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When Type 1 von Willebrand Disease Lives Together with Hashimoto Thyroiditis, Hypothyroidism, Hypoparathyroidism, Morbid Obesity, and Bariatric Surgery: A Case Report

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Abstract

Von Willebrand disease (vWD) is the most common bleeding disorder with type 1 being the more prevalent, although underdiagnosis is an actual concern. This case is the first clinical report of a type 1 vWD with several comorbidities submitted to bariatric surgery. The authors demonstrate the importance of a diagnosis and the consideration of other diseases or disturbances in vWD patients' perioperative management. A multidisciplinary approach is crucial for minimizing and preventing bleeding risk.

Keywords: von Willebrand disease, Type 1 von Willebrand disease, Bariatric surgery, Bleeding risk, Perioperative management

1. Introduction

Hematological diseases can challenge anesthesiologists in the perioperative period. The bleeding risk should never be neglected regardless of surgical procedure and patients' comorbidities, such as von Willebrand disease (vWD).

Von Willebrand factor (vWF) is a glycoprotein produced by endothelial cells and megakaryocytes, contributing to both hemostasis and thrombosis [1-3]. Its primary function stands with platelet aggregation and endothelium adhesion as well as protects and prolongs factor VIII (FVIII) action on thrombus formation [1,3-4].

vWD is the most common bleeding disorder in the general population [1,5]. The prevalence is unknown, and the presentation heterogeneity contributes to the diagnosis complexity [6]. Safe perioperative care is implemented when caregivers explore the mechanisms of innate and iatrogenic etiologies of disordered vWF in surgical populations.

Besides inherited vWD, acquired von Willebrand syndrome (AvWS) is also a possible but rare form of vWF dysfunction [3,5,7]. Increased vWF destruction by the immune system or drugs such as anticoagulants and antiplatelet agents or reduced vWF synthesis are possible causes for AvWS [5,7]. An underlying cause or potential disease differentiates AvWS from vWD [7], demonstrating the importance of a diagnosis for proper management.

Nevertheless, the vWD estimated prevalence is around 1 case in 10,000 people [8]. Diagnosis is more common in women; however, the distribution is similar in both sexes [6]. The diagnostic value of vWF is below 30%, with levels between 30% and 50%, known as low vWF, with increased bleeding risk [4].

vWD has three main types: type 1, a mild quantitative deficiency; type 2 with subtypes 2A, 2B, 2M, and 2N with the difference between the quality of vWF multimers; and type 3, a severe quantitative or absent vWF form. Type 1 is the most prevalent (60%-80% of patients), followed by types 2 (20-30% of patients) and 3 [2,4].

The clinical manifestations are mucocutaneous bleeding, such as epistaxis, menorrhagia, and easy bruising, as well as gastrointestinal bleeding [2,4,8-9]. Usually, the first surgical manifestation is bleeding after dental treatments [4]. The

treatment must consider the type and the severity of vWD. Furthermore, it might include the administration of vWF or an increase in the vWF plasma concentration with desmopressin (DDAVP) [4].

In the anesthetic domain, perioperative management is determined by the surgical procedure, the type of vWD, the laboratory values of vWF and FVIII, and the personal history of bleeding manifestations [9].

To our knowledge, we are presenting the first case report related to a patient with type 1 von Willebrand disease, Hashimoto thyroiditis, hypothyroidism, hypoparathyroidism, and morbid obesity submitted to bariatric surgery. The authors pretend to analyze the case according to multiple factors that may contribute to and interfere with perioperative management.

2. Case Description

Written informed consent was given to the anesthesia team from the patient for the use of clinical information for publication.

2.1 Preoperative Management

A 48-year-old woman was scheduled for bariatric surgery due to morbid obesity with a body mass index (BMI) of 44.27 kg/m2 (weight of 105 kg and height of 154 cm). Her medical record included type 1 vWD, hypothyroidism (previous thyroidectomy for toxic multinodular goiter and Hashimoto disease), hypoparathyroidism with hypocalcemia, controlled class III hypertension, chronic anemia, and obstructive Sleep Apnea (OSA) under nocturnal Continuous Positive Airway Pressure (CPAP). Her prescription medication consists of levothyroxine, calcium carbonate, calcitriol, vitamin D, indapamide, losartan, bisoprolol, and fluoxetine. A previous intrauterine progestin device was placed to control menorrhagia. Total thyroidectomy with incidental parathyroidectomy, numerous dental extractions, and cesarean section without bleeding complications were reported, although hematology consultation was scheduled after an observed prolonged activated partial thromboplastin time (aPTT) of 35.4 seconds. For the total thyroidectomy procedure, prophylactic preoperative desmopressin and tranexamic acid were administrated, with no bleeding complications noted.

