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CASE REPORT

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Female case with misdiagnosis of hemophilia A who underwent total knee arthroplasty: A case report

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Abstract

A female was diagnosed with hemophilia A. She had undergone bilateral total knee arthroplasty. She had a history of numerous hemorrhages including hemarthrosis. After further investigations, the diagnosis of von Willebrand disease type 2N was confirmed. The differential diagnoses for hemophilia A include von Willebrand disease, rare bleeding disorders, and severe platelet disorders.

KEYWORDS

arthroplasty, case report, hemarthrosis, hemophilia, misdiagnosis, von willebrand disease

1 | INTRODUCTION

Hemophilia A (HA) is a bleeding disorder caused by a lack of or a reduction in coagulation factor VIII. It is often seen in men. HA is the most common type of inherited coagulation factor deficiency worldwide.[1] It was categorized into three types based on factor VIII levels in plasma (severe <1%, moderate 1%–5%, and mild 5%–40%). This disorder can be seen in any part of the world and among all ethnic groups.[2] According to the World Federation of Hemophilia (WFH), it is estimated that about more than 400,000 patients with hemophilia are present worldwide.[3] It has an X-linked pattern of inheritance. Hence, females are mostly carriers of the disorder to the next generation. The hemorrhagic picture ranges from lethal bleeding in the central nervous system to mild ecchymosis. Bleeding episodes may occur spontaneously or post-trauma/surgery. The severity of bleeding episodes is usually compatible to somehow with the severity of the disorder and the levels of the coagulation factor VIII in plasma.[4] The severe HA is the most challenging form of the disorder, which has a high risk for spontaneous bleeding.[2] Spontaneous muscle and joint bleeding are the hallmarks of severe hemophilia. Hemarthrosis, if left untreated and prolonged, will lead to recurrent inflammatory episodes in the joints, resulting in permanent arthropathy and disability.[5] The presence of hemophilia in females is a rare occurrence. A female with hemophilia can occur due to X-inactivation (Lyonization), daughter of a carrier mother and a father with hemophilia, as well as in Turner's syndrome.[6]

Von Willebrand disease (vWD) is a semi-similar bleeding condition to hemophilia. vWD is the most common inherited hemostatic disorder. The von Willebrand factor (vWF) has critical roles in the coagulation system. It mediates the adhesion of platelets to subendothelium of the injured vessels and serves as a carrier protein for circulating factor VIII.[7] Both men and women are affected by this bleeding disorder. Since the relevant gene is located on chromosome 12, the inheritance pattern is autosomal type. It is estimated that about 580,000 symptomatic individuals with vWD exist in the world.[8] An uncomplicated classification of the disorder, based on pathophysiology, divides

vWD into three types. Type 1 has partial deficiency of the von Willebrand factor antigen (vWF: Ag). Type 2 comprises of the defects in the quality of vWF. And finally, type 3 has severe deficiency of vWF: Ag.[9] A case with type 2N vWD who was previously diagnosed, treated, and underwent total knee arthroplasty as a case with hemophilia A is defined here. This case shows the importance of considering differential diagnosis in initial workup of a bleeding patient. Moreover, the history of this case demonstrates that how a misdiagnosis of a bleeding disorder can terminate to improper management of bleeding disorders.

2 | CASE HISTORY

A female case of hemophilia A (HA) was discovered after checking medical records at Ghaem hospital in Mashhad city using the international classification of diseases code for hemophilia (ICD-10: 68). Last year, she had undergone right total knee arthroplasty (TNA) at Ghaem hospital. She was a 30-year-old female patient with a factor VIII level of 3%, according to her medical records. Moreover, she had a history of multiple hemarthrosis in both knees. Her knee motions had been restricted due to repeated episodes of hemarthrosis. We contacted her to schedule an appointment for a full medical history and physical examination. She was admitted to Imam Reza Hospital, Mashhad, to have her second knee arthroplasty at the time of the call. The patient and her mother met us the day before her surgery. It was discovered that both knees had been operated on around 20 years due to the limitation of knee movement. Despite this, her knee range of motion did not improve. About six months before her surgery, she had a baby delivery. After the birth, her legs inflated and her range of motion deteriorated. At the time of her hospitalization, she did not have a flexion contracture on examination. She had undergone TNA for her right knee last year with a diagnosis of HA. She underwent left TNA at Imam Reza Hospital, the day after meeting with her to record the history of bleeding pictures in more details. In both TNA surgeries, her bleedings were controlled using the infusion of factor VIII concentrates at pre-surgery, during surgery, and post-surgery times.

