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Recurrent Cyst within Willebrand Disease: Place of Surgery?

Meriem Nafidi, Amal Khald, Abderrahim Aboulfalah, Abderraouf Soummani

Obstetrics and Gynecology Department, Mohammed VI University Hospital Center, Faculty of Medicine and Pharmacy, Marrakech, Morocco
Email: meriem.nafidi@gmail.com

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Abstract

Von Willebrand factor is a multimeric glycoprotein that plays an essential role in platelet-rich thrombi formation under high shear stress. The heterogeneity of Von Willebrand disease (vWD) illustrates the complex physiology of this protein. For women, menstrual patterns and heavy menstrual bleeding are the most frequent disorders within the inherited bleeding disorders population. Pelvic pain due to recurrent hemorrhagic ovarian cyst does not appear to have a higher frequency in the vWD population. Though, it can be a source of impaired quality of life and many invasive procedures. In this report, we will describe the management of a recurrent ovarian cyst and show the importance of medical/conservative treatment without loaning to surgery.

Subject Areas

Gynecology & Obstetrics, Hematology

Keywords

Willebrand Disease, Recurrent Ovarian Cyst, Medical Treatment

1. Introduction

Von Willebrand (vWD) disease is one of the most common inherited bleeding disorders in terms of incidence and severity resulting from a quantitative or a qualitative defect of von Willebrand factor (vWf) [1]. It is inherited as a Mendelian dominant and affects both sexes. The bleeding tendency is usually manifested in childhood and characterized by a prolonged bleeding time: taking the form of epistaxis, haemorrhages from the gums, easy and extensive bruising, bleeding following accidental or surgical trauma; menorrhagia is a particularly prominent feature, and postpartum haemorrhage is often severe [2].

Considering bleeding is the most frequently encountered functional sign, pelvic algia has rarely been described as a telltale sign of vWD disease. Since the surgical and obstetric difficulties now can be largely overcome, it seems to be worthwhile to draw attention to this problem. However, should surgery be the first option for vWD management while conservative treatment is preferred nowadays?

2. Case Report

The patient was a 29 years old woman, no gesture, with as antecedent a vWD's disease type 1 discovered since the age of 15 ans; her father and 2 brothers are followed in Hematologic department for hemophilia (Figure 1).

The patient consults at 8 pm in emergency for acute pelvic algia evolving for 2 days, progressive worsening localized in the right iliac side. She could not obtain relief from the pain after changing position, and it was accompanied by nausea, vomiting with absence of hemorrhagic signs in the pelvis and all mucous membranes. Physical examination was strictly normal except for sensitivity in the right iliac side.

She reports episodes of pelvic algia since her menarche at the age of 12 years but spontaneously resolving. The synchronous character with ovulation could not be specified. The interrogation as well as the clinical examination with VT and speculum were not in favor of pregnancy. A plasmatic BHCG test was performed returning negative. White blood cell counts and CRP realized were not in favor of an infection.

Pelvic & transvaginal ultrasound highlighted (Figure 2) a right ovary increased in size, multiloculated continuing with a heterogeneous hypoechogenic formation of 41 × 35 mm vascularized to the Doppler, associated with a peritoneal effusion of medium abundance finely echogenic.

The uterus appeared normal, without any intracavitary or myometrial findings. The endometrial lining was smooth and at all times of appropriate premenstrual thickness. No evidence of torsion was described.

Given the stable state of the patient, medical (non-surgical) care was decided. The decrease in the hemoglobin level from 10.1 g/100ml to 9.2 g/100ml required a blood transfusion in red blood cells and fresh frozen plasma after hematological

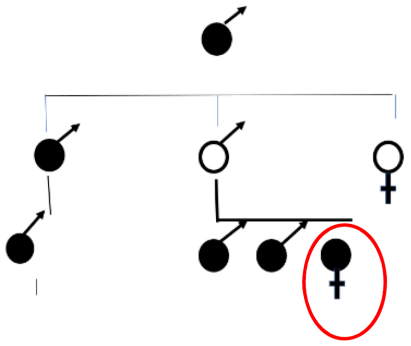

Figure 1. Genealogic family tree of the patient.

