The association between aortic stenosis and intestinal angiodysplasia – the Heyde’s Syndrome (RCD code: VIII-1)

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Abstract

Heyde’s syndrome is defined as a combination of gastrointestinal bleeding from a gastrointestinal angiodysplasia in patients with aortic stenosis. An acquired von Willebrand factor deficiency secondary to aortic stenosis is considered to be the major abnormality in Heyde’s syndrome. Management of Heyde’s syndrome requires cooperation of many different kinds of specialists: cardiologists, gastroenterologists, hematologists, general surgeons and cardio surgeon. We present a case report of 62 years old female with no history of cardiovascular disorders referred to the Centre of Rare Cardiovascular Diseases in Kraków for cardiological evaluation of a heart murmur prior to a surgical procedure of a vascular malformation in colon. JRCD 2014; 1 (7): 17–20

Key words: Heyde’s syndrome, gastrointestinal bleeding, aortic stenosis, acquired von Willebrand factor deficiency

Background

Heyde’s syndrome is defined as a combination of gastrointestinal (GI) bleeding from a GI angiodysplasia in patients with aortic stenosis (AoS). Edward Heyde was the first to publish, in 1958, a report of 10 patients with both AoS and GI bleeding [1]. In 1992 Olearchyk identified this association of symptoms as Heyde’s syndrome [2]. It has been proven furthermore, that GI bleeding terminates after the aortic valve replacement surgery [3].

Case presentation

62 years old Caucasian female with a history of familial thrombocytopenia was referred to the Centre of Rare Cardiovascular Diseases in Kraków in June 2013 for cardiological evaluation of a heart murmur prior to a surgical procedure of a vascular malformation present in her ascending part of the colon. She had no history of cardiovascular disorders whatsoever. Comorbidities included left adrenal adenoma under evaluation, glaucoma of both eyes with her left eye blind.

She was hospitalized in November and December 2012 due to recurrent massive bleedings from the lower gastrointestinal tract. Each time, she required multiple blood transfusions due to hemorrhagic anemia (altogether 10 units of packed red blood cells). No abnormalities or source of bleeding had been found in repetitive colonoscopies or gastroscopies.

In December 2012 the patient was consulted by the hematologist because of the familial thrombocytopenia, also diagnosed in her daughter, siblings and mother. The platelet count was about 100 000/mcl at that time. Considering the fact that she has never presented any signs of cutaneous or mucosal bleeding and there has not been detected splenomegaly on abdominal ultrasound examination, thrombocytopenia could not be recognized as the cause of the recurrent bleeding and therefore further diagnostics was advised. Furthermore, administration of tranexamic acid and etamsylate for at least two weeks after the bleeding was recommended. It was also advised to avoid antiplatelet medications and transfuse platelet concentrate in the case of recurrence of bleeding.

In April 2013 the patient was hospitalized due to gastrointestinal bleeding and posthemorrhagic anemia once again. A capsule endoscopy was performed revealing a vascular malformation of the ascend-
ing colon (Figure 1) and therefore a surgical removal of the malformation was planned. In the course of routine presurgical evaluation, a heart murmur was found and she was referred to her cardiologist. On admission to our cardiology department she presented dizziness, what previously was associated with the anemia and eye problems. She denied fatigue, shortness of breath on exertion, chest pain or arrhythmia. Physical examination confirmed holosystolic murmur that was the best audible at the upper right sternal border in the 2nd right intercostal space and radiated do the carotid arteries bilaterally. Moreover, her skin and conjunctiva were pale. No signs of heart failure were noted.

The basic blood laboratory tests revealed posthemorrhagic anemia and hypercholesterolemia (Table 1). There were no significant abnormalities in the platelet aggregation panel found (Table 2). On echocardiography normal size of the left ventricle (47/30 mm) was seen with the hypertrophy of the heart muscle (posterior wall – 13/20 mm, interventricular septum – 15/18 mm). There were no wall motion abnormalities and the ejection fraction was 65% (Figure 2). Severe aortic stenosis with moderate regurgitation was diagnosed. Aortic leaflets were thickened and calcified, transvalvular gradient was 148/95 mmHg and the aortic valve area was 0.4 cm² (Figure 3).

She was scheduled for coronary angiography, which revealed right coronary artery stenosis with 75% narrowing of the lumen located in between segment I and II (Figure 4). Aortography showed calcified aortic ring and stenotic movement of the leaflets together with mild aortic regurgitation.

At this point suspicion of Heyde's syndrome was drawn. For the confirmation the level of von Willebrand cofactor and antigen together with factor VIII were tested (Table 3).

