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Case Report

HEYDE SYNDROME: CASE REPORT

Abstract

Heyde syndrome was first described by Edward Heyde in 1958 in ten patients with calcific aortic stenosis and gastrointestinal hemorrhage. This syndrome is characterized by calcific aortic stenosis, acquired von Willebrand disease, and angiodysplasia in colon and caecum causing gastrointestinal hemorrhage. A 71 years old male was admitted to our clinic, because of fatigue, melena, and hematochezia. On medical history, there was an aortic valve replacement due to aortic stenosis six months ago and gastrointestinal hemorrhage three months ago. After colonoscopic examination, multiple angiodysplasia was detected at sigmoid colon. The level of von Willebrand factor was low. The patient was diagnosed as Heyde syndrom. Heyde syndrome should be considered in patients with von Willebrand disease, aortic valve replacement and gastrointestinal hemorrhage due to intestinal angiodysplasia.

Key Words: Heyde Syndrome, Gastroinestinal Hemorrhage, Angiodysplasia, von Willebrand Disease.

Olgu Sunumu

HEYDE SENDROMU: OLGU SUNUMU

Öz

Heyde Sendromu; ilk kez 1958 yılında Edward Heyde tarafından kalsifik aort stenozu ve gastrointestinal kanaması olan 10 hastada tanımlanmıştır. Bu sendrom kalsifik aort stenozu, edinsel von Willebrand hastalığı ve gastrointestinal kanamaya neden olan kolon ve çekumda anjiyodisplazi ile karakterizedir. 71 yaşında erkek hasta kliniğimize melena, hematokezya ve halsizlik yakınmaları nedeniyle başvurdu. Özgeçmişinde altı ay önce aort stenozu nedeniyle aort kapak replasmanı ve üç ay önce gastrointestinal kanama vardı. Kolonoskopik incelemeden sonra sigmoid kolonda çoklu anjiodisplazi saptandı. von Willebrand faktör düzeyi düşüktü. Hastaya Heyde Sendromu tanısı konuldu. Heyde sendromu aort kapak replasmanı, von Willebrand hastalığı ve intestinal anjiodisplaziye bağlı gastrointestinal kanamalı hastalarda düşünülmelidir.

Anahtar Sözcükler: Heyde Sendromu; Gastrointestinal Kanama; Anjiodisplazi; von Willebrand Hastalığı.

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Introduction

Heyde syndrome was first described by Edward Heyde in 1958 in ten patients with calcific aortic stenosis and gastrointestinal hemorrhage (1). This syndrome is characterized by calcific aortic stenosis, acquired von Willebrand disease (vWD), and angiodysplasia in colon and caecum causing gastrointestinal hemorrhage (2). The frequency of Heyde syndrome is not known certainly. It is diagnosed, when a patient with calcific aortic stenosis sufferes from anemia and gastrointestinal hemorrhage due to intestinal angiodysplasia (3). Gastrointestinal hemorrhage in patients with calcific aorta stenosis is encountered 100 times more than normal population (4). Here we report a patient with Heyde syndrome, presenting with gastrointestinal hemorrhage due to intestinal angiodysplasia, vWD, and aortic valve replacement.

Case Report

A 71 years old male was admitted to our clinic, because of fatigue, melena, and hematochezia. On medical history, there was an aortic valve replacement due to aortic stenosis six months ago and gastrointestinal hemorrhage three months ago. The patient had been receiving 5 mg/day warfarin, 20 mg/day amiodarone, 5 mg/day amlodipin, and 10mg/day rosuvastatin. On physical examination, there were pallor, blood pressure 140/90 mmHg, pulse rate 108/min. Rectal examination revealed melena and hematochezia. Hematological parameters were hemoglobin level 8.8 g/dl, hematocrit level 27%, platelet count 341.000/mm^3, white blood cell count 9.400/mm^3, uncorrected reticulocyte ratio 3%, prothrombin time (PT) 52 sec, active partial thromboplastin time (aPTT) 63.4 sec, and fibrinogen level 240 mg/dl (Normal range: 212-488 mg/dl). PT and aPTT levels returned to normal levels after mixing test. Biochemical tests were normal except of LDH 588 IU/L (Normal range: 243 IU/L). Warfarin treatment was stopped. 10 mg/day vitamin K, 20 ml/kg fresh frozen plasma, and packed red blood cell transfusion were given to the patient. At the third day, PT and aPTT levels were 55 sec and 62.2 sec, respectively. Gastrointestinal hemorrhage stopped. The findings on transthoracic echochardiography were normo-functional aort valve replacement with max/mean gradient 44/24 mmHg, 3.8 cm aortic diameter, grade 1 aortic insufficiency, and mild enlargement of aortic root. After the endoscopy of upper gastrointestinal system, milimetrical erosion on cardia region and erosive bulbitis were detected, but there was not any lesion to cause active hemorrhage. The colonoscopic examination showed four angiodysplastic lesions. One of them was actively bleeding on the ascending colon. At the 20th day, PT and aPTT levels were 49 sec and 54 sec, respectively. The platelet aggregation tests with epinephrine, collagen, and ADP were normal. The platelet aggregation test with ristosetin was 59% (N: %70-98) and co-factor activity was 31%. von Willebrand Factor (vWF) level was 52% (Normal range: 80-120%). This level was accepted as low because the patient's blood group was A Rh(+) and acquired von vWD type 1 was suspected. The activities of coagulation factors were 44% (N: 50-150%) for factor 8, 52% (normal range: 50-150%) for factor 9, and 50% (normal range: 50-150%) for factor 7. Other coagulation parameters were not evaluated. The patient was diagnosed as Heyde syndrome and warfarin was stopped. During 11-months of follow-up period, no hemorrhage occurred.