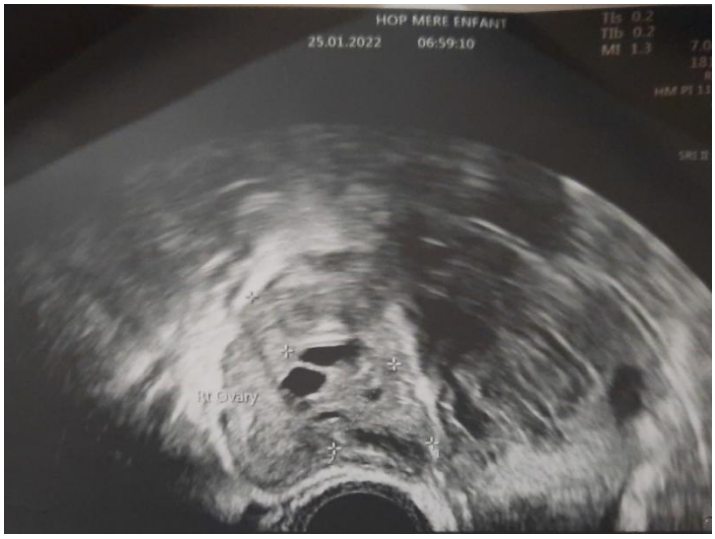

Figure 2. Transvaginal ultrasound shows a right ovary increased in size with a peritoneal effusion.

advice: 2 spread red blood cells, and 5 fresh frozen plasma 15 ml/kg.

The most likely diagnosis was a hemorrhagic cyst in the process of liquefaction given the clinical picture and imaging. The patient was closely monitored for surgical treatment if clinical worsening or hemodynamic instability.

The absence of vWD factor and factor 7 during the patient's hospitalization required initial transfusion-based medical management for hemostasis correction. Oral Desmopressin marketed in Morocco as MINIRIN MELT 60 was not available until one week after the incident.

Resolution of symptomatology and ultrasound regression of peritoneal effusion as well as mass size made it possible to abstain from surgery. The patient benefits from a weekly clinic-ultrasound check-up for 1 month with stability of the condition and a sensitization of possible gynecological and obstetric complications specific to vWD's disease was provided.

3. Discussion

VON WILLEBRAND'S DISEASE (vWD) is an autosomal inherited disorder resulting from a quantitative or a qualitative defect of von Willebrand factor (vWF) which is involved in primary hemostasis (adhesion of platelets to sub-endothelium and platelet aggregation) and acts as the carrier of coagulation factor VIII [3].

Von Willebrand disease is the most frequent inherited bleeding disorder and seems to be not that rare in the population 1% [4]. It is mainly responsible for symptoms such as mucocutaneous bleeding and excessive bleeding after trauma or invasive procedures, but can also cause gastro-intestinal bleeding or hemarthrosis in the most severe forms of the disease. There are numerous causes of physiological variation of von Willebrand factor plasma levels which can be responsible for diagnostic difficulty or changes in symptoms over time.

Expected plasma levels of vWF range from 50 to 200 IU/dL. Many genetic and

physiological factors lead to variations in this rate. The ABO blood type is the genetic factor that most significantly influences vWF levels. THE ABH antigens expressed on the N-glycosylated chains of the vWF influence its clearance and proteolysis [5], thus group O subjects have lower vWF levels of about 25 IU/dL due to accelerated clearance and increased susceptibility to proteolysis by ADAMTS13 [6] with an estimated lower limit value of 40 IU/dL [7]. Subjects of African descent have higher vWF levels of about 15 IU/Dl [8]. This rate also fluctuates during the menstrual cycle with a lower rate observed during menstruation [9]. During pregnancy, it gradually increases from the 11th week of amenorrhea until it reaches 3 times the baseline rate by the end of the 3rd trimester [10]. Taking an estrogen pill raises this rate more moderately [11]. These variations explain the fluctuations in the rate of vWF in a subject and the possible difficulty of making a diagnosis of vWD, so repeat testing and consultation with a hematologist regarding additional tests may be necessary for patients with strong personal and family histories of menorrhagia.

In these cases of difficult diagnosis, the clinical history can be helpful. A hereditary bleeding disorder which affects both sexes and is transmitted as a Mendelian dominant immediately suggests von Willebrand's disease. It is important, however, to remember that a negative family history, as in haemophilia, does not exclude the diagnosis [12].

Diagnosis relies primarily on clinical symptoms but requires the use of several laboratory analyses: von Willebrand factor activity and antigen testing and factor VIII activity. The ristocetin cofactor assay of von Willebrand's factor (vWF) function may be the best single screening test for von Willebrand's disease [13]. More specialized assays allow classification of the disease in various types and subtypes which imply different management strategies (**Table 1**) (types 1, 2A, 2B, 2M, 2N, and 3). It should be determined which type of von Willebrand's disease a particular patient has because treatment depends on type.

The most important clinical manifestations mainly affect women. Although autosomal transmission predicts a similar prevalence of Willebrand disease in both sexes, menstruation, pregnancy and childbirth contribute to a higher prevalence of clinical manifestations of the disease in women, in the order of 60%.

Table 1. Different types of vWD disease.

