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CASE REPORT

Artificial Heart (Clinical)

Intractable bleeding tendency due to acquired von Willebrand syndrome after Jarvik 2000 implant

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Abstract A 61-year-old man was implanted with a Jarvik 2000, a continuous axial flow type left ventricular assist device (LVAD), for end-stage heart failure due to dilated cardiomyopathy. One month later, his postoperative course was complicated with intractable oozing-type gastrointestinal bleeding from multiple small shallow ulcers and erosions in the colon. In addition, repeated bleeding episodes were encountered at around thoracentesis site for pleural effusion. Hematological examination showed that platelet counts and coagulation factors were kept within normal ranges. We, thereafter, revealed remarkable loss of the large multimers of von Willebrand factors (VWFs), which might be closely associated with his intractable bleeding tendency.

Keywords Ventricular assist device · Bleeding tendency · Von Willebrand factors · Acquired von Willebrand syndrome

Introduction

Gastrointestinal bleeding is a well-known complication [1] as a consequence of anticoagulant therapy after LVAD implantation. Recently, acquired von Willebrand syndrome (aVWS) has been raised as an underlying mechanism for bleeding in HeartMate II or HVAD recipients [2].

However, a potential association between aVWS and Jarvik 2000 (Jarvik Heart, Inc., New York, USA), a continuous axial flow type LVAD, has become to be defined yet. There has been a report on Jarvik 2000-associated aVWS as a format of 'letter to the editor'. We herein report a case of intractable bleeding tendency most likely due to aVWS after Jarvik 2000 implant.

Case

A 61-year-old man with end-stage heart failure exhibiting catecholamine dependency was consulted to our department for LVAD implantation. He had a long clinical history of dilated cardiomyopathy and had been admitted to our hospital for the treatment of exacerbated cardiac failure 12 times over the last 6 years.

He was listed as a candidate for heart transplantation, and subsequently underwent the implantation of Jarvik 2000 as a bridge to heart transplantation. His height was 1.73 m, weight was 71.1 kg and body surface area (BSA) was 1.80 m^2. Jarvik 2000 assisted his circulation sufficiently by generating flow at a rate of 4–5 L/min with a high-speed rotation of the axial pump at 10,000 rpm. His postoperative course was stable until 1 month. A postoperative echocardiography exhibited optimal findings: (1) left ventricular end-diastolic dimension (LVDd) became smaller from preoperative 65–42 mm, (2) aortic valve opened intermittently and regurgitation was trivial, and (3) tricuspid valve regurgitation was mild without pulmonary hypertension pattern. However, he suddenly suffered from melena at the postoperative day 35 (POD 35). His hemoglobin level decreased from 8.5 to 6.9 g/dL, and packed red

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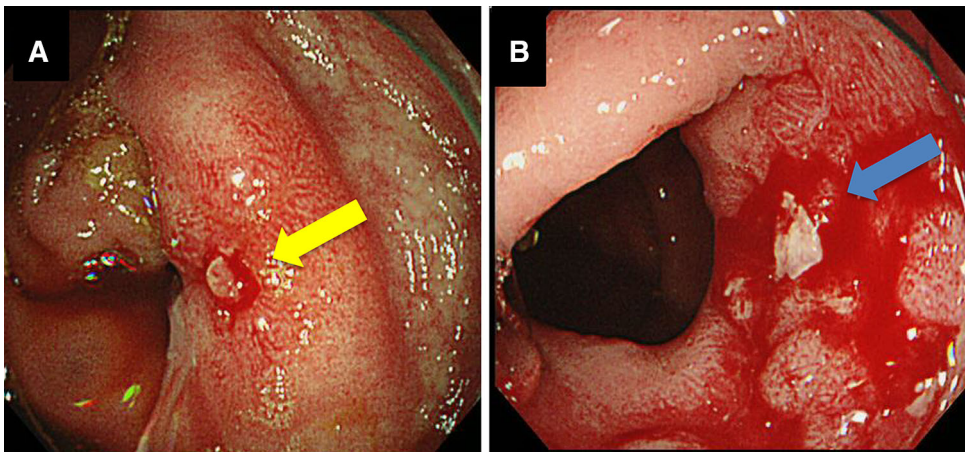

