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Hemorrhagic complications in a patient with von Willebrand disease

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SUMMARY

Von Willebrand disease (vWD) is one of the most common congenital bleeding disorders. Its prevalence in the general population is estimated at approximately 0.3–1.3%. Depending on the type, it is inherited as an autosomal dominant trait, or more rarely as a recessive disease. It is caused by deficiency or dysfunction of von Willebrand factor (vWF). The disease usually presents with spontaneous bleeding from mucous membranes and soft tissues. Increased bleeding occurs during surgical or dental procedures, and abundant menstrual periods are additionally present in women. During pregnancy, the level of von Willebrand factor normalizes and symptoms tend to become less severe. However, the risk of hemorrhage increases in the postpartum period due to a rapid decline in vWF level, hence this period requires special attention. The aim of the study is to present a case of a young woman diagnosed with von Willebrand disease, who had bleeding after cesarean section in early puerperium and after endometrial cyst removal 5 years later.

Key words: von Willebrand disease; cesarean section; endometrial cyst

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INTRODUCTION

The hemostasis system is a complex of the body's protective mechanisms, enabling the maintenance of continued blood circulation and protecting from blood loss due to disrupted vascular continuity. The formation of a proper thrombus is the responsibility of, amongst others, vascular contraction, formation of a hemostatic plug by platelets and its stabilization by the activation of the coagulation protein cascade [1]. Bleeding disorders can be simply referred to as a tendency to bleeding. Based on their etiology, they can be divided into vascular, platelet and plasma types [1]. The vascular type is usually a consequence of vascular damage. The platelet type may be caused by too low platelet levels or their abnormal function. Low platelet levels are associated with disrupted platelet formation or their excessive elimination from the organism. The case presented below is an example of the plasma type, with vWF deficiency and secondary factor VIII deficiency.

Von Willebrand disease (vWD) was first described by Finnish pediatrician Erik Adolf von Willebrand in 1926 [2]. At that time, due to the lack of knowledge on the pathogenesis, it was treated as a variant of hemophilia. Today, we know that von Willebrand factor (vWF) is a glycoprotein essential in the process of platelet adhesion to a damaged vessel. It is also responsible for the protection of factor VIII, which is an element of the cascade of transformations that lead to fibrin formation. vWD is the most common bleeding disorder with the prevalence of 0.6–1.3% in the population; it is equally common in males and females [2].

The symptomatology of vWD depends on the type of the disease. Mild forms are characterized by bleeding from the skin and mucous membranes, heavy and long menstruation (>7–10 days) and more intense bleeding during

surgical and dental procedures. Severe forms manifest with gastrointestinal bleeding and hemarthroses [2–4].

There are three main types of vWD. Types 1 and 3 are characterized by quantitative defects, while type 2 – by a qualitative defect of vWF. Type 1 accounts for 75% of vWD cases and produces mild symptoms. It is an autosomal dominant or, more rarely, recessive disease. A vWF release defect or excessive vWF proteolysis is observed in type 2 of vWD. The symptoms may be moderate, moderate-to-severe and severe. Type 2 is additionally divided into four subtypes: 2A, 2B, 2M and 2N, which are inherited in the autosomal dominant or, rarely, recessive way. The least common (<3%) is type 3, which manifests with a severe bleeding disorder. It is an autosomal recessive disease and is characterized by a complete vWF deficiency.

Patients with type 2B account for 5–8% of all vWD patients. What distinguishes this type from others is thrombocytopenia (platelet counts are normal in types 1 and 3). Platelet deficiency is found in 30–57% of patients with type 2B. Thrombocytopenia may be caused by: platelet aggregation by mutated vWF, removal of aggregates by the reticuloendothelial system and impaired megacariopoesis. In some patients, thrombocytopenia is only periodical: after surgeries, in the course of infections, stress or during pregnancy. With a decline in the platelet level below 140 thousand/uL, the risk of bleeding increases by 8-fold [5].

The therapy of vWD involves 3 types of intervention: stimulation of endogenous vWF, transfusion of plasma-derived factor VIII concentrates with vWF and administration of drugs that enhance coagulation and wound healing [2].

During pregnancy, factor VIII activity increases and vWF reaches normal levels in women with vWD [3]. This usually leads to the withdrawal of symptoms and normalization of the blood coagulation profile. However, there is a risk of premature birth. It is 15–20-fold greater than in women without a bleeding disorder [6].

