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Administration of plasma-derived coagulation factor VIII during the perioperative period of mastectomy for breast cancer with acquired von Willebrand syndrome

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Abstract

Background: Acquired von Willebrand syndrome (aVWS) is a rare bleeding disorder with laboratory findings similar to those of congenital von Willebrand disease (VWD). Patients with aVWS may require prophylactic treatment to prevent excessive bleeding following surgery. To our knowledge, to date, there have been no reports on perioperative management for breast cancer patients with aVWS.

Case presentation: A 60-year-old woman with breast cancer was diagnosed with aVWS due to polycythemia vera. Pre-operative laboratory testing showed a high platelet count and low von Willebrand factor (VWF) activity. The VWF activity did not improve despite an attempt to suppress platelet count with hydroxyurea. Therefore, we decided to perioperatively supplement with plasma-derived factor VIII (FVIII) containing von Willebrand factor (FVIII/VWF concentrates) to perform curative surgery for breast cancer safely. Consequently, the patient did not develop hemorrhage during/after surgery and was discharged on postoperative day 7, as planned, without problems.

Conclusions: For a patient with aVWS, which carries a high risk of hemorrhage during the perioperative period, initiation of appropriate management like supplementation of FVIII/VWF concentrates might enable safe curative surgery for breast cancer, and collaboration with the hematology department is critical.

Keywords: von Willebrand syndrome, Breast cancer, Perioperative management, Polycythemia vera

Background

Outline of von Willebrand syndrome

Von Willebrand factor (VWF) is a crucial factor for primary hemostasis after vascular damage as it functions in platelet adhesion. Since VWF and coagulation factor VIII (FVIII) circulate in blood as a tight complex, VWF stabilizes the structure of FVIII and protects from proteolytic degradation [1]. Either a numerical disorder or dysfunction of VWF could cause hemorrhagic diathesis [2]. Von Willebrand disease (VWD) is defined as congenital if a patient has abnormality of the *VWF* gene, or acquired if the disease developed following malignant hematologic disease or cardiovascular disease [3, 4]. Acquired von Willebrand syndrome (aVWS) is considered rare, though the exact prevalence remains unknown. As far as we know, only 266 cases were reported from 1968 to 2000, the first of which was reported by Simone et al. [3–7]. A recent report suggested that the incidence of aVWS has increased in patients with cardiovascular disease such as aortic stenosis [8, 9]. One reason for this phenomenon may be the rise in awareness of this disease among cardiologists.

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Perioperative management for patients with aVWS

Supplementation of FVIII containing von Willebrand factor (FVIII/VWF concentrates) and desmopressin, which promotes the release of VWF, have reportedly been employed for patients with VWD as part of perioperative management. FVIII/VWF concentrates might be used for several consecutive days after surgery to maintain effective levels in the blood [3, 10]. Tight blood monitoring during the perioperative period is advisable, particularly for a patient undergoing major cardiac or orthopedic surgery [10–13].

We herein report a breast cancer patient with aVWS at high risk of hemorrhage during the perioperative period. The patient safely underwent curative surgery for her breast cancer with supplementation of FVIII/VWF concentrates. To our knowledge, to date, there have been no reports on perioperative management for breast cancer patients with VWF; thus, we believe that our report may provide useful information for clinicians involved in breast cancer treatments or other invasive procedures.

Case presentation

60-year-old female

A diagnosis of polycythemia vera (PV) with *JAK2* V617F mutation was made at age 47, and aspirin therapy was initiated. However, the treatment was changed to and continued with hydroxyurea (HU) and phlebotomy due to persistent purpura. At age 56, calcifications of the right breast were noted during mammography screening. During stereotactic vacuum-assisted biopsy, she experienced difficult hemostasis and necrotic ulcer of the skin developed due to delayed wound healing from hematoma. The biopsy of the breast tissue showed sclerosing adenosis, and the patient was followed up routinely.