Fig. 1 Lower gastrointestinal endoscopic examination at POD49 revealed multiple small ulcers/erosions with oozing hemorrhage (**a**, **b**)

blood cell transfusion was performed. He had been treated with warfarin by adjusting prothrombin time international normalized ratio (PT-INR) at around 2.5 and 100 mg/day of aspirin. His platelet count was 105,000/mm^3. Lower gastrointestinal endoscopic examinations revealed oozing hemorrhages from multiple shallow ulcers and erosions in his ileocecal, ascending and transverse colons (Fig. 1). Endoscopic clipping or thermocoagulation were carried out, but failed to resolve hemorrhage completely. Administration of warfarin and aspirin was discontinued, and oral intake prohibited. Lower gastrointestinal bleeding was stabilized temporarily, although it recurred 2 weeks later.

The gastrointestinal bleeding compromised his general conditions, and serum protein and albumin levels dropped down 5.2–2.2 g/dL, respectively. Pleural effusion emerged and increased in his left thoracic cavity. On POD 61, when a drainage tube was placed into his left thoracic cavity with maximal precaution, massive bleeding unexpectedly occurred and hematoma occupied most of his left thoracic cavity. After the initial episode of lower gastrointestinal bleeding, he took no aspirin or warfarin, and alternatively received 10,000 IU/day of heparin intravenously. Data of laboratory examination were as follows: platelet count was 54,000/mm^3, PT-INR was 1.05, activated partial thromboplastin time (APTT) was 47.8 s (standard 29.6–40.8 s) and fibrinogen content was 289 mg/dL (standard 208–400 mg/dL). Since his hemodynamic state became unstable, surgical hemostasis was performed with thoracotomy. Bleeding from the surface of lingular segment of his left lung was visualized and hemostasis was achieved. Nonetheless, the intra-thoracic bleeding recurred from the sites of dissected surface of previously adhered parietal pleura. Since his left thorax became filled with hematoma and atelectatic lung (Fig. 2), surgical hemostasis was repeatedly performed three more times and finally the bleeding was controlled. During the period an approximately 4,800 ml of packed red blood cell was transfused over 9 days.

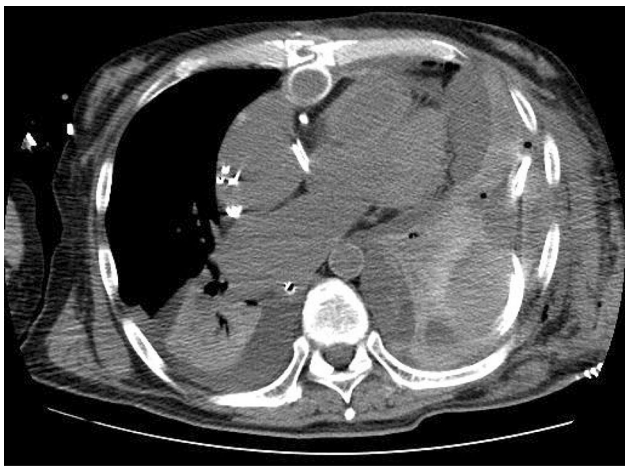

Fig. 2 Bleeding in thoracic cavity. A photo of computed tomography on POD 62 that revealed the left thoracic cavity filled with atelectasis and massive hematoma

At this stage, we highly suspected that hemorrhagic tendency might be associated with aVWS.

The data of hematological examination during the clinical course were relatively stable with platelet transfusion as necessary: platelet count at 50,000–100,000/mm^3, PT-INR and APTT were within therapeutic ranges and further VWF antigen level and its activity were within normal ranges. On the other hand, an apparent loss of VWF large multimers was detected (Fig. 3, lane 2).