The type 1 vWD diagnostic was based on an aPTT of 46.8 seconds, a FVIII:C of 48.5%, a vWF:Ag of 33.2%, a vWF:Rco of 22% and a vWF:CBA 0.21 U/mL. The genetic test confirmed the findings. A DDAVP test was performed, and we present the value findings according to time-related administration and compared to the value above: thirty minutes after DDAVP administration: aPTT of 28.2 seconds, a FVIII:C of 328%, a vWF:Ag of 172.7%, a vWF:Rco of 148% and a vWF:CBA 0.88 U/mL; between thirty minutes and four hours: aPTT of 34.1 seconds, a FVIII:C of 210.20%, a vWF:Ag of 151.5%, and a vWF:Rco of 141%; and after four hours: aPTT of 34.7 seconds, a FVIII:C of 139.20%, a vWF:Ag of 105.8%, and a vWF:Rco of 92%.

Given the medical background, a laparoscopic gastric sleeve was proposed to reduce the total body weight. The patient was admitted two days before the surgery for evaluation since hematology follow-up was lost in 2017 after the thyroidectomy. The preoperative laboratory testing revealed a prolonged aPTT of 40.7 seconds with normal complete blood count and prothrombin time. The remaining bloodwork had no changes. According to the hematology consultation, 30 minutes before the surgery, 1.5 g intravenous (iv) tranexamic acid and 24 mcg iv desmopressin should be administrated. During the postoperative period, the treatment should continue with 1.5 g iv tranexamic acid every 8 hours during a hospital stay and 24 mcg iv desmopressin 12, 24, and 48 hours after the first administration.

The anesthesiologists' team developed the perioperative plan taking into consideration the hematologist's prescription. The preoperative bleeding score [1] was below 4, which indicates the absence of bleeding after a hemostatic challenge considering two dental extractions or surgeries.

2.2 Intraoperative Management

The anesthesia team took particular care to plan a strategy with reduced risk of bleeding during intravenous general anesthesia. Patient monitoring was applied, and we describe the approach using the ABDCE protocol:

2.2.1. Airway: The preoperative airway evaluation identified a thyromental distance of < 6 cm and a large neck circumference (43 cm). We decided on rapid sequence induction with tracheal intubation using videolaringoscopy to prevent any direct trauma or aspiration with direct laryngoscopy.

2.2.2. Breathing: Protective ventilation was used (pressure control ventilation with volume guaranteed (PCV-VG)) mainly because of pneumoperitoneum, with an oxygen saturation target between 96% and 100%. Recruiting maneuvers were done as needed.

2.2.3. Circulation: Monitored invasive arterial blood pressure using right radial line was introduced to anticipate the impact of possible hemodynamic changes such as blood loss or arterial vascular resistance disturbances. Non-invasive hemodynamic management monitoring was achieved using Starling SV. Two intravenous catheters, 18G and 22G, were guaranteed. An intravenous balanced solution was started according to monitoring, and 24 mcg iv desmopressin and 1.5 g iv tranexamic acid were administrated before anesthesia induction.

2.2.4. Disability: Brain function monitoring was achieved using a bilateral processed electroencephalogram (BIS™) with Density Spectral Array (DSA) included. The level of parasympathetic activity was also monitored using the Analgesia Nociception Index (ANI®).

2.2.5. Exposure: Body temperature monitoring control with a warmed forced air blanket and anti-Trendelenburg positioning were carefully made.

The uneventful surgical procedure lasted 1 hour.

2.3 Postoperative Management

During hospitalization, the patient complied with the remaining treatment (1.5 g iv tranexamic acid every 8 hours and 24 mcg iv desmopressin 12, 24, and 48 hours after the initial administration).

The patient was discharged after two days with no hemorrhagic or other complications.

At one month of follow-up, weight loss was 13 kg, with a total body weight of 94 kg (BMI of 39.66 kg/m2). When questioned about bleeding complications, there were none noted.

3. Discussion

3.1 vWD Diagnosis

The anesthesia and surgical team must address the bleeding concerns and take action to prevent them. And the hematologist consultation is always required. Bleeding disorders tend to manifest in childhood; however, several individuals remain without diagnosis until adult life due to a lack of hemorrhagic symptoms. This fact intensifies the need for a diagnosis of hematological diseases, especially those that relate to major bleeding risk.

During previous hematology follow-up, medical history found a history of epistaxis during childhood, easy bruising with minor trauma, and menorrhagia without a familial history of bleeding disorders. Diagnosis of type 1 vWD was achieved (vWF:Rco of 22%, which is lower than 30%), and DDAVP response was performed, which is critical for prophylaxis and treatment [4]. Orphanet is a European resource that gathers information to help caring patients with rare diseases. This patient carries an ORPHA 166078 card, the codification for type 1 vWD.

We also hypothesized that AvWS was also a possibility since the patient had hypothyroidism and a history of Hashimoto thyroiditis [5]. However, there was a history of bleeding symptoms in childhood, and control of thyroid disease was obtained before the time of the diagnosis.