Discussion

After post-mortem examinations, Bose and Rosenbaum reported the distension of vessels of bowel mucosa in cases with aortic stenosis (AS) and hemorrhage in 1971. They explained that low degree chronic hypoxemia lead to ectasia on vessel walls by reflex sympathetic vasodilatation and smooth muscle relaxation. Another theory depicts that alternating pulse waves due to cholesterol emboli from aortic valve/aortic stenosis may lead to colonic mucosal hypoxia. In various studies it was reported that stenosis of the aortic and mitral valves increased the rates of gastrointestinal hemorrhage (3).

von Willebrand disease is the most common hereditary bleeding disorder. Its prevalence according to laboratory data is approximately 1% and data based on symptomatic cases revealed a prevalence rate in 0.1 % of population. vWF displays two roles on coagulation; the first is as the major adhesion molecule that adhers platelets to subendothelium, and the second is as a binding protein for factor VIII, resulting in significant prolongation of the factor VIII half-life in circulation. The platelet-adhesive function of vWF is critically dependent on the presence of large vWF multimers, while factor VIII binding is not. Most of symptoms of vWD are similar to those in factor VIII deficiency (hemophilia A) except of platelet type. vWD is classified into three groups. The most common type is type I (80% of all cases) in which there is a parallel decrease in the vWF function and factor VIII levels. Patients with type 2 vWD have functional defects; so vWF antigen measurement is significantly higher than function test. Ristosetin cofactor or vWF activity measured for collagen binding activity is decreased in types 2A, 2B, and 2M. Decreased function in type 2A is related to increased affinity to detachment of ADAMTS13 which causes loss of moderate or high molecular weighted (HMW) multimers or the decreased secretion of these multimers by the cell.

Acquired vWD is a rare disorder, most commonly seen in patients with underlying lymphoproliferative disorders, such as monoclonal gammopathies of undetermined significance (MGUS), multiple myeloma, and Waldenstrom's macroglobulinemia. MGUS should be suspected especially in elderly patients with new onset of severe mucosal bleeding symptoms (5).

Gastrointestinal hemorrhage due to colonic angiodysplasia is a well known complication of vWD. A few causes of relationship between aortic stenosis, vWD, and angiodysplastic hemorrhage have been cited in the literature. High-molecular weight (HMW) vWF multimers in angiodysplasia are needed to maintain the normal homeostasis and decreasing and/or depletion of these multimers is the most important cause of bleeding secondary to angiodysplasia. However, the reason of affinity to hemorrhage in aortic stenosis is increased pretolysis of HMW multimers by the vWF-cleaving metalloprotease (6). Acquired platelet function disorder is seen as a cause of prolonged bleeding time in aortic stenosis. Normalization of the bleeding time after aortic valve operations supports these hypothesis of platelet interaction in calcified regions and function disorder. Acquired platelet function disorder may be an etiological factor in Heyde syndrome in which bleeding time becomes normal after aortic valve replacement (7). Also our patient was using warfarin after aortic valve replacement and he suffered from gastrointestinal hemorrhage previously three times. With colonoscopy we detected four foci of angiodysplastic lesions, one of which was actively bleeding. Adrenaline was applied to bleeding lesion for homeostasis.

In patients with aortic stenosis, turbulence occurs while passing through from the stenotic region,. This turbulance causes increased activation of vWF divisive metalloproteinase and leads to a decrease in vWF multimers. As a result factor 8 level decreases secondarily and platelet adhesion to subendotelial junction is disturbed. The causes of gastrointestinal hemorrhage due to angiodysplasia are multifactorial. HMW vWF multimers are decreased in patients with O blood group. Increase of the vWF- cleaving metalloprotease results in proteolysis of the vWF. Azotemia/uremia, low platelet count, and anemia may contribute to bleeding (4,8). In our patient, low levels of vWF l, co-factor, and factor 8 were detected. Acquired vWD type 1 was considered. However, type 2A was not excluded, because moderate to high weight VWF multimers were not examined. The relation between type 1 vWD and angiodysplasia is not clear (5). The definition of acquired vWD may be more correct. Hemorrhage generally occurs in caecum and ascending colon in which angiodysplasia appears (4). In our patient, angiodysplasia was detected in the ascending colon.

Both Heyde syndrome and vWF levels increase with aging (9). vWF level was detected as low in our patient. He was 71 years old. In these patients, when aorta valve replacement is necessary; bioprosthesis is advised because of probability of increased bleeding risk with anticoagulant treatment, also signs generally regress after valve replacement. There are many methods of Heyde syndrome therapy. However, aortic valve replacement should be recommended as a 'gold standard'. It is proven that aortic valve replacement corrects the blood supply in the gut. It is reported that 95% of AS-patients with gastrointestinal hemorrhage due to angiodysplasia have no bleeding symptoms after aortic valve replacement (10). However, bleeding tendency may not ameliorate completely or it may recur as in the current case (4,9).

In conclusion, Heyde syndrome should be considered in the patients with gastrointestinal hemorrhage due to intestinal angiodysplasia, vWD, and aortic valve replacement.

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