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Acquired Postpartum Hemophilia A: About 3 Cases

Dr. Widad Rhandour[1*], Dr. Hajar Masrour[1], Dr. Latifa Laaghrib[1], Pr. Naoual Oubelkacem[1], Pr. Zineb Khammar[1], Pr. Rhizlane Berrady[1]

[1]Department of Internal Medicine and Onco-Hematology CHU Hassan II Fès-Morocco

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***Corresponding author:** Dr. Widad Rhandour
Department of Internal Medicine and Onco-Hematology CHU Hassan II Fès-Morocco

Abstract **Case Report**

Introduction: Acquired hemophilia A (AHA) is a rare but severe autoimmune disorder. It is caused by the acquisition of autoantibodies to factor VIII (FVIII). These post-partum autoantibodies account for 7-21% of all cases of AHA and most often develop after the first pregnancy. We report 3 new cases of postpartum-acquired hemophilia A. ***Observations:*** Three young women with no prior pathological history presented with a spontaneous and heterogeneous hemorrhagic syndrome, two cases of deep hematomas, and haematuria with ecchymosis in the 3rd patient. The diagnosis was made in all our patients based on plasma FVIII activity <50% and the presence of an FVIII inhibitor. Immunological tests and neoplastic research were negative in all our patients. Hemostatic treatment combined with corticosteroid therapy and immunosuppressive drugs were used for the 3 patients. ***Conclusion:*** AHA is a rare disease, and its diagnosis is often underestimated in our population. It is essential to make clinicians aware of this pathology and to be able to evoke it in young patients of childbearing age. A relapse is possible in future pregnancies, so long-term follow-up is recommended.

Keywords: Acquired hemophilia A, autoimmune disorder, pregnancy, spontaneous.

INTRODUCTION

Acquired hemophilia A (AHA) is a rare but serious bleeding disorder. Clinically, it manifests as spontaneous bleeding from the skin, soft tissues and mucous membranes in patients with no personal or family history of bleeding disorders [1]. The discovery of these autoantibodies in the postpartum period accounts for 7-21% of all cases of AHA, and most often develops after the first pregnancy [2]. We report 3 new cases of acquired hemophilia A of the postpartum period.

OBSERVATION 1

A 31-year-old primiparous G1P1 woman with no notable pathological history presented to the emergency department at 3 months postpartum for spontaneous ecchymoses appearing on the right lower limb, with no other associated signs. Symptoms were enhanced 15 days later by macroscopic hematuria.

The blood count showed microcytic hypochromic anemia at 8.2 g/dL, with normal leukocytes and platelets. A normal prothrombin rate of 100% and a prolonged aPTT of 75 sec/control, a Rosner test of 12 and a coagulation factor assay showing a factor VIII level of less than 1%, with the presence of an anti-factor VIII of 39.7 Bethesda units. Renal and hepatic function tests were without anomalies. The immunological work-up showed positive anti-nuclear antibodies at 1/320 of speckled nuclear type with positive SM/RNP identification at 28 UA/ml. 24-hour proteinuria was negative. Cardiac ultrasound was without abnormalities. Chest X-ray was normal. Thoracoabdominal CT scan revealed inflammatory ureteral thickening.

The diagnosis of idiopathic acquired AHA was established. The presence of autoimmune markers was observed, with no other signs of autoimmune disease. Treatment with corticosteroids at a dose of 1 mg/kg/day was started, together with oral cyclophosphamide. Hemorrhagic signs were controlled and the inhibitor control assay at 3 weeks of treatment was 9.5 Bethesda units with a factor VIII level of 31%.

OBSERVATION 2

A 34-year-old female patient with a history of deep vein thrombosis of the left lower limb, who consulted the emergency department at 9 months postpartum for severe right thigh root pain associated

with functional impotence of the right lower limb. The rest of the somatic examination was unremarkable.

An abdominal angioscan revealed a voluminous collection in the iliac crest of the right iliopsoas muscle, heterogeneous, containing spontaneously hyperdense, thin-walled areas enhanced after injection of contrast medium, measuring 87x52x175 mm.

The blood count showed normocytic normochromic anemia at 9 g/dL, with normal leukocyte and platelet counts. A normal prothrombin rate of 100% and a prolonged aPTT of 114. A coagulation factor assay showed a factor VIII level of 0.5%, with the presence of an anti-factor VIII at 5 Bethesda units.

Liver and kidney function tests were normal. 24-hour proteinuria was negative. Antinuclear antibody and phospholipid antibody tests were negative, as were HIV, viral hepatitis B and C serologies.

Thoracic-abdominal-pelvic computed tomography was without abnormality apart from the hematoma of the iliac head and the right iliopsoas muscle.

The diagnosis of idiopathic AHA was established. Treatment with corticosteroids at 1 mg/kg/day was initiated, with transfusion with fresh frozen plasma. Hemorrhagic signs were initially controlled, but the evolution was marked by the reappearance of the same symptomatology associated with ecchymoses on both upper limbs. The FVIII assay was 2.5%, with stability of the hematoma on re-evaluation CT scan. The patient was put back on corticosteroids combined with azathioprine, with good clinical progression. FVIII and inhibitor assays are ongoing.

OBSERVATION 3

A 27-year-old primiparous G1P1 woman with no significant pathological history presented to the emergency department at 1 month postpartum with swelling of the left lower limb associated with spontaneous ecchymoses. Clinical examination revealed functional impotence of the left lower limb, and the rest of the somatic examination was unremarkable.

