Occult Gastrointestinal Bleeding due to Acquired von Willebrand Syndrome in a Patient with Hypertrophic Obstructive Cardiomyopathy

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Abstract

A 69-year-old woman presented with a harsh systolic murmur and severe anemia. Echocardiography demonstrated hypertrophic obstructive cardiomyopathy with a peak pressure gradient of 154 mmHg. Endoscopic examinations disclosed an angiodysplasia and multiple diverticula in the colon, but no active bleeding was noted in these lesions. A selective defect of large multimers of von Willebrand factor was detected by electrophoresis. After collection of anemia and Ca antagonist therapy, left ventricular obstruction was relieved and cessation of the occult gastrointestinal bleeding was obtained. This is the first report whereby acquired type 2A von Willebrand syndrome was caused by hypertrophic obstructive cardiomyopathy.

Key words: von Willebrand factor multimers, hypertrophic obstructive cardiomyopathy, angiodysplasia, Ca antagonist

(DOI: 10.2169/internalmedicine.46.6026)

Introduction

Severe anemia due to gastrointestinal bleeding is not rare in patients with aortic stenosis, and cessation of the bleeding may be achieved after aortic valve replacement (1). The mechanism of these phenomena is explained by acquired type 2A von Willebrand syndrome, in which a selective loss of large multimers of von Willebrand factor occurs under high shear stress conditions and restoration of the large multimers is achieved after aortic valve surgery (2). However, no previous reports have demonstrated an association between type 2A von Willebrand syndrome and hypertrophic obstructive cardiomyopathy which resembles aortic stenosis in that obstruction to the left ventricular outflow tract generates high shear stress conditions.

Case Report

A 69-year-old woman was admitted to the hospital because of severe anemia on December 15, 2005. She began to experience general fatigue and exertional dyspnea a few days earlier. She had been treated for essential hypertension at a local clinic for 2 years, and her hemoglobin level had been around 11 g/dl. On physical examination, her heart rate was 91 beats/min and blood pressure was 102/62 mmHg. No rales or rhonchi were heard over lung fields. There was a grade IV/VI harsh systolic murmur at the lower left sternal border and a grade III/VI holo systolic murmur at the apex. Initial laboratory studies indicated that she was severely anemic, with a red blood cell count of 201×10⁴/mm³, hemoglobin 6.3 g/dl, hematocrit 19.4%, and platelet count 4.0×10⁴/mm³. The international normalised ratio of prothrombin time was 1.16, and activated partial thromboplastin time was 25.7 sec. An electrocardiogram showed left ventricular hypertrophy with nonspecific ST segment and T wave abnormalities, and a chest x-ray film showed mild cardiomegaly with clear lung fields. Echocardiography demonstrated asymmetric left ventricular hypertrophy with an interventricular septal thickness of 18 mm and a posterior wall thickness of 12 mm. The left ventricular wall motion was hyperdynamic, and obstruction to left ventricular outflow tract was produced by...
Figure 1. Continuous-wave Doppler recording. Echocardiographic examination demonstrated hypertrophic cardiomyopathy with obstruction to the left ventricular outflow tract. Continuous-wave Doppler showed a late peaking profile with a maximum velocity of 6.2 m/s, corresponding to a peak pressure gradient of 154 mmHg.

Figure 2. Electrophoretic analysis of the von Willebrand factor multimers.
A: A significant defect of the high molecular weight von Willebrand factor multimers was observed in comparison with the normal controls.
B: The loss of large von Willebrand factor multimers was restored at the time of reexamination 5 months later.
L, M, S, and SS represent large, middle, small and very small multimers, respectively.

Acquired type 2A von Willebrand syndrome is characterized by the loss of the largest multimers of von Willebrand factor, which circulates in the blood as a gigantic, multi-
Figure 3. Relief of left ventricular outflow tract obstruction. After restoration of hemoglobin and verapamil administration, repeated Doppler echocardiography showed an estimated pressure gradient of only 25 mmHg. Meanwhile, no further gastrointestinal bleeding occurred.

Figure 4. Clinical course. After Ca antagonist therapy, her hemoglobin level was maintained at her previous level with no further episodes of melena.

meric protein. Von Willebrand factor mediates platelet adhesion and aggregation at the site of vascular injury because of its action as a bridge between platelet receptors and the collagen of the subendothelium as well as between platelets themselves (3). The size of von Willebrand factor multimers varies from 500 to more than 20000 kilodaltons, and agarose-gel electrophoresis allows visualization of small, medium, and large molecular weight multimers (3, 4). The distribution of these multimers reflects an equilibrium between the secretion of large multimers and their cleavage to smaller, inactive derivatives. The cleavage of von Willebrand factor is mediated by a plasma metalloprotease ADAMTS 13. The proteolytic activity of ADAMTS 13 is significantly augmented under conditions of high fluid shear stress, because the structural changes of the von Willebrand factor molecule from coiled coil to elongated filament result in exposure of the cleavage site between Tyr842 and Met843 (3, 5, 6). A deficiency of large multimers of von Willebrand factor may secondarily occur in patients with high shear stress conditions, such as stenotic heart valve, ventricular septal defect or patent ductus arteriosus (3). Meanwhile, the large multimers of von Willebrand factor also play an essential role in primary hemostasis under the local high shear conditions of gastrointestinal lesions including angiodysplasia and telangiectasia (7). Therefore, conditions with high shear stress may cause acquired type 2A von Willebrand syndrome through the loss of large multimers, and predispose to gastrointestinal bleeding from coexisting angiodysplasia.