Type	Description
1	Partial quantitative deficiency of vWF
2	Qualitative defects of vWF
2A	Decreased vWF-dependent platelet adhesion and absence of vWF polymers
2B	Increased binding affinity of vWF for platelets
2M	Decreased vWF-dependent platelet adhesion; presence of vWF polymers
2N	Markedly decreased binding affinity of vWF for factor VIII
3	Virtually complete deficiency of vWF

Menorrhagia is common (65% compared to 9% - 14% in non-sick women).

Women with vWD's disease often complain about bleeding disorders with significant negative impact on the quality of life. There is also an increased likelihood of developing endometriosis, bleeding and pain with ovulation, and sometimes haemoperitoneum [14]. Severe menorrhagia and life-threatening postpartum haemorrhage are frequent in the families of sufferers from von Willebrand's disease and it is surprising to find little reference to these problems in standard texts (only 74 articles that discuss gynecologic & obstetrical disorders within patients with vWD disease from 1960 to 2021), although all are well recognized in the literature. Even less common to find data on pelvic algia without menorrhagia that we report.

The evaluation and management of women presenting abnormal uterine bleeding have been discussed in multiple ACOG publications [15] [16].

The menstrual cycle is characterized by mid-cycle ovarian follicular rupture. Ovulation is not normally accompanied by any significant bleeding, but women who have a congenital bleeding disorder such as Willebrand disease, a bleeding potential exists into the peritoneal cavity or into the residual follicle, resulting in a hemorrhagic ovarian cyst or retroperitoneal hematoma.

The most common clinical presentation of a hemorrhagic ovarian cyst is the sudden onset of pelvic or lower abdominal pain. The term mittelschmerz is used to describe the midcycle, localized, typically unilateral pain experienced every month with ovarian cyst rupture or hemorrhage; pain usually resolves spontaneously within 48 hours [17].

Intra or extracystic hemorrhage can occur in different types of functional cysts. The appearance varies depending on the time between hemorrhage and the time of ultrasound. The appearance, therefore, can sometimes be confusing and evolution over time is important for the positive diagnosis. The use of other explorations is proving to be sometimes necessary [18].

The frequency of benign ovarian lesions has made it possible to push explorations including MRI to deliver more characters on pelvic masses. MRI can make a strong case for benignity of a lesion, as in the case of teratomas, in objectifying a fatty component. MRI can also be offered for young patients with large ovarian cysts to assess the remaining ovarian parenchyma before surgery and the operative risk of an oophorectomy. So staging is no longer just surgical.

Surgery is indicated usually by laparoscopy for ruptures with effusion to be explored, and for cysts of moderate size in the first line (by laparotomy for very large cysts). Indications include cysts of very large size or with local compression, or cysts with criteria of malignancy in ultrasound, persisting at 3 months and in postmenopausal women. We perform an oophorectomy by taking the cyst away without breaking it with extemporaneous pathological examination.

A cyst of benign appearance in a young woman with no criteria of malignancy in ultrasound does not require specific therapy. The symptomatology will regress spontaneously, and we just follow the evolution at 3 months by a new ultrasound. The disappearance confirms the functional nature.

Acute treatment of hemorrhagic ovarian cysts can be based on surgical therapy, tranexamic acid and substitution with coagulation factor VIII or recombinant vWF concentrate.

Treatment options include also oral contraceptive drugs, desmopressin acetate, antifibrinolytic agents, and plasma-derived concentrates rich in the high-molecular-weight multimers of vWF. Consultation with or referral to a hematologist is frequently helpful to assist in the management of patients with severe disease. Oral contraceptive therapy has been successfully used by gynecologists as first-line therapy for the management of von Willebrand's disease for many years. Oral contraceptives have been reported to be successful in the management of menorrhagia associated with von Willebrand's disease in 88% of patients [13]. Hormonally induced therapeutic amenorrhea may be appropriate for patients with severe disease.

Desmopressin acetate, which is available in parenteral form for intravenous use and in a highly concentrated intranasal spray formulation, is the treatment of choice for classic type I disease. It can be used as home therapy before the onset of menses or only during menses [14].

The major interest of a conservative treatment based on medical treatment and sparing surgery is to allow subsequent fertility and avoid repetitive surgical interventions, given that the symptomatology is recurrent.

4. Conclusions

Von Willebrand disease is very heterogeneous in its clinical, biological and molecular aspects. Most patients are affected by a moderate form that does not affect their daily lives. However, these people are vulnerable in case of accidents or surgical interventions, even minor, and their treatment is very special. That's why this hemorrhagic disease requires a perfect knowledge and multidisciplinary care by a specialized center in order to put an adequate therapeutic strategy. There are currently two major therapeutic possibilities of the disease: desmopressin and plasma concentrate rich in vWF or FVIII.

Surgery must always be preceded by a conditioning and drug preparation beforehand because hemostasis cannot be only surgical and the medical component proves to be primordial and decisive.

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Conflicts of Interest

The authors declare no conflicts of interest.

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