An augmented aPTT is associated with an abnormally heightened risk of bleeding. In this case, the patient had previous surgeries without bleeding complications, one of them being a cesarean section. In patients with mild type 1 vWD, vWF or FVIII deficiency is minimal during pregnancy, particularly during the third trimester [4]. This fact probably justifies the undiagnosed vWD at that time.

Furthermore, the prophylaxis and treatment costs justify the attention to perioperative management. Morgan et al. calculated the possible costs (direct medical, direct non-medical, and indirect) in different European countries [8], and the results notice that higher costs are associated with type 3, probably due to the need for intensified replacement therapy. However, the mean direct medical costs of type 1 vWD was €23287 per patient [8]. We verify the importance of adequate diagnosis, which, in addition, reduces bleeding risk and avoids unwanted and unnecessary costs for both the patient and the hospital.

3.2 vWD Perioperative Management

Perioperative management of patients with type 1 vWD is achieved with DDAVP or vWF/FVIII administration associated with antifibrinolytic agents, including tranexamic acid or ε-aminocaproic acid [3].

3.2.1 DDAVP: DDAVP, a synthetic molecule of vasopressin [4], causes vWF release from vascular endothelial cells [5-6] and is the first option for iv administration in type 1 vWD [6]. Subcutaneous and intranasal routes may also be valid [4,6]. When administered intravenously at a dose of 0.3 mcg/kg in 50 mL saline over 30 minutes, vWF and factor VIII increase up to 5 times within one hour until six to eight hours [1-2,4]. There are a few well-tolerated side effects: mild tachycardia, hypotension, headache, facial flushing, and hyponatremia [1,4,6] due to the antidiuretic effect of DDAVP.

In the perioperative period, another concern is the possibility of tachyphylaxis, contributing to lower efficacy throughout three to four days [1,4]. We noted that the patient did DDAVP until 48 hours after the first administration to reduce this effect.

The initial test with DDAVP during diagnosis identifies whether the response is acceptable and recognizes which patients need another approach [4]. Regarding contraindications for DDAVP, FVIII/vWF concentrates are preferred when cardiovascular disease, hypertension, or concomitant use of diuretics are present [1]. Although this patient had hypertension, the blood pressure control put no concern in using DDAVP [1]. Hyponatremia during surgery was a possible concern, yet the gasometrical assessment demonstrated a sodium value of 141 mg/dL.

3.2.2. Antifibrinolytic Agents: The fibrinolysis inhibitors stand as coadjuvant therapy, with highly recommended use in patients undergoing surgeries [8-9]. Tranexamic acid helps clot aggregation and stabilization [2,9]. The dosage administration is 15 to 25 mg/kg every 8 hours oral or iv for three to six days [4]. The major issue was the increased risk of thromboembolic events; however, this concern has not been proven [9]. Further literature review indicates the benefit of tranexamic acid in reducing bleeding risk in sleeve gastrectomy [1,14].

3.2.3. Recombinant FVIII and Vwf: As discussed above, vWF/FVIII concentrates are the first choice when the patient has contraindications, no response, or unsatisfactory response to DDAVP [3-4]. The vWF dosage varies with surgical procedure (20-60 IU/kg per day) and the FVIII recommended dose is 30-40 IU/kg. Dose adjustments should be done according to FVIII and vWF levels and clinical symptoms [4].

Some authors recommend these factors as the first option in major surgery [3]. Considering the venous thromboembolism events as a possible complication after vWF infusions (justified by FVIII accumulation), its use must be carefully decided [3,9]. The estimated rate of thrombotic complications is 1.9% among all vWD patients and is more common in the presence of thrombotic risk factors, such as obesity, confirming the low but no absent risk [9].

3.3. Patient Comorbidities and vWD Influence

3.3.1. Hypocalcemia and other hydroelectrolytic imbalances: Calcium is crucial for coagulation as it reduces FVIII procoagulant activity and stabilizes thrombin-activated FVIII and vWF [15].

In the described case, the incidental removal of parathyroids during thyroidectomy caused hypoparathyroidism and hypocalcemia. The patient had little to no parathyroid activity, so calcium repositioning is an actual imperative management for the avoidance of hypocalcemia and hemorrhagic symptoms. Gasometrical evaluation noted ionized calcium with values of 1.18 mmol/L and 1.20 mmol/L when pH 7.4, within the normal range.

OSA contributes to acidosis related to hypercapnia. Hypocalcemia and acidic pH can compromise vWF activity [4]. During surgery, gasometrical values demonstrated a pH of 7.434 with arterial CO2 41,6 mmHg. Nocturnal CPAP is beneficial to OSA patients for adequate ventilation and PH balance. The weight loss after laparoscopic gastric sleeve might improve or even solve OSA.