The aim of this article was to present a case of vWD in a young woman who had hemorrhage after cesarean section and after removal of ovarian endometriosis 5 years later.

CASE PRESENTATION

A twenty-three year-old primiparous woman with type 2B von Willebrand disease was admitted to the Department of Gynecology and Obstetrics in week 36 of gestation. She was diagnosed for vWD at the age of 3 years due to a significant family history: vWD had been previously diagnosed in her father and two brothers. At admission, the patient reported typical symptoms described in the literature, such as prolonged menstrual bleeding, epistaxis, gingival bleeding and prolonged bleeding after tooth extraction. She provided results of laboratory tests conducted during pregnancy (Tab. 1).

On day 14 of hospitalization, as pregnancy reached 38 weeks, it was decided to terminate pregnancy via cesarean section due to obstetric indications (cephalopelvic disproportion). Before the surgery, the patient received 3 packages of a product containing factor VIII and vWF. Because of thrombocytopenia (PLT 44 thousand at admission), the patient had also platelet concentrate transfused. During cesarean section, the uterine incision was made in its lower segment and a live full-term newborn girl was delivered with birth weight of 3080 g. The neonate was tested for vWD, and the results returned negative.

On day 6 after delivery, the patient developed vaginal hemorrhage. Carbetocin, an oxytocin analogue, was administered as first-line treatment, but the expected uterine atonic reaction did not follow. Moreover, prostacyclin was administered directly into the myometrium. At the time of bleeding, the platelet level was 70 thousand. A product with factor VIII and vWF, tranexamic acid and etamsylate were ordered, and packed red blood cells (pRBC) and platelet concentrate were transfused. Despite this pharmacological management, the patient's

Tab. 1. Results of factor VIII and vWF activity, vWF concentartion and platelet level in the patient in week 8 and 31 of gestation

	8 weeks	31 weeks
Factor VIII procoagulant activity (%)	40	97
Ristocetin cofactor activity vWF: Rco [%]	19	40
vWF concentration vWF:Ag [%]	52	98
Platelet count [thousand/uL]	159	115

condition deteriorated. Several hours later, it was decided to perform hysterectomy without salpingo-oophorectomy as a life-saving surgery. Administration of products rich with factor VIII and vWF, tranexamic acid and etamsylate continued after the surgery. The patient was discharged in an overall good condition with orders to continue treatment and monitoring at a hematology clinic.

Five years later, the patient was referred to the Department from a lower-degree center for surgical treatment of a left ovarian cyst. For the previous five years, the patient was under constant care of a hematology clinic, and test results were all within normal ranges. At admission, the patient reported pain on the left side of the lower abdomen. Laboratory tests performed on the day of admission revealed platelets of 157 thousand/uL, factor VIII activity of 40%, ristocetin cofactor activity of 19% and vWF level of 52%. After administration of factor VIII with vWF, factor VIII activity increased to 80%. The patient was then deemed eligible for a laparoscopic procedure.

Due to numerous adhesions found intraoperatively, it was decided to convert to laparotomy. Bilateral paratubal cysts and the endometrial cyst of the right ovary were removed, and extensive adhesiolysis was performed. The surgery proceeded with no complications. In the direct postoperative period, a significant amount of sanguineous content evacuated by a drain from the abdominal cavity was observed along with increasing abdominal pain. The patient was administered a product with factor VIII and vWF and tranexamic acid; also packed red blood cells, platelet concentrate and fresh frozen plasma were transfused. Due to the deteriorating condition of the patient, developing hypovolemic shock (despite the implemented treatment, including administration of recombinant factor VIIa) and peritoneal bleeding depicted on urgent computed tomography (CT), it was decided to re-operate. The surgery consisted in the removal of blood clots and application of fibrin sponges (Tachosil, Surgispon) onto oozing adhesions uncovered during the surgery. No sites of bleeding were discovered. Directly after the surgery, the patient was sent to the intensive care unit (ICU) for further treatment. On day 1 after relaparotomy, the activity of factor VIII and vWF was 157% and 150%, respectively. Platelets: 80 thousand/uL. The treatment with factor VIII and vWF, tranexamic acid, etamsylate and fresh frozen plasma was continued. Due to symptomatic anemia and thrombocytopenia, packed RBCs and platelet concentrate were transfused. After 4-day treatment at the ICU and improvement of the general condition, the patient was transfer-

