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CASE REPORT

Successful Treatment of Refractory Uterine Bleeding in a Female Patient with Type 3 Von Willebrand Disease and Inhibitor

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1. Introduction

von Willebrand disease (VWD) is a common bleeding disorder. It is seen mostly in female patients due to the occurrence in the high rate of obstetric and gynecologic problems such as heavy menstrual bleedings and postpartum hemorrhage [1]. The cause is usually an abnormality of the gene that controls von Willebrand factor (VWF), which plays a key role in the platelet-plug formation and Factor VIII (FVIII) stabilization at an injury site. The VWD is classified as Type 1 (partial deficiency of VWF), Type 2 (functional deficiency of VWF), or Type 3 (complete deficiency of VWF) [1]. Various treatment regimens, such as VWF/FVIII concentrate, antifibrinolytic, and desmopressin, have been used for years in these patients; however, there is a 5% to 10% risk that a treated individual will develop inhibitors [1–3]. Such alloantibodies mounted against VWF are an uncommon but serious complication of exogenous factor replacement therapy, especially in patients with Type 3 VWD. Managing bleeding in patients with inhibitors is difficult, and these individuals are also at risk of developing anaphylaxis against VWF/FVIII concentrate [2]. Hemophilia patients who have VWD and inhibitors can be treated with bypassing agents or high-dose recombinant FVIII (rFVIII) concentrate [2, 3].

We present the case of a female patient who was diagnosed with Type 3 VWD in infancy and observed inhibitor in adult life and was successfully treated for refractory uterine bleeding.

2. Case Description

A 33-year-old woman was admitted to the emergency room with heavy menstrual bleeding. She had been diagnosed with Type 3 VWD during infancy and had been followed regularly. The patient was also severely anemic (hemoglobin 7.7 g/dL) and was hospitalized and transfused with red blood cell concentrate (Fig. 1). Human VWF/FVIII concentrate (Haemate P®; CSL-Behring, Marburg, Germany; two doses of 1,500 IU (50 IU/kg of VWF: RCo)) was also administered; however, this elicited an allergic reaction. Four doses of 15 mg/kg tranexamic acid were given. At the time of presentation, laboratory testing revealed VWF antigen (Ag) 0.01 IU/mL, VWF:RCo 0.01 IU/mL, FVIII coagulant activity 0.03 IU/mL, and prolonged clotting time. The patient's VWF inhibitor was 1.02 BU. Her inhibitor titer was repeated and was found as 1.22 BU.

When none of the above treatments halted the bleeding, oral contraceptive was initiated; however, the bleeding continued. Red blood cell concentrate was transfused intermittently to treat anemia. Eight doses of 90 µg/kg recombinant factor VIIa (Novoseven®; Novo Nordisk, Bagsvaerd, Denmark) were administered at 3-h intervals throughout the first 24 h of hospital admission. The bleeding severity decreased after 3 days of Novoseven® administration, but bleeding continued (Fig. 1).

Considering the lack of response to bypassing treatment, high doses of rFVIII devoid of VWF (Advate®; Takeda, Japan) were administered by intravenous infusion as 2×4000 IU, followed by hysteroscopy in the operating room. This examination revealed widespread bleeding from the uterine walls, and tranexamic acid packing

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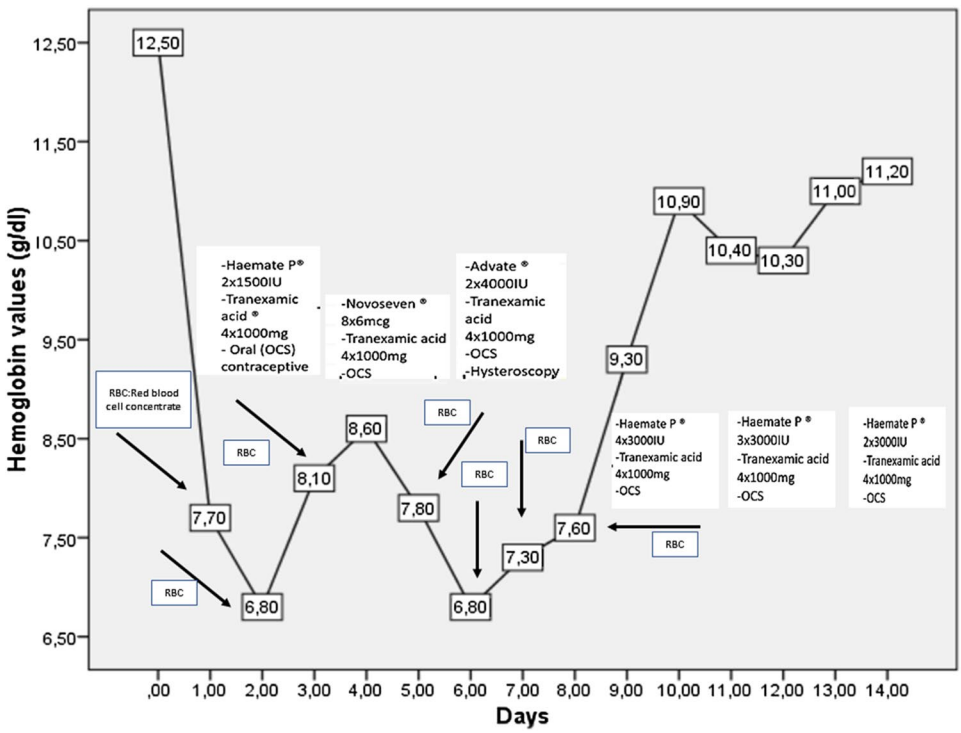