Evidence that sevoflurane and propofol might compromise platelet normal function and that propofol inhibits calcium mobilization challenges the anesthetic management of this case [3].

3.3.2. Hypothyroidism: The diagnosis of hypothyroidism precedes total thyroidectomy, as, in 2015, the patient had bloodwork with TSH 5.3 UI/mL, with a marked increase in 2016 to 59.84 UI/mL. T3 and FT4 values in 2015 were, respectively, 1.83 ng/dL and 0.9 µg/dL. Analytic evaluation for antibodies revealed anti-thyroglobulin antibodies of 2.7 IU/ml, anti-thyroid peroxidase antibodies of 5370 IU/ml, and thyroglobulin of 200 ng/mL, diagnosing the patient with Hashimoto thyroiditis.

AvWS is related to autoimmune, cardiovascular, oncological, and hematological disorders [7]. Estimated prevalence of AvWS caused by hypothyroidism is 8% [7]. Evidence recognizes that patients with hypothyroidism have reduced vWF and FVIII synthesis and circulation release, mainly related to AvWS [5,7].

The authors consider the influence of thyroid disorder on vWD even before the diagnosis. After thyroidectomy, the aPTT remained elevated, so the hypothesis of AvWS is less probable. Evidence of a possible relationship between type 1 congenital vWD and hypothyroidism was studied, with vWD as an independent prognostic factor for hypothyroidism development [7].

3.3.3. Obesity: With aging, other diseases may appear in patients with vWD. Currently, obesity is one of the most prevalent diseases in the occidental population. Data concerning the prevalence demonstrates that 42.2% of adults aged 20 or older in the United States in 2017-2018 were obese, and 9.2% had criteria for morbid obesity diagnosis [10]. BMI remains the standard measure for classifying its severity [11]. Obesity diagnosis occurs when the BMI is above 30 kg/m2 and has three grades: grade I (BMI between 30 and 34.9 kg/m2), grade II (BMI between 35 and 39.9 kg/m2) and grade III or morbid obesity (BMI above 40 kg/m2) [11]. When abdominal obesity is present, the inflammatory risk is substantial, even if the patient is overweight (BMI between 25 and 29,9 kg/m2 [16,17].

Obesity is a metabolic disease associated with chronic inflammation [10] and endothelial dysfunction, impairing hemostasis and fibrinolysis [16]. Although there seem to be increased FVIII factor levels in obese patients [16], bleeding complications occur in substantial dimensions [17]. Evidence also points to differences in VWF antigen and FVIII levels on BMI ≤85th-95th and ≥ 95th percentile and on race, where black people tend to have higher vWF antigen levels and white people have the highest vWF activity/antigen ratio [10]. There is still no evidence for vWF levels [17].

These increased factor levels can mask the deficiency of vWF or FVIII factors in vWD [10]. We postulate that this patient does not have bleeding symptoms due to these masked augmented factors, meaning the correct levels are even lower.

Bariatric surgery has proved effective for weight loss in morbid obesity, with excellent short and long-term outcomes [12]. The principal indication sticks with patients diagnosed with morbid obesity when a BMI above 40 kg/m2 or a BMI above 35 kg/m2 associated with a metabolic disease [10-11].

In recent years, surgeons have implemented laparoscopic techniques in this type of surgery since they are associated with reduced hemorrhage and infection risks, faster recovery, and lower pain scores. Laparoscopic gastric sleeve is one of the standard surgical treatments for weight loss, associated with lifestyle measures and medication [10]. Initially, the surgical team proposed laparoscopic gastric bypass roux-en-y but due to patient comorbidities with a high risk of bleeding and postoperative malabsorption was decided to change to a laparoscopic gastric sleeve.

The malabsorptive syndrome associated with bariatric surgery could mimic a myelodysplastic syndrome with an impact on bleeding disorders [12].

Conclusion

The first reported case of a type 1 vWD patient with several metabolic comorbidities submitted to bariatric surgery was described. Inflammatory diseases (Hashimoto thyroiditis with hypothyroidism and morbid obesity), hypoparathyroidism with hypocalcemia, and OSA present in our clinical case can also contribute to worse outcomes and diagnosis complexity. The anesthesia team took particular care in planning a strategy based on ABDCE protocol to reduce bleeding risk in the perioperative period.

vWD is the most common bleeding disorder but is still underdiagnosed due to presentation heterogeneity in the general population. Knowledge of vWD etiologies is fundamental as this disease can be inherited or acquired. The underlying mechanism

directly and indirectly influences perioperative care.

The authors show the importance of aging in vWD patients and the appearance of other diseases or disturbances impacting blood disorders.

The prophylaxis and treatment of vWD patients depend on the type of vWD diagnosis, associated symptoms following the procedure, and the patient's pathologies.

A multidisciplinary approach is critical in patients with vWD.

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