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(CASE REPORT)

Acquired hemophilia successfully treated with recombinant factor VIIa: A case report

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Abstract

Acquired Hemophilia A (AHA) is a disorder characterized by the impaired clotting ability of the blood, primarily resulting from a deficiency in factor VIII, a crucial clotting protein. It is an infrequent disorder that affects a minority of individuals. This condition can pose a life-threatening risk, with reported mortality rates reaching as high as 22%. The diagnosis of AHA is challenging owing to its non-specific presentation and low prevalence rate. The primary objectives of treatment for AHA encompass the cessation and prevention of bleeding episodes, eradication of the inhibitor, and management of the underlying disease in secondary cases. This case report summarizes the successful treatment of a patient with AHA and major bleeding with the repeated use of prednisolone, recombinant factor VIIa, and rituximab.

Keywords: Hemophilia A; Recombinant factor VIIa; Rituximab

1. Introduction

In the field of gynecology, some diseases such as ovarian cancer, Hemophilia, and endometriosis present significant challenges due to their complex and often elusive nature [1-3]. Hemophilia A is a disorder characterized by the impaired clotting ability of the blood, primarily resulting from a deficiency in factor VIII, a crucial clotting protein. This condition, also known as factor VIII deficiency, is associated with compromised coagulation. Hemophilia A typically follows an inherited pattern, wherein mutations in the factor VIII gene situated on the X chromosome are responsible for its occurrence. However, it is worth noting that roughly one-third of hemophilia A cases result from sporadic gene mutations that arise spontaneously [2,3].

Acquired Hemophilia A (AHA) is an infrequent disorder that affects a minority of individuals. In the United States, its estimated annual incidence stands at 1 per 1 million persons [4,5]. This condition can pose a life-threatening risk, with reported mortality rates reaching as high as 22% [5]. Patients with AHA exhibit the presence of an autoantibody directed against factor VIII, referred to as an inhibitor. Considering the compromised clotting ability in individuals with hemophilia, they face an elevated susceptibility to severe bleeding complications following surgical interventions or trauma [6]. AHA predominantly manifests in two distinct age groups: young women during the postpartum period and elderly patients. In the elderly, it is frequently associated with autoimmune diseases, malignant conditions, and hypersensitive reactions to medications [7,8]. Specific conditions linked to AHA are outlined in **Table 1**. The most prevalent sites of bleeding in AHA patients include subcutaneous tissues, gastrointestinal tract, and muscular tissues [9].

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The diagnosis of AHA is challenging owing to its non-specific presentation and low prevalence rate. Patients with abnormal hemorrhage, normal prothrombin time (PT), and prolonged activated partial thromboplastin time (aPTT) should be considered for AHA as a possible diagnosis, especially in those who are at a higher risk of having AHA as mentioned earlier [4,10]

Table 1 Conditions linked with acquired hemophilia

-Idiopathy
-Pregnancy or postpartum period
-Autoimmune disorder (Systemic lupus erythematosus, Rheumatoid arthritis, Multiple sclerosis, Giant cell arteritis, Sjögren's syndrome, Autoimmune hemolytic anemia, Good-Pasture syndrome, Myasthenia Gravis, Graves' disease, Autoimmune hypothyroidism, and Inflammatory bowel disease)
-Dermatologic disorders (psoriasis and pemphigus vulgaris)
-Respiratory diseases (asthma, chronic obstructive pulmonary disease)
-Allergic reaction to drug (Penicillin and derivates, Quinolones and sulfamides, Griseofulvin, Phenytoin, Chloramphenicol, Methyldopa, Levodopa, Interferon alpha, Pegylated interferon, Fludarabine, BCG vaccine, Clopidogrel, Antidepressants, Hydralazine, and Acetaminophen)
-Acute hepatitis B or C
-Malignant disease (solid tumor or hematologic)

The primary objectives of treatment for AHA encompass the cessation and prevention of bleeding episodes, eradication of the inhibitor, and management of the underlying disease in secondary cases. Due to the limited availability of robust evidence, treatment decisions in AHA frequently rely on clinical expertise. Nevertheless, internationally recognized guidelines exist, offering recommendations for the comprehensive care of AHA patients [2,5]. General recommendations are presented in **Table 2**.

Table 2 General recommendations of AHA management

First-line treatment of active bleeding	
Agent	**Dosage**
Activated prothrombin complex concentrate (aPCC)	50-100 U/kg every 8-12 h; Do not exceed 200 U/kg/d
Recombinant FVII activated (rFVIIa)	70-90 mcg/kg every 2-3 h until Hemostasis achieved
Recombinant porcine FVIII (rpFVIII)	200 U/kg initially, titrate according to clinical bleeding and factor VIII activity level
First-line treatment of inhibitor eradication	
Agent	Dosage

Corticosteroids	Prednisone 1 mg/kg PO daily
Corticosteroid and cyclophosphamide	Prednisone 1 mg/kg PO daily, plus cyclophosphamide 1-2 mg/kg PO daily
Second-line treatment of inhibitor eradication	
Rituximab	Rituximab 375 mg/m2 IV weekly×4 doses

Recombinant factor VIIa (rFVIIa) represents a synthetic form of factor VII, an essential clotting protein. As previously stated, its utilization has been proposed for the management of bleeding episodes in individuals suffering from Acquired Hemophilia A (AHA). Nonetheless, the precise safety and efficacy of rFVIIa in such circumstances remain inadequately established. In this report, we present a case of AHA wherein successful treatment was achieved through the administration of rFVIIa, shedding light on its potential therapeutic implications.