Tab. 2. Replacement treatment regimen including products with factor VIII and vWF as used in the discussed patient, and factor VIII and vWF activities assayed in the postoperative period

	Number of administered IU of factor VIII and vWF	Factor VIII activity [%]	vWF activity [%]
Day 1 – day of surgery and hemorrhage before surgery After 8 hours After the next 8 hours	1,000 IU of VIII + 1,200 IU of vWF 1,000 IU of VIII + 1,200 IU of vWF 1,000 IU of VIII + 1,200 IU of vWF	81%	80%
Day 2 – day of re-laparotomy Time: 15.00 Time: 18.00	0	 157% 147%	 150% 150%
Day 3.	0	207%	160%
Day 4.	0		
Day 5.	0	139%	130%
Day 6.	500 IU of VIII + 600 IU of vWF		
Day 7.	500 IU of VIII + 600 IU of vWF		
Day 8.	500 IU of VIII + 600 IU of vWF		
Day 9.	500 IU of VIII + 600 IU of vWF	97%	90%
Day 10.	0		

red back to the Department of Gynecology. Table 2 presents the regimen of the factor VIII and vWF replacement therapy implemented in the discussed patient and factor VIII and vWF activities assayed in the postoperative period.

DISCUSSION

The management of patients with vWD during pregnancy and perinatal period as well as before surgical procedures is a challenge for physicians. It requires cooperation of hematologists, gynecologists and obstetricians as well as neonatologists and anesthetists [7]. Major procedures and treatment of severe hemorrhages should be conducted in referral hospitals of higher levels where factor VIII and specialist drugs used in vWD can be administered and where a laboratory is able to assay the activity of coagulation factors and vWF. The hospital in which the patient was treated met these conditions.

The literature has, to date, reported few cases of postpartum hemorrhage in women with vWD [6,7]. The discussed case presents two bleeding episodes: postpartum hemorrhage and bleeding associated with a surgery that required extensive adhesiolysis. This coincidence indicates that one bleeding episode is a risk factor during subsequent surgical interventions. Bleeding prevention in patients with vWD requires observance of general principles, such as avoidance of drugs that reduce blood coagulability, including NSAIDs (with anti-platelet effects) and intramuscular medicinal products.

Patients with vWD are also recommended desmopressin, a drug that releases endogenous vWF and factor VIII reserves from the vascular endothelium. It is a drug of choice in type 1 and mild type 2 vWD. In the patient discussed above, desmopressin was not used due to the risk of greater thrombocytopenia [6] as well as a high risk associated with the extensive procedure. This approach was assumed even though a desmopressin test performed during the previous hematological treatment was positive, i.e. factor VIII and vWF activities did increase.

Plasma-derived factor VIII concentrate with vWF is used when desmopressin is ineffective or contraindicated. IV administration of 1 IU of vWF activity/kg increases plasma vWF activity by ca. 2% of the norm [1]. Moreover, the discussed patient was also given active factor VII in order to enhance the coagulation cascade. Moreover, drugs improving coagulation were also administered, e.g. tranexamic acid which inhibits plasminogen conversion to plasmin and stabilizes the thrombus, and fibrin and gelatin sponges were applied locally. The patient had platelet counts monitored and platelet concentrate transfused repeatedly. The literature states that a safe platelet level is 50 thousand before natural vaginal delivery and 80 thousand before cesarean section [7]. These recommendations also suggest that PLT levels should be monitored at least once a month. In pregnant patients, thrombocytopenia in the course of vWD should be discriminated from platelet count decline caused by severe pre-eclampsia, primary immune thrombocytopenia or thrombotic thrombocytopenic purpura.