Fig. 1 Changes of hemoglobin level in a patient with Type 3 von Willebrand disease during refractory uterine bleedings

was applied locally. This reduced the refractory uterine bleeding while it was applied, but more intense bleeding resumed when the tampon was removed.

At this stage, the patient had a low inhibitor titer (2.42BU). She was started on Haemate P® 3,000 IU (100 IU/kg of VWF: RCo) every 6 h for the first day, followed by the same dose every 8 h for the next two days. This resulted in a rise of factor levels as follows: VWF:Ag 57 IU/mL, VWF:RCo 91 IU/mL, FVIII:C:50 IU/mL at 1 h and VWF:Ag 10 IU/mL, VWF:RCo 15 IU/mL, FVIII:C:8 IU/mL at 3 h after the high dose VWF/FVIII concentrate infusion. After 3 days of high-dose Haemate P® administration, the severity of bleeding had decreased dramatically such that there was spotting only. The red blood cell transfusion was no longer required. Haemate P® (3,000 IU twice daily) was administered for 4 more days, at which stage the bleeding had completely stopped. Subsequently, prophylactic Haemate P® was prescribed with 1,500 IU three times per week, and this regime was continued for 3 years. At the time of writing, the patient was well with a low inhibitor titer of 1.1BU, and she had a healthy child who was 7 years of age.

3. Discussion

Bleeding is difficult to manage in Type 3 VWD patients who develop inhibitors because there is insufficient hemostatic response to VWF/FVIII concentrate and VWF is cleared rapidly. In addition, VWF and alloantibodies can cause life-threatening anaphylactic reactions from immune complex formation and complement activation [2]. It has been reported that even minimal alloantibodies are capable of inducing the formation of immune complexes that activate the complement system and cause allergic reactions. It was similar to these findings; our patient had an allergic reaction to Haemate P®. Recombinant factor VIIa as bypassing agent has been used in acute bleeding. It is also noteworthy that rFVIIa is thought to bind to activated platelets at the site of a bleeding vessel and induce a thrombin burst. This proposed mechanism of action is supported by the observation that rFVIIa is effective at stopping or preventing bleeds in both VWD and Glanzmann's thrombasthenia, both of which are associated with defects of platelet-plug formation [2, 3]. Recombinant FVIII has also been used in acute bleeding, but in the absence of its carrier VWF, the half-life of the infused FVIII is very short (1–2 h). Therefore, rFVIII must be administered at very high doses to maintain hemostatic levels. Therefore, as in patients with hemophilia, bypassing agents and high-dose rFVIII infusion have been reported to be successful in patients with VWD and inhibitor [2, 3]. In our case, all these treatments were tried, but a complete response was observed only when high-dose short-term VWF/FVIII concentrate was administered with premedication. The only other similar case in the literature was a pregnant woman with VWD who had a low antibody titer and successfully gave birth after receiving high-dose VWF/FVIII concentrate [4]. Our experience suggests that,

for patients with severe VWD and low-level inhibitors who develop refractory bleeding, high-dose VWF/FVIII concentrate may effectively saturate the alloantibody and maintain hemostatic levels of VWF. As well, gynecologists and hematologists should be aware that refractory uterine bleeding can be caused by alloantibodies against VWF in a female patient with type 3 VWD.

Declarations

Conflict of interest The authors have no conflict of interests.

Informed consent Informed consent was obtained from the patient.

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