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CASE REPORT

# Diagnosis and Management of Post-Partum Hemorrhage Caused by Acquired Hemophilia A: A Case Report

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ABSTRACT

Acquired hemophilia A (AHA) is an uncommon autoimmune bleeding disorder in which autoantibodies that affect the functions of factor VIII (FVIII) are present in the blood. The initial diagnosis of AHA is difficult as the presentations of AHA differ from those of congenital hemophilia A. Moreover, the treatment of AHA is more complex due to the presence of autoantibodies against FVIII. Here, we present a case report of postpartum AHA, to increase the perception and knowledge regarding the recognition and management of such cases. We present a young female with the chief complaint of vaginal bleeding and upper arm ecchymosis. Laboratory results exhibited isolated prolonged activated partial thromboplastin time (APTT) and FVIII inhibitors. The patient was treated with corticosteroids, FVIII concentrates, and a bypassing agent. In conclusion, unexplained postpartum bleeding, unmanageable with basic hemostatic measures, should lead to clinical suspicion of an acquired bleeding disease.



## INTRODUCTION

Acquired haemophilia A (AHA) is an unusual yet potentially critical autoimmune haemostatic disorder where IgG autoantibodies against coagulation factor VIII (FVIII) are present in the circulation [1, 2]. Several basic differences between AHA and congenital FVIII deficiency exist. First, is the presence of autoantibodies that neutralize the action of FVIII in AHA. Second, most of AHA patients have cutaneous and intramuscular haemorrhage rather than haemarthrosis, which is the hallmark of congenital haemophilia A [2]. Moreover, patients with AHA vary in their bleeding symptoms with some complaining of mild symptoms while others having major bleeding, which confuses the diagnosis [2]. Because of these differences and the absence of a past history of bleeding in most of the patients, AHA is often not suspected, which may delay the patient's correct diagnosis and management [2, 3]. In view of the high mortality rate of AHA, prompt diagnosis and management are crucial in reducing negative outcomes [3]. More than 50% of the AHA cases are idiopathic [4], still many conditions have been frequently related to AHA including malignancy [5], autoimmune diseases [6], and drug administration. A rare presentation of AHA has been observed among women in the peripartum period. The aetiology of pregnancy-induce FVIII autoantibodies remains unclear; a possible hypothesis is that the mother is subjected to fetal FVIII during delivery. AHA is more commonly diagnosed in elderly patients of both gender in equal proportion who are aged between 61~80 years, while a small peak (about 8% of patients) are seen in women at the third to fourth decade. This smaller age peak associated mostly with younger female cases,

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exhibiting postpartum haemorrhage (PPH) [7]. In our Kurdistan Region of Iraq (KRI), we seldomly encounter such cases of AHA that may lead to under diagnosis of these seriously ill patients. By highlighting the current case report, we hope to improve awareness and knowledge about diagnosis and management of AHA.