At age 60, ultrasound from a routine check-up showed a hypoechoic lesion in the upper-inner area of the left breast. Pre-biopsy laboratory testing showed a high platelet count of 688,000/μL and low VWF activity of 28% (reference value 60–170%); thus, the patient was diagnosed with aVWS. Low VWF activity is usually accompanied by a tendency for bleeding, but unlike congenital VWD, VWF activity may be normalized with treatment of the underlying condition (3). Therefore, we attempted to increase the HU dose, but there was no improvement and the biopsy was performed with administration of FVIII/VWF concentrates. The biopsy result showed apocrine carcinoma, so the patient was referred to our hospital for treatment.

Although treatment for PV was continued, prolonged activated partial thromboplastin time (APTT), low VWF activity, and low activity of factors IX, XI, and XII persisted. Two units of fresh frozen plasma (FFP) were used to replete coagulation factors, which did not result in improvement in APTT and a mixing study showed an inhibitor pattern, plus the patient was positive for lupus anticoagulant (LA), so FFP alone was determined to be inadequate. FVIII/VWF concentrate administration was tried instead in an outpatient setting, which yielded VWF/VIII activity higher than the reference values at 1 h post-administration (Fig. 1), so we determined that mastectomy was possible with FVIII/VWF concentrates. Despite the use of FVIII/VWF concentrates,

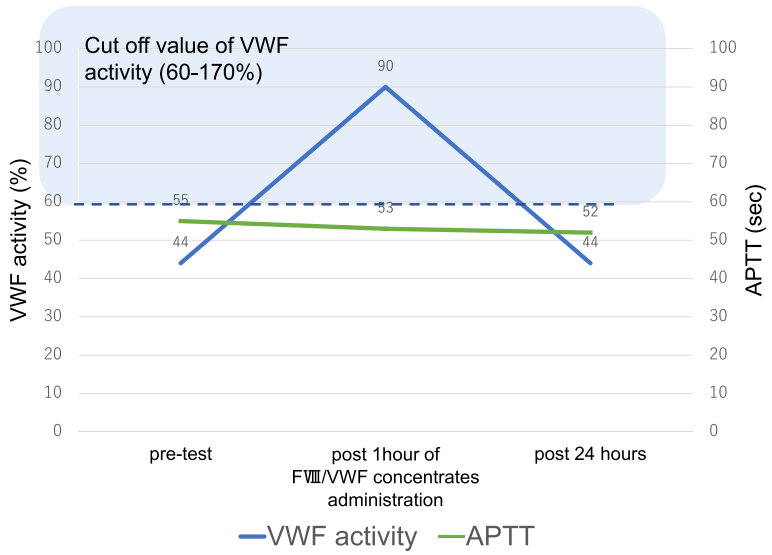

Fig. 1 Change in VWF activity and APTT after test administration of FVIII/VWF concentrates. VWF activity is higher than the reference values at 1 h post-administration VWF: von Willebrand factor, APTT: activated partial thromboplastin time,

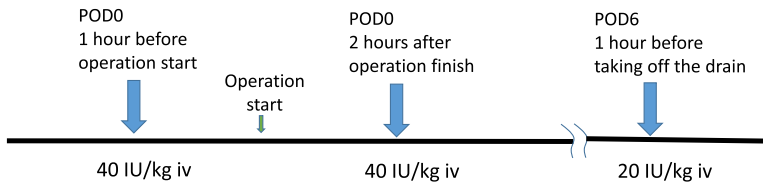

Fig. 2 Timeline of the perioperative management for administration of FVIII/VWF concentrates. IU, international unit; iv, intravenous dosage; POD, postoperative day

APTT did not improve, due to not only the presence of aVWS, but also LA positivity.

Perioperative management was done in close collaboration with the hematology, anesthesiology, and pathology departments according to the timeline on administration of FVIII/VWF concentrates shown in Fig. 2. The dosage of FVIII/VWF concentrates was planned according to Table 1. Table 1 shows the initial dosing recommendations for FVIII/VWF concentrate replacement for the prevention of bleeding in perioperative coagulation management [10, 14]. Left mastectomy and sentinel lymph node biopsy were performed with an operative duration of 63 min and intraoperative blood loss of 3 mL. The drain was placed only above the inframammary fold; a shorter drain was used to reduce stimulation during its removal. Suture ligation was used rather than an electric scalpel for better hemostasis. To ensure a short operative duration, the pathology department was informed in advance so that lymph node biopsy could be quickly diagnosed.

