Octreotide for Heyde’s syndrome: A case report

Syndrome de Heyde et octréotide : à propos d’un cas

In 1958, E.C. Heyde reported a case series of 10 patients with calcific aortic valve stenosis and massive gastrointestinal bleeding [1]. Submucosal angiodysplasia were subsequently identified as the source of bleeding, however the mechanisms of such an association are elusive and the best treatment strategy remains controversial.

Case report

A 72-year-old man presented with relapsing enterorrhagia and progressive anemia. Multiple sites of complex mucosal angiodysplasia in the jejunum were shown upon video capsule endoscopy after repeated upper and lower gastrointestinal tract endoscopies and angiographic studies that failed to disclose the origin of the bleeding. His previous history included a severe calcified aortic stenosis (mean pressure gradient of 56 mmHg, maximal gradient of 77 mmHg, functional area of 0.87 cm²), hypertension, coronary artery disease, chronic kidney disease stage III, and a re-stenosis of a left internal carotid artery graft, for which the patient was taking clopidogrel, simvastatin, ramipril, and metoprolol.

Laboratory findings disclosed iron deficiency and anemia with hemoglobin (Hb) 6.1 g/dL; two units of packed red blood cells were transfused, clopidogrel was withdrawn, and selective angiography of the superior mesenteric artery with embolization of multiple areas of the jejunal angiodysplasia was performed. The patient was discharged on the 6th day with Hb 10.5 g/dL and no evidence of active bleeding from the gastrointestinal tract. He remained stable and clopidogrel (75 mg daily) was re-instituted with the development of gastrointestinal angiodysplasia and its recurrence [1]. Submucosal angiodysplasia were subsequently identified as the source of bleeding, however the mechanisms of such an association are elusive and the best treatment strategy remains controversial.

Discussion

Heyde’s syndrome refers to an acquired type 2A von Willebrand syndrome that is characterized by the loss of the largest polymers of vWF [2]. The high shear forces generated through the stenotic aortic valve are postulated to expose the bond between amino acids 842 and 843 of vWF, which is sensitive to the action of ADAMTS13, ultimately resulting into the proteolysis and loss of the highest-molecular-weight vWF polymers [2]. Abnormalities in vWF function can be found in up to 92% of patients with severe aortic stenosis and seem to correlate significantly with the hemodynamic severity of valve stenosis [3]. The full resolution of vWF abnormalities and ceasing of gastrointestinal bleeding within hours of valve replacement and their reappearance in close relationship with the recurrence of the valve stenosis or when there is a mismatch between the patient and the prosthesis lend support to the central role of this mechanism [3]. Furthermore, vWF proteolysis and loss of the highest-molecular-weight vWF polymers have been demonstrated also in other cardiac disorders characterized by high shear stress such as hyperthermic obstructive cardiomyopathy and the use of left ventricular assist device support [2]. It remains unclear if vWF is directly involved in angiogenesis under physiological conditions; nonetheless qualitative or quantitative vWF defects are associated with the development of gastrointestinal angiodysplasia and greatly increase both the bleeding propensity and its severity [2].

Our patient had all the clinical features of Heyde’s syndrome. Even though we did not perform gel electrophoresis of vWF, i.e. the gold standard to show the loss of large vWF polymers, nonetheless all other laboratory studies did not disclose any abnormalities of platelets, coagulation parameters and vWF levels and function. It should be taken into account that all these tests remained within the normal range over a prolonged follow-up after the start of octreotide therapy and while the patient was not taking any anti-platelet or anticoagulant medications and laboratory studies repeatedly showed normal values of bleeding time (3 minutes, normal 2–7), platelet count (276/mm³, normal 150–300/mm³), activated partial-thromboplastin time (29 seconds, normal 27–35), international normalized ratio (1.1, normal 0.9–1.1), factor VIII coagulant level (93 IU/dL, normal 50–150), von Willebrand factor (vWF) antigen (110 IU/dL, normal 50–150) and vWF ristocetin cofactor activity (125 IU/dL, normal 50–150).
noted that all patients with aortic stenosis and acquired von Willebrand syndrome in the series from Vincentelli et al. had normal levels of factor VIII coagulant activity and vWF antigen [3]. We speculate our case could represent the tip of the iceberg of a subset of patients with Heyde’s syndrome in whom the underlying mechanistic explanation for the association between aortic stenosis, intestinal angiodysplasia, and gastrointestinal bleeding might be not provided by the development of type 2A von Willebrand syndrome. Alternative mechanisms ranging from age-related degeneration to mucosal ischemia and cholesterol embolization have been advocated to explain the development of angiodysplasia and gastrointestinal bleeding in patients with aortic stenosis [4]. Differences in genetic backgrounds and causative mechanisms that are so far unrecognized could lead to the definition of Heyde’s subsyndromes, which will probably need different therapeutic approaches. There is no consensus about the best treatment strategy of gastrointestinal bleeding in patients with Heyde’s syndrome. A wide spectrum of options are available and current evidence indicates that octreotide and other somatostatin analogues can be helpful particularly in patients with refractory gastrointestinal bleeding associated with Willebrand disease and other coagulation disorders and in those at high risk for invasive procedures [5]. A wide spectrum of mechanisms ranging from decreased splanchnic blood flow to increased vascular resistance and improved platelet aggregation could be involved in the action of octreotide in this setting [5]. Furthermore, anecdotal experience in patients with von Willebrand’s disease and bleeding intestinal angiodysplasia suggests that the response to octreotide may be mediated by increased levels and functional activity of vWF [2]. However, few studies have focused on the use of somatostatin analogues in patients with Heyde’s syndrome. There is only one report of the successful treatment with octreotide of one patient with Heyde’s syndrome who had no improvement in gastrointestinal bleeding after aortic valve replacement [6]. Furthermore, Rennyson et al. have described a patient in whom left ventricular assist device-related gastrointestinal hemorrhage was effectively stopped with a combination of subcutaneous and intramuscular depot formulations of octreotide [7]. In our case, the patient remained free of bleeding while on long-term treatment with octreotide with stable Hb levels over more than two years of follow-up. This suggests that the duration of octreotide therapy could be the critical point to achieve the full control of gastrointestinal bleeding in Heyde’s syndrome.

In conclusion, we suggest that octreotide and possibly other somatostatin analogues could be a valuable alternative to aortic valve replacement for the management of gastrointestinal bleeding in patients with Heyde’s syndrome who are not eligible for aortic valve replacement.

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References


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