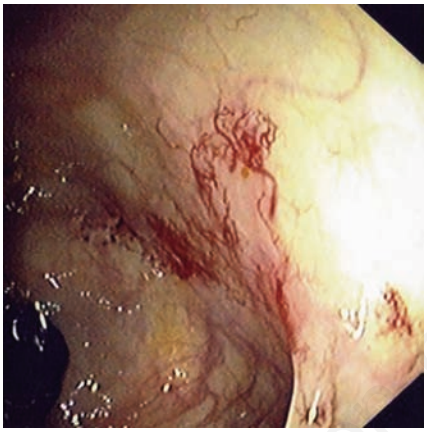

Figure 1. Colonoscopy showing bleeding due to angiodysplasia in the ascending colon.

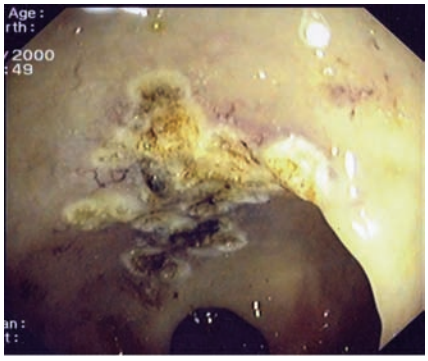

Figure 2. Colonoscopy showing the results of argon laser photocoagulation of the angiodysplasia.

Conclusions

Hyede's syndrome is a disorder in which aortic-valve stenosis can be complicated by GI bleeding due to angiodysplasia and type 2A von Willebrand disease; physicians should be aware of the possibilities of acquired von Willebrand disease and gastrointestinal bleeding from angiodysplasia in patients with aortic valve stenosis because a right diagnosis affects the management of patients with gastrointestinal bleeding and aortic-valve stenosis. Of course, we must be aware that digestive endoscopy should be carried out after causes of bleeding eventually associated with Heyde's syndrome have been ruled out such as epistaxis, ecchymoses, menorrhagia or metrorrhagia, hematuria, or bleeding induced by dental extraction.[44]

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