FVIII/VWF concentrates were used again at the time of drain removal on postoperative day 6. No bleeding was observed, and the patient was discharged. The surgical site healed without major complications, and no bleeding was observed during outpatient seroma drainage.

The pathological diagnosis result of the surgical specimen showed a 5-mm-diameter apocrine carcinoma with NG2 ly (−), v (−), ER (−), PgR (−), HER2 (1+), Ki-67 (10%), pT1aN0M0 Stage I. Because the patient had a triple-negative pT1aN0 tumor, adjuvant chemotherapy was not performed, and further postoperative follow-ups are planned.

Discussion

It is reported that one in ten patients with PV may develop aVWS, and most of such patients develop bleeding disorders [15]. In the present case, VWF activity did not improve despite the attempt to suppress platelet count with HU. FVIII/VWF concentrates were used during perioperative management instead, as it was effective in improving VWF/FVIII activity. Meanwhile, perioperative use of desmopressin is not recommended for major surgery, as repeated use can lead to tachyphylaxis [16, 17]. The reference dose of FVIII/VWF concentrates is reported for various invasive procedures [10], but there is no clear standard. Administration is between one and three times per day, and use is recommended when the patient shows a tendency for bleeding. High plasma levels of FVIII are thought to be correlated with the risk of thrombosis [18–20]. It should especially be used with caution in patients who have known risk factors for venous thrombosis such as old age, previous thrombosis, obesity, and cancer [13]. One report stated that levels of circulating FVIII greater than 150 IU/dL yielded a high risk of thrombosis with an adjusted odds ratio of 4.8 (95% CI 2.3–10.0) [21].

Test administration of FVIII/VWF concentrates was done with the confirmation of VWF/FVIII activity higher than the reference values at 1 h post-administration. Dosage times were scheduled based on the drug effect duration. Since VWF levels require 2–5 days to measure, FVIII level and APTT are useful for the timely evaluation of a patient's coagulation status. However, if prolonged APTT is related to another pathophysiology as in this case, it is useful to measure FVIII/VWF activity after a trial dose of FVIII/VWF concentrates.

Table 1 Perioperative coagulation management on administration of FVIII/VWF concentrates in patients with aVWS

		Therapeutic goal VWF activity	Loading dose	Maintenance dose	Number of doses a day
Minor surgery	Day of surgery	50–100%	40–60 IU/kg	30–40 IU/kg	2
	2–7 days	30–50%		20–30 IU/kg	1–2
Major surgery	Day of surgery to 3 days	100%	30–60 IU/kg	40 IU/kg	2–3
	4–7 days	50–100%		30–40 IU/kg	2
	8–14 days	30–50%		20–30 IU/kg	1–2

IU international unit

As for systemic therapies, there are some drugs that might cause hemorrhage such as cyclophosphamide and bevacizumab. However, to our knowledge, there is no established evidence linking patients with aVWD to increased risk of adverse events during systemic therapies. Thus, we believe that control of background disease and decent monitoring of FVIII level are crucial if systemic treatments are needed.

Conclusions

For a patient with aVWS, which carries a high risk of hemorrhage during the perioperative period, initiation of appropriate management like supplementation of FVIII/VWF concentrates might enable safe curative surgery for breast cancer, and collaboration with the hematology department is critical.

Abbreviations

APTT: Activated partial thromboplastin time; aVWS: Acquired von Willebrand syndrome; FFP: Fresh frozen plasma; HU: Hydroxyurea; LA: Lupus anticoagulant; PV: Polycythemia vera; VWD: Von Willebrand disease; VWF: Von Willebrand factor

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Authors' contributions

RS carried out the acquisition of data and drafted the manuscript. YH was involved in drafting the manuscript. YE, TO, and NK treated the patient hematologically and suggested perioperative management. RS and MS were responsible for the overall care of the patient. JM and MS critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report.

Competing interests

The authors declare that they have no competing interests in this case (TO has received research funding outside of this case).

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