A soft tissue ultrasound with Doppler showed a heterogeneous echogenic collection containing non-vascularized partitions on color Doppler, fusing along the calf and measuring 4cm in thickness, associated with soft tissue infiltration.

CBC showed microcytic hypochromic anemia at 6.2 g/dL, with normal leukocytes and platelets. A normal prothrombin rate of 87% and a prolonged aPTT of 100 were observed. A coagulation factor assay showed a factor VIII level of less than 1%, with the presence of 5 Bethesda units of anti-factor VIII. The rest of the factors (IX, XI, XII and won-Willebrand) were normal. Renal and hepatic function tests were without abnormality. The immunological workup and neoplastic investigation were negative.

The diagnosis of idiopathic AHA was established. Treatment with corticosteroids at a dose of 1 mg/kg/day was started, together with transfusion with fresh frozen plasma, with momentary control of the haemorrhagic syndrome. One month later, the same symptomatology reappeared, with functional impotence of the left lower limb, associated with swelling of the left elbow extending to the arm and forearm, complicated by paralysis of the left hand. Radiological examination showed infiltration of the soft tissues of the right upper limb, without individualization of a hematoma, and an increase in the hematoma of the left lower limb.

The patient was put on bolus corticosteroids for 3 days, followed by oral corticosteroids and azathioprine-type immunosuppressive therapy at a dose of 2 mg/ kg/day. She also received FEIBA-based haemostatic therapy. Hemorrhagic signs were controlled and factor VIII levels normalized with irradiation of inhibitors. Currently, the patient is off treatment with a 4-year follow-up without recurrence, and her 2nd pregnancy was uneventful.

DISCUSSION

Acquired hemophilia A is a rare bleeding disorder, characterized by the sudden appearance of autoantibodies that partially or completely neutralize the activation or function or accelerate the clearance of factor VIII [2]. It affects both men and women with no family or personal history of bleeding, unlike congenital hemophilia, which affects only men with a long history of bleeding [4].

In the largest available European cohort of 501 patients, the median age was 74 [4], in line with what has been reported by Tiede *et al*., [1] and Huang *et al*., [6]. Another peak is seen in middle-aged women, particularly with the reported cases of post-partum AHA [5], and hemorrhagic symptoms usually present 1 to 4 months after delivery, and can occur up to 1 year after parturition. The mode of presentation remains similar, even with variation in the days of onset [6]. Hemorrhagic symptomatology is heterogeneous in our patients, with the appearance of deep hematoma reported at 1 month and 9 months postpartum respectively. The 3rd patient presented hematuria with ecchymosis at 3 months postpartum.

In about half the cases, no cause or triggering factor was recognized [8]. In the other half, it was associated with solid and hematological malignancies, autoimmune conditions such as systemic lupus erythematosus, dermatological conditions, as well as

pregnancy and recently reported with COVID-19 and post-COVID vaccines [8, 7]. No etiology was revealed in any of our patients.

The clinical picture is variable, ranging from mild to life-threatening bleeding. In the context of pregnancy and the post-partum period, the hemorrhagic syndrome may also affect the newborn, due to transplacental transfer of immunoglobulin G (IgG) antibodies [10]. The diagnosis of AHA is based on plasma FVIII activity <50% and the presence of an FVIII inhibitor. There is no correlation between FVIII level and inhibitor titre and clinical presentation [8]. However, they should not influence the therapeutic decision.

Given the rarity of this entity, the therapeutic course of action is not codified and must rely on recommendations that are generally based on the clinical judgment and expertise of providers who have treated patients with AHA. The therapeutic approach can be divided into two components: hemostasis management and inhibitor eradication.

Hemostatic treatment depends primarily on the severity and location of bleeding. It is based on the use of bypass agents such as recombinant factor VIIa and activated prothrombin concentrate complex, and recombinant porcine factor VIII. The choice of hemostatic drug is based on the center's experience, its availability and the patient's previous response, if known [12].

Emicizumab is a bispecific, FVIII-mimetic therapeutic antibody that has significantly reduced annual bleeding rates in congenital hemophiliacs with and without inhibitors. Several case reports have been published on the use of emicizumab in the treatment of AHA [11, 15]. According to these studies, this hemostatic therapy appears to be effective, with the advantages of subcutaneous administration, good hemostatic efficacy, early discharge and reduced immunosuppression and adverse events.

The protocol for inhibitor eradication treatment varies from team to team and from published registry to published registry, and is based on corticosteroid therapy alone or in combination with cyclophosphamide or rituximab, depending on the team's preference. The use of mycophenolate mofetil has also been reported [13, 1, 7].

Therapeutic response is defined as an undetectable autoantibody titre (<0.6 BU) and normal factor VIII levels (>50%). Second-line treatment includes factor VIII levels that do not increase and autoantibody titers that do not decrease at 3 to 5 weeks with appropriate treatment and patient compliance. Relapses may occur, requiring long follow-up [14, 3, 18].

CONCLUSION

AHA is a rare and serious acquired hemostatic disorder, its diagnosis underestimated in our population. It manifests as a sudden, life-threatening hemorrhagic syndrome outside the context of trauma. It is essential to raise awareness among clinicians in order to achieve early diagnosis and treatment, and thus avoid morbidity and mortality.

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