She was the youngest of seven children, six girls and one boy. The parents were married in a consanguineous relationship. The family's son has a history of bleeding tendency as well. He had enrolled in the hemophilia center with the diagnosis of HA in another province. He had two healthy boys who had no sign of bleeding manifestation. In addition, the patient's aunt had a boy with a bleeding history and a diagnosis of HA. The diagnosis of the case was established when she was a toddler. She had multiple ecchymosis on her feet and buttocks at the time. At the age of 22, she had experienced post-dental extraction bleeding, severe bleeding of wounds, post-cesarean surgery bleeding, a history of bruising at exposed sites, a history of oral cavity bleeding, and multiple episodes of hemarthrosis. In her previous pregnancy, she had a history of unintended abortion at the seventh week of pregnancy. She also has a two-year-old daughter who has been diagnosed with HA and has a factor VIII level of 11%.

3 | DIFFERENTIAL DIAGNOSIS AND INVESTIGATIONS

The condensed MCMDM-1 bleeding questionnaire was completed for her as a predictor of bleeding tendency and subsequently calculated. The score ranged from −1 (absence of any symptom) to 4 (bleeding needs medical intervention, including blood transfusion or infusion of coagulation factor concentrate). The MCMDM-1 helps in determining the severity of bleeding and ruling out vWD. A score of less than four indicates abnormal bleeding.[10] She obtained a score of 14 in MCMDM-1 questionnaire.

The following points convinced us to check this case for vWD:

A HA often occurs in males.
B The pattern of bleeding pictures and history of bleeding in this patient.
C The model of inheritance of the disorder in the family.

Accordingly, she was invited to measure the level of von Willebrand factor antigen (vWF: Ag) about two months post her last surgery. The vWF: Ag concentration was measured using an enzyme-linked immunosorbent assay (ELISA) method (Stago Company, France). The plasma level of vWF: Ag was 84.4% (Reference range: 50%–150%). The result of APTT test was 33 s. The platelet count was $394 \times 10^3/\mu l$. Therefore, the case was diagnosed with vWD with a subtype of 2N. It was needed to evaluate decreased binding affinity of vWF to factor VIII through vWF: FVIIIB test, but this test was not available in our center.

After agreement of the case for publishing her medical history and the current approach to reach the correct diagnosis, the regional Ethic Committee in Mashhad University of Medical Sciences approved this manuscript for publishing.

4 | DISCUSSION

The initial workup for the diagnosis of vWD necessitates both taking history of bleeding tendency (in personal and family) and the laboratory assay of vWF: Ag. A platelet

count should carry out to rule out low platelet situation as the leading cause of bleeding tendency. Moreover, by carrying out PT and APTT, any possible defect in the coagulation system would be rejected. Type 2N of VWD inherits as a recessive trait. It is also known as autosomal hemophilia or Normandy variant of vWD. Except for the fact that subtype 2N VWD is inherited by both males and females, bleeding signs of subtype 2N VWD are not differentiable from hemophilia. Type 2N and type 3 of VWD can be suspected in a female with a diagnosis of hemophilia after soft tissue bleeding or a male with a diagnosis of hemophilia and no response to treatment with purified factor VIII concentrate.

This case cannot be a female with hemophilia based on the following criteria:

1. Females are usually carrier of HA. Both females and males are diagnosed with hemophilia in this case.
2. Individuals with plasma levels of coagulation factor VIII 1%–5% are considered as moderate HA. This case had experienced multiple hemarthrosis in both knees joint. The severity of her hemarthrosis episodes had reached the point that she finally needed to TNA. Hemarthrosis is regarded as a hallmark of severe HA. Moreover, she earned a score of 14 from the condensed MCMDM-1 bleeding questionnaire. This score is high in terms of the severity of the bleeding pictures. These findings are not usually compatible with moderate hemophilia.

Before starting any invasive treatment, like TNA, it is critical to identify and diagnose bleeding disorders. Orthopedic surgeries are usually stressful and challenging processes. They may be dangerous if they are will be associated with bleeding episodes. Patients with bleeding disorders can experience joint destruction secondary to hemarthrosis. They usually refer to orthopedic clinics to consult for ameliorating movement of their joints. Sometimes they undergo amendment surgeries.

The bleeding symptoms of type 2N and type 3 are similar to hemophilia. Hence, female with bleeding tendency and reduced coagulation factor VIII should undergo von Willebrand profile tests to exclude or confirm the diagnosis. In developing countries, where consanguineous marriages are common, this point should be kept in mind. The bleeding tendency in this patient was managed using factor VIII concentrate. If the correct diagnosis of the case had been obtained before the surgery, the management of bleeding was safer and more efficient using factor VIII concentrate with vWF or recombinant vWF. Furthermore, optimal management of hemarthrosis in this case with vWF containing factor VIII concentrate might prevent severe damage to her knees.

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CONFLICT OF INTEREST

The authors declared no conflict of interest, which might perceive as posing a conflict or bias.

AUTHOR CONTRIBUTION

H. Mansouritorghabeh reviewed medical documents, did experiment, and wrote draft of the manuscript. **A. Bari** visited the patient and interpreted the results, followed the patient, and approved final draft of the manuscript.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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