## CASE

The illustrated case report was approved by the ethical committee of Hiwa Hemato-Oncology Center (No. 72) on November 4th 2022. A 23 years old female presented on September 14th 2021 to Hiwa Haemato-Oncology Center-Sulaymaniyah-KRI with post-partum vaginal bleeding and upper arm ecchymosis (Figure 1). Pregnancy was uneventful and she delivered a healthy male baby. The bleeding was severe and starts suddenly three days after normal vaginal delivery. The vaginal bleeding was increasing and the patient's condition deteriorated. At the beginning of her condition on the September 10th she was admitted to the Sulaymaniyah Gynaecology hospital and managed with supportive treatments including transfusions with whole blood and fresh frozen plasma. Following this, the patient's bleeding ceased and was discharged from hospital. After few day other attacks of severe vaginal bleeding occurred. The patient was admitted at this time to Hiwa Hemato-oncology Center for further assessment and work up. She was referred to our hospital with severe anaemia (Hb 7.3 g/dL) and a prolonged APTT (68.0 seconds). Additional laboratory works up revealed 2% FVIII activity. The APTT was corrected immediately after mixing equal volumes of the patient's plasma with pooled normal plasma. While, it was prolonged again following incubation of the mixture at 37°C for two hours indicating the presence of time-dependant circulating anti-FVIII inhibitors, whilst, excluding immediate-acting inhibitors and factor deficiencies. The quantitative measurement of FVIII inhibitor (Bethesda Assay) showed a high titre inhibitor of 13.4 Bethesda units/mL as illustrated in Table 1. The coagulation works up with the mentioned clinical data indicated acquired FVIII inhibitor. As part of the coagulation work up, the patient was tested for other relevant factor deficiencies such as FIX and vWF assay that showed normal values 65% and 124%, respectively. From Sep 15th to Sep 21st she was started on prednisolone tablet 20 mg 1×3, FVIII concentrate 2500 mg 1×2, and tranexamic ampule 1 mg 1×3. In addition, she received antibiotics (metronidazole bottle 500 mg 1×3, ciprofloxacin tablet 500 mg 1×2), omeprazole capsule 40 mg 1×1, and paracetamol tablet 500 mg 1×3. Her FVIII activity was improving along with shortening of her APTT and some decreasing of inhibitor levels. The patient was kept in our center under supervision. Although, the patient was stable, her APTT was still prolonged. Therefore, on the 3rd and 4th of October she received recombinant activated FVII 1 mg 1×6. Next, the steroid was tapered within 2 weeks (30-20-10 mg). One month following her diagnosis she was home, still followed by our center. The current case report illustrates aspects associated with aetiology, diagnosis and treatment of AHA in postpartum women.

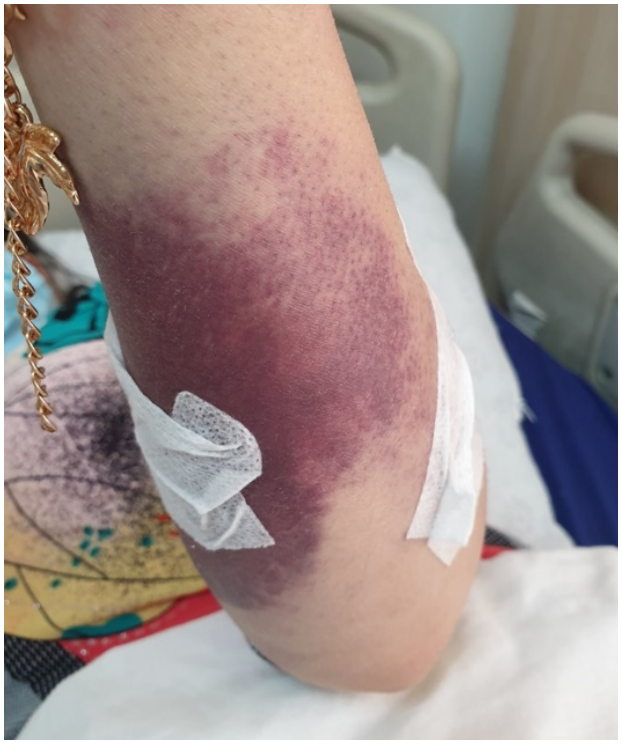

**Figure 1.** Shows a large area of ecchymosis on the forearm of the case.

**Table 1.** Coagulation study and complete blood count of the present case on admission

| | |
|---|---|
| Coagulation test | |
| PT | 12.3 s (control 12.1 s) |
| APTT | 68 s (control 31.8 s) |
| FVIII assay | 2.0% (NR: 50~150%) |
| Mixing study (50:50 with pooled normal plasma) | |
| Immediate APTT | 41.5 s (corrected) |
| APTT after incubation at 37°C for two hours | 60.8 s (not corrected) |
| Bethesda assay | 13.4 BU/mL |
| Complete blood count | |
| RBC | $2.61\times10^{12}$/L |
| Hb | 7.3 g/dL |
| Hct | 21.8% |
| WBC | $5.4\times10^{9}$/L |
| Platelet | $401\times10^{9}$/L |

Abbreviations: PT, prothrombin time; APTT, activated partial thromboplastin time; FVIII, factor VIII; RBC, red blood cell count; Hb, haemoglobin; Hct, haematocrit; WBC, white blood cell; NR, normal.