After the events of bleeding of thoracic wall, his renal function was severely damaged and he was finally treated with continuous hemodiafiltration (CHDF). In the mean time, infection at the thoracotomy wound developed. Furthermore, he was suffered from gastrointestinal bleeding many times. Due to compromised his general condition, the output of LVAD was increased, causing severer loss of VWF large multimer was detected (Fig. 3, lane 3). In spite of intensive therapy, he died at POD 248 of multiple organ

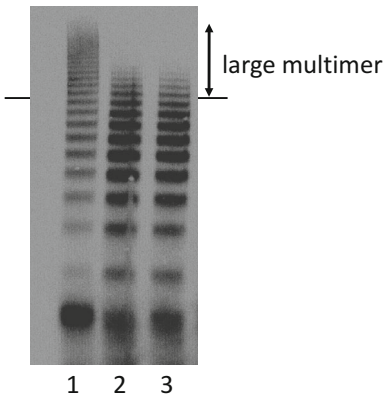

Fig. 3 VWF multimer analysis revealed severe loss of VWF large multiers in patients (Lanes 2 and 3) compared to that in the normal control (Lane 1). Note that the loss was slightly more severe in Lane 3 at POD 200, where the pump was operated at the level 4 (rotation speed at 11,000 rpm) than that in Lane 2 at POD 101, where it was operated at the level 3 (rotation speed at 10,000 rpm)

failure following the perforation of the digestive tract. In the autopsy, there were no organized thrombi around the inflow cannula besides post-mortem formation of fresh thrombi.

Discussion

VWFs play critical roles in hemostasis and thrombosis. They are produced from endothelial cells and megakaryocytes as giant multimers and shear stress dependently cleaved by ADAMTS13, the specific cleaving enzyme of VWF, into 2–80 multimers [3]. It is known that large multimers of VWFs play dominant roles in inducing platelet thrombus. Accordingly, loss of the large multimers causes hemorrhagic tendency classified as acquired von Willebrand syndrome (aVWS) [4].

Since various types of implantable LVADs with a high-speed rotary pump have widely been used in clinical arena, increasing awareness for aVWS has been directed to the medical specialists engaged in LVAD management. Precise mechanism that relates to evolution of aVWS associated with LVAD has not been fully elucidated. In general, excessive shear stress due to high-speed rotation of the pump is attributed to cleavage of the large VWF multimer. The structure in the machinery may also be linked to alteration in flow dynamic stress, whereupon, each implantable LVAD may inherently carry unique property in terms of generation of shear stress. We have demonstrated the evidence of loss of VWF large multimer in our case with Jarvik 2000. Previously, Coutance et al. briefly described their observation of loss of VWF large multimers in 6 patients in the form of 'letter to the editor' for the first time. However, precise degree of cleavage in VWF was not shown in their report [5]. We have recently proposed the VWF large multimer index, which is the ratio of VWF multimer in an affected patient to that in normal control from investigation for aortic stenosis related gastrointestinal (GI) bleeding [6], known as the Heyde's syndrome [7]. In that study, most of patients with severe aortic stenosis have exhibited loss of the VWF large multimer in proportion to pressure gradient, yet the indices in those patients decreased no less than 50 %. On the other hand, the VWF large multimer index in our present case was 10.5 %, indicating that the hematological severity of aVWS was profound compared to the patients with severe aortic stenosis. It is uncertain whether such degree of aVWS is universally the case with Jarvik 2000, because more than 1,000 identical devices have been implanted safely to date (data is not shown.). Of note, our patient presented the initial episode of GI bleeding 1 month after implantation despite that cleavage of VWF large multimer is considered to take place immediately after implantation. Co-presence of microscopic angiodysplasia or aspirin-induced ulcer might be another predisposition for emergence of his GI bleeding. If the hematological severity of aVWS in LVAD patients is associated with bleeding complications, it may be better to treat the LVAD patients with reduced anticoagulant therapy targeting lower PT-INR levels with lower dose of warfarin. In addition, optimization of antiplatelet drug can also be performed according to the various circumstances that each patient faces. Titration of anticoagulant and antiplatelet therapy is, in fact, conducted out of necessity in the clinical setting. However, modification of anticoagulation protocol in patients with LVAD-associated aVWS warrants further clinical investigation to establish conclusive evidences.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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