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**Table 1. Abnormal laboratory tests revealing posthemorrhagic anemia and hypercholesterolemia**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>5.35</td>
<td>10³/mlC</td>
<td>[3.80–10.00]</td>
</tr>
<tr>
<td>RBC</td>
<td>3.54</td>
<td>10⁶/mlC</td>
<td>[3.70–5.10]</td>
</tr>
<tr>
<td>HGB</td>
<td>9.8</td>
<td>g/dL</td>
<td>[12.0–16.0]</td>
</tr>
<tr>
<td>HCT</td>
<td>31.8</td>
<td>%</td>
<td>[37.0–47.0]</td>
</tr>
<tr>
<td>MCV</td>
<td>89.8</td>
<td>fl</td>
<td>[80.0–99.0]</td>
</tr>
<tr>
<td>MCH</td>
<td>27.7</td>
<td>pg</td>
<td>[27.0–35.0]</td>
</tr>
<tr>
<td>MCHC</td>
<td>30.8</td>
<td>g/dL</td>
<td>[32.0–37.0]</td>
</tr>
<tr>
<td>RDW</td>
<td>19.0</td>
<td>%</td>
<td>[11.5–14.5]</td>
</tr>
<tr>
<td>PLT</td>
<td>140.0</td>
<td>10³/mlC</td>
<td>[140–440]</td>
</tr>
<tr>
<td>T-CHOL</td>
<td>7.58</td>
<td>mmol/L</td>
<td>[3.10–5.00]</td>
</tr>
<tr>
<td>LDL-C</td>
<td>6.04</td>
<td>mmol/L</td>
<td>&lt;3.00</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.35</td>
<td>mmol/L</td>
<td>&gt;1.20</td>
</tr>
<tr>
<td>TG</td>
<td>1.34</td>
<td>mmol/L</td>
<td>&lt;1.70</td>
</tr>
</tbody>
</table>


**Table 2. Platelet aggregation panel**

| AGAA      | 93%   | [74–99] |
| AGADP10   | 74%   | [71–88] |
| AGEPINE   | 82%   | [78–88] |
| AGKOLAG   | 73%   | [70–94] |
| AGRIS15   | 85% L | [87–102] |

[Due to the low platelet count 156 000/mlc, the result may be unreliable.]

AGAA – Aggregation with arachidonic acid in concentration 0.5 mM, AGADP – Aggregation with ADP in concentration 10 μM, AGEPINE – Aggregation with epinephrine in concentration 1 μg/mL, AGKOLAG – Aggregation with Collagen in concentration 1 μg/mL, AGRIS15 – Aggregation with Ristocetin in concentration 1.5 mg/mL.

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**Figure 1.** Capsule endoscopy. Vascular malformation (arrow) in the ascending colon

**Figure 2.** Transthoracic echocardiography. Parasternal long-axis view. M-mode presentation. The measurement of the size of the left ventricle (LV), intraventricular septum (IVS), left ventricle posterior wall (LVPW) and ejection fraction (EF)
The Heyde’s Syndrome

With the new clinical and laboratory data she was reconsulted with the hematologists. Because of not characteristic for the acquired von Willebrand syndrome disproportion of the ratio of the von Willebrand cofactor and von Willebrand antigen, the hematologist suggested that evaluation of vWF multimers distribution should be considered.

However, due to limitations of this method and literature reports indicating effectiveness of cardiac surgery even in patients with normal distribution of von Willebrand multimers, it was concluded that further evaluation of von Willebrand syndrome is not necessary to determine the management.

The patient was qualified for the bioprosthetic aortic valve replacement and right coronary bypass grafting based on an opinion of a group of experts composed of cardiologists, cardiac surgeons, anesthesiologists, gastroenterologists and coagulation disorders specialists.

Pathogenesis

An acquired von Willebrand factor (vWF) deficiency secondary to aortic stenosis is considered to be the major abnormality in Heyde’s syndrome [4]. vWF plays an important role in the process of the adhesion of platelets to the subendothelium of injured vessels, inducing their aggregation.

In Heyde’s syndrome, stenotic aortic valve causes proteolysis of the vWF protease (ADAMTS13) what provokes conformational change of the vWF multimers. Reduced number of the multimers impairs platelet-mediated hemostasis especially in the areas of high shear stress, such as angiodysplastic vessels, and causes the bleeding. Angiodysplasia is a small microvascular malformation of the GI tract. It results from multiple episodes of increasing wall tension during colonic contractions. This eventually causes dilation of the submucosal veins resulting in angiodysplasia.

In healthy vessels, presence of high molecular weight vWF multimers (HMWM) is substantial for the hemostasis [5, 6].

Management strategy

Management of Heyde’s syndrome requires cooperation of many different kinds of specialists: cardiologists, gastroenterologists,
hematologists, surgeons etc. In most cases aortic valve replacement (AVR) provides definitive therapy and decreases GI bleeding in most patients with angiodysplasia (ca. 93%), while the GI surgery has a very low durable remission rate of approximately 5% [5, 7].

However, AVR is associated with the risk of bleeding. Surgical procedure requires administration of heparin intraoperatively for the cardiopulmonary bypass. Another factor to consider is that after AVR procedure an anticoagulation therapy is necessary. The use of bioprosthetic valve might be a solution for this problem, however it is not applicable for every patient [5, 8].

General surgery procedures for the treatment of the GI bleeding due to the vascular malformations involves endoscopic, selective artery embolization and colectomy. It is however important to notice, that endoscopic treatment may be ineffective because of the multifocal pattern of angiodysplasia, the selective artery embolization may increases the risk of bowel infarction and colectomy is a very invasive procedure [5].

For unstable patients before AVR surgery therapeutic alternatives include supplementation of vWF or perioperative Contact F (a combination of vWF and factor VIII). Fresh-frozen plasma, 1-desamino-8-darginine vasopressin, cryoprecipitate or recombinant vWF do not have sufficient success rate in acquired von Willebrand syndrome. For elderly patients who refuse AVR, the treatment includes iron supplementation and regular blood transfusion, if necessary [5].

Conclusions

However, the association between aortic valve stenosis and intestinal angiodysplasia seems not to be obvious, noticing it is essential for the proper proceeding. Not the GI surgery but the aortic valve replacement is a treatment of choice and offers the long-term resolution of the GI bleeding.

References