## DISCUSSION

The diagnosis of AHA is thought out as a challenge because of its nonspecific presentation and low prevalence across the world. A common approach to management is to stabilize the patient at the beginning then figure out the cause of bleeding starting with platelets counts and coagulation screen [8]. Evaluation of coagulation tests exhibits isolated prolonged APTT which could be due to many causes such as deficiency of intrinsic clotting factors (FVIII, IX, XI, XII) and the existence of coagulation factor inhibitors. Therefore, quantitative assays of clotting factors activity and evaluation of coagulation factors inhibitor level are contemplated as an essential diagnostic step [9]. Finally, mixing study assists in discrimination between coagulation factor deficiency and the presence of coagulation factor inhibitor, and it is performed by mixing patient's plasma with normal plasma in 1:1 ratio, which should shorten APTT if the case had factor deficiency. However, if the mixing study didn't correct APTT, this demonstrates the presence of a factor inhibitor. This test should be repeated after 1 to 2 hours of incubation [10]. In AHA, coagulation study demonstrates isolated prolonged APTT, decreased factor VIII activity, increased coagulation factors inhibitor levels in BU, and mixing study unable to correct APTT. FVIII activity and inhibitor titers are not related to each other and neither to the severity of bleeding or treatment effect [11]. In our case, the patient was admitted with severe anemia with hemoglobin level of 7.3 g/dL, coagulation profile shows elevated APTT, mixing studies failed to shorten APTT, FVIII activity was low, and inhibitor levels were increased.

Treatment of AHA involves two substantial aspects, the control of hemostasis and immunosuppressive therapy, to eradicate the inhibitor. Most low titer inhibitors seems to disappear spontaneously, whereas cases with high titer inhibitors may be difficult to manage. The hemostatic arm applies for patients with severe bleeding. Interestingly, because AHA antibodies could be non-neutralizing, some AHA patients benefit from continuous administration of FVIII concentrates, specifically if the inhibitors level are low (<5 BU) [12]. Coagulation-bypass agents like recombinant activated FVII (90 μg/kg every 2~3 hours), and activated prothrombin complex concentrate (50~100 IU/kg every 8~12 hours, maximum of 200 IU/kg/day) are also applied to treat severe bleeding. For cases with minor bleeding, desmopressin can be used [11]. The immunosuppression arm uses steroids (prednisone, 1 mg/kg/day for 4~6 weeks), with multiple immunosuppressants (eg, cyclophosphamide cyclosporine, azathioprine, 6-mercaptopurine, and vincristine). The main treatment lines that have been used recently includes corticosteroid alone, corticosteroid with cyclophosphamide, and corticosteroids with rituximab [12].

In the current case, the patient received multiple doses of recombinant activated FVIII and steroids for few days with some improvement and further was treated with recombinant activated FVII and steroid. She was eventually discharged on a steroid taper after elevation of FVIII levels.

AHA can be fatal if there is a delay in timely diagnosis, which is a major factor contributing to its high mortality

rate. Prognosis highly relies upon clinical course, bleeding severity, underlying cause, and the company of comorbidities. Spontaneous recovery occurs in 25% of the cases, especially in those with medication or pregnancy-induced AHA [13]. In a study by Collins et al, mortality rate of AHA was 41%, with survival being affected by only increasing age, without any significant effect of gender, underlying disease, and factors levels [14]. Relapse is common up to 20% in the first 2 years and thus close follow-up is required [11, 14]. One of the approaches includes evaluating FVIII activity every month for the beginning 6 months, every 2 to 3 months for the next 6 months, and every 6 months later.

AHA is a rare hematologic disease where autoantibodies that inactivate FVIII are formed. It is concomitant with increased morbidity and mortality. As it tends to happen in patients without previous history of bleeding disorders, early diagnosis is often difficult. Diagnosis of AHA is established on the basis of the identification of low FVIII levels in the presence of FVIII inhibitors. The main steps of AHA therapy include controlling and preventing further bleeding, eradicating FVIII inhibitors, and treating the underlying cause or factor that leads to the inhibitor formation.

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