Pregnancy is a period of physiological hypercoagulability and increased activity of coagulation factors. This also concerns vWD patients. These changes within vWF were observed in the discussed case as well. Pregnant women are recommended two assays of coagulation activity of factor VIII – FVIII:C, von Willebrand

Tab. 3. General recommendations concerning the levels of FVIII:C, VWF:RCo and platelets for natural vaginal delivery, cesarean section and in the postpartum period in vWD patients as well as dosage of FVIII/vWF concentrate for the prevention and treatment of hemorrhage in patients with severe vWF and FVIII deficiency [2,4,6,8]

	Recommended level of FVIII:C and/or vWF:RCo	Dosage of FVIII/vWF concentrate for the prevention and treatment of bleeding	Recommended platelet count
Natural vaginal delivery	> 50 IU/dl	40 units/kg every 24 h	>50 thousand
	A level of >50 IU/dL should be maintained for at least 3–4 days		
Cesarean section	>50 IU/dL; 800–100 IU/dL in type 2B	Before surgery, a bolus of 50 units/kg of VIII/vWF concentrate, and then every 12–24 hours	>50 thousand
	In the postoperative period >50 IU/dL for 7–14 days (at least 5 days)		After cesarean section >20 thousand for at least 5 days

factor antigen – vWF:Ag and vW ristocetin cofactor activity – vWF:RCo: before conception or at the beginning of pregnancy and between weeks 28 and 34 [4]. The tests should be repeated prior to invasive procedures, such as trophoblastic biopsy, amniocentesis or cervical cerclage [2].

Pregnant patients with vWD are recommended natural vaginal delivery as it is less invasive and carries a lower risk of hemorrhage in the mother [7]. Due to a 50% probability that the neonate will have the disease, it is recommended not to apply traumatizing labor procedures, such as forceps or vacuum delivery. Natural vaginal delivery may yield complications in the form of a vulvar hematoma caused by bleeding to soft tissues [4]. In the discussed patient, cesarean section was selected for obstetric indications. The patient was prepared for this procedure as for any major surgery. As recommended, a bolus with 50 units/kg of factor VIII concentrate with vWF was administered before the procedure [2]. Subsequently, two further doses were given; factor VIII and vWF activity was maintained at the level of 80–100 IU/dL [6]. According to the recommendations, platelet counts were maintained at a level >50 thousand [8]. The summary of the recommendations implemented in the patient is presented in Table 3.

The cesarean section was performed under general anesthesia. This choice was dictated by an increased risk of a hematoma during spinal anesthesia in type 2 disease [9]. Hemorrhage in the patient was noted on day 6 after delivery. This is concordant with the literature which states that hemorrhage in such cases may develop from several hours to a dozen or so days after delivery [2,3,4,7] and is linked with a decline in the concentration of coagulation factors [4]. According to different authors, even 29–56% of pregnancies in women with vWD may be complicated with postpartum hemorrhage [3,4,10]. Bleeding occurs early in 20% of women, and late (later than 24 h after delivery) also in 20% of women [3]. The replacement therapy continuation is therefore recommended for further 3–4 days after natural vaginal delivery [4] and for 7–14 days after cesarean section [7]. In the analyzed case, hemorrhage occurred on day 6 after delivery in spite of continued treatment. It was caused not only by the hemostasis disorder, but also by uterine atony. Active treatment with uterotonic agents brought no effects, and hysterectomy was performed several hours later as a life-saving procedure. After uterus removal, further hospitalization during the puerperium proceeded without complications. Factor VIII and vWF tested in the neonate were normal. It must be emphasized that no injection had been made and vitamin K had been administered orally until these results arrived [4].

Five years after delivery, the patient reported to the Department due to ovarian cysts and endometriosis. This is also in line with the observation that vWD patients are more susceptible to the development of cysts and endometriosis [2,4]. The patient was selected for a laparoscopy. However, due to numerous pelvic adhesions, a conversion to laparotomy was necessary. The surgery was followed by a hemorrhage. Bleeding was not caused by the lack of hemostasis, but by released oozing adhesions. This complication was treated by re-laparotomy involving removal of extravasated blood and application of hemostatic sponges. Hemorrhagic complications did develop despite the implementation of proper replacement treatment. It must be remembered that the exacerbation of a bleeding disorder in patients with vWD and thrombocytopenia not always correlates with ristocetin cofactor and severity of thrombocytopenia [5]. The pathomechanism of type 2B vWD is very complex. The inability to order a complete test panel that would allow precise determination of the subtype of the disease or concomitant hemostasis disorders results in the fact that, despite the management concordant with recommendations, patients may not always be protected from hemorrhagic complications.

CONCLUSIONS

Late postpartum hemorrhage in the patient with von Willebrand type 2B disease developed despite proper preoperative preparation. The occurrence of bleeding after removal of the endometrioid ovarian cyst leads to the conclusion that such patients are also at risk of hemorrhage after gynecological procedures.

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