Heyde initially questioned the relationship between idiopathic gastrointestinal bleeding and aortic stenosis in 1958 (8). Since then, sporadic case reports have described bleed-
ing from angiodysplasia in patients with aortic stenosis and its cessation after aortic valve replacement. Angiodysplasias, predominantly observed in patients older than 60 years, occur as single or multiple lesions especially in the cecum or proximal ascending colon (7). Although aortic stenosis was initially considered as a cause of angiodysplasias, subsequent studies suggested that acquired type 2A von Willebrand syndrome could be the link between aortic stenosis and bleeding from angiodysplasias (9). Aortic stenosis predisposes blood flow to high shear stress, and a selective loss of large von Willebrand factor multimers is demonstrated in patients with aortic stenosis and bleeding angiodysplasia (10). The decrease in large multimers, despite normal levels of von Willebrand factor, correlates with the severity of aortic stenosis. Furthermore, the loss of large von Willebrand factor multimers is promptly restored after aortic valve replacement, while the recurrence of aortic stenosis is associated with the recurrence of abnormalities in von Willebrand factor (4). These findings confirm the previous observation that aortic valve replacement, rather than surgical resection of the affected bowel tract, is the most effective treatment to prevent recurrent gastrointestinal bleeding (1). Hence, aortic stenosis complicated by recurrent gastrointestinal bleeding is explained by acquired type 2A von Willebrand syndrome due to a selective loss of large von Willebrand factor multimers under high shear stress conditions.

Hypertrophic obstructive cardiomyopathy resembles aortic stenosis in that obstruction to the left ventricular outflow tract generates high fluid shear stress. This feature may therefore predispose to a deficiency of large multimers of von Willebrand factor, thus leading to gastrointestinal bleeding. Although some previous reports have suggested the relationship between hypertrophic obstructive cardiomyopathy and coexisting acquired type 2A von Willebrand syndrome (11), this is the first report demonstrating the deficiency of large multimers of von Willebrand factor. There are only 8 reports, including ours, describing a patient with hypertrophic obstructive cardiomyopathy complicated by gastrointestinal bleeding (11-17). These reports involve 7 females and 1 male, all of them are older than 55 years of age. Angiodysplasias were detected in 7 patients (11-16). Peak pressure gradients across the left ventricular outflow tract were at least 75 mmHg in 5 patients with available data (11, 12, 16, 17). Direct hemostasis of angiodysplasia was achieved by surgical removal (12-14) or endoscopic intervention (11) in 4 cases. However, negative inotropic agents (15), surgical septal myectomy (16), or percutaneous alcohol septal ablation (17) was also effective in preventing recurrent bleeding, as is the case with aortic stenosis, through the reduction of pressure gradients. In addition, the present case indicates that immediate correction of the hemoglobin level should be considered because the pressure gradient and high shear stress condition may be exacerbated by severe anemia in hypertrophic obstructive cardiomyopathy. Therefore, patients with hypertrophic obstructive cardiomyopathy and bleeding tendency should be screened for a deficiency of large multimers of von Willebrand factor, and alleviating the left ventricular outflow tract obstruction may represent an important therapeutic approach for recurrent gastrointestinal bleeding rather than surgical resection of the lesions.

Some speculations can be made for the lower incidence of gastrointestinal bleeding in hypertrophic obstructive cardiomyopathy than in aortic stenosis. Aortic stenosis predominates in the elderly in concurrence with angiodysplasia, because both of them are associated with the degenerative aging process (7). In contrast, hypertrophic obstructive cardiomyopathy develops in younger individuals. The younger patients with hypertrophic obstructive cardiomyopathy may be free from gastrointestinal bleeding merely because they do not have developed angiodysplasias. Moreover, high shear stress conditions may be less severe in hypertrophic obstructive cardiomyopathy which is characterized by dynamic obstruction with late systolic narrowing of the left ventricular outflow tract, as compared with those in aortic stenosis which is fixed obstruction throughout the ventricular systole. It is to be clarified whether the deficiency of von Willebrand factor large multimers preexists in these younger patients with hypertrophic obstructive cardiomyopathy and whether the severity of left ventricular outflow tract obstruction is correlated with the degree of deficiency of von Willebrand factor large multimers.

References


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