2. Case Presentation

A 20-year-old white woman was referred to Alzahra Hospital, affiliated with Isfahan University of Medical Sciences, with hemodynamic instability. Four days prior to her admission, she had vaginal delivery. One day after delivery, she was discharged with normal vaginal exams and vital signs (Systolic Blood Pressure [SBP]:105 mmHg, Diastolic Blood Pressure [DBP]: 55 mmHg, Pulse Rate [PR]: 78 beats/min, Respiratory Rate [RR]: 18 breaths/min, and body temperature: 36.9 ºC). The next day, she presented to the emergency unit with severe vaginal bleeding. Therefore, an emergency postpartum hysterectomy was done for uncontrolled postpartum hemorrhage. and after pelvic packing, the patient was transferred to the Alzahra Hospital.

In the first visit, she was ill and pale, with a PR of 130 beats/min, SBP of 80 mmHg, DBP of 50 mmHg, RR of 20 breaths/min, and body temperature of 37.0 ºC. Among laboratory findings, she presented normochromic, normocytic anemia (hemoglobin [Hb]: 7 g/dL) with mild thrombocytopenia (platelet [PLT] count:137 × 10^3 cells/µL) and normal leukocytes. Moreover, he had a prolonged Partial Thromboplastin Time (PTT) of 86 seconds with a normal prothrombin time (PT) of 9.3 seconds, International Normalized Ratio (INR) of 1, and a normal fibrinogen of 423 mg/dL. The laparotomy was done by a general surgeon and a gynecologist checked the bights and there was no bleeding. However, there was an oozing of pelvic walls and as a result, hematoma of the rectus sheath has been controlled. During surgery, the patient received 6 units of packed red blood cells, 4 units of whole blood, 7 units of cryoprecipitate, and 10 units of fresh frozen plasma (FFP). On the third day after surgery, we observed more disturbance in her coagulation tests as follows: PTT> 120 seconds, PT> 43 seconds, and INR> 5.5. The next day, she presented heavy bleeding from the catheter, hematuria, and melena. Therefore, a hematology consultation was requested. In the first visit, hematologists requested further coagulation tests including factor VIII, IX, XI, and their inhibitors. We determined that the patient had factor VIII deficiency (titre 1%) and her factor VIII inhibitors levels were 200 Bethesda units. As a result, the diagnosis of AHA was confirmed. Following the diagnosis of AHA, rFVIIa (3 g every 3h), prednisolone (50 mg PO daily), and FFP were administered. After 48 hours, the bleeding was controlled, however, rFVIIa continued for one week. To eradicate the factor VIII inhibitors completely, rituximab was administered after one week. The patient responded to this regimen successfully and stayed in the Hospital for 50 days. At discharge, she presented normal lab tests (PTT: 52 seconds, PT: 12 seconds, and INR: 1.1) and continued to consume prednisolone 50 mg PO daily.

Informed consent to publish was obtained from the participant/s involved in the current study.

The data that support the findings of this study are available from Alzahra Hospital data base, but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. The data are, however, available from the authors upon reasonable request and with the permission of Alzahra Hospital data base**.**

3. Discussion

Owing to the ambiguity of making a diagnosis, AHA can be underestimated. The majority of patients with a low titer of inhibitors may remain undiagnosed until they undergo surgery or trauma [3]. According to available evidence, most AHA-related deaths take place within the first few weeks after its appearance with an overall mortality rate of 7.9% to 22% [11].

Recombinant factor VIIa (rFVIIa) is a medication used to treat bleeding episodes in people with hemophilia who also have inhibitory antibodies to factor VIII (FVIII) or IX (11). At concentrations of 20 nmol/L or greater, rFVIIa improves the production of thrombin on activated platelets [12]. The binding of rFVIIa to activated platelets relies on the Gla-domain of rFVIIa and involves negatively charged phospholipids on the activated platelets along with proteins such as GPIb/IX/V and/or endothelial protein C receptor [12].

rFVIIa is a bypassing agent and is categorized as the first-line therapy of bleeding in AHA. Previous reports showed that the overall efficacy rate of rFVIIa was ≥ 90% in various populations [14,15]. However, rFVIIa should be administered with caution owing to its association with the risk of arterial thromboembolic events (such as cerebral artery occlusion and cerebrovascular accidents) and specific venous thromboembolic events (such as pulmonary embolism and deep vein thrombosis). The incidence of thromboembolic events is reported to be 1-10 %, although the overall risk relies on patients co-existing disease. Hence, caution should be exercised in applying rFVIIa in the elderly and those with cardiovascular disease and malignancies [15].

A systematic review was done by Tiede and co-workers in 2018 among 671 patients with AHA who received rFVIIa. They reported that rFVIIa had ≥ 90% homeostatic efficacy with a favorable safety profile [16]. Another study by Lak et al. reported clinical features and treatment of 34 cases of AHA. Five patients were treated with rFVIIa and the outcome was efficient in all of them. An analysis of hemostasis and thrombosis research society registry AHA study revealed that rFVIIa with a dose of 90 μg/kg was effective in stopping bleeding in 85% of cases. Moreover, out of 110 patients who received rFVIIa, one thromboembolic event was reported [17]. However, two recent Cochrane reviews regarding the management of AHA reported that owing to the limited evidence, clinicians should base treatment on the available literature, usually in the form of case reports, case series, and observational studies. [18,19]

4. Conclusion

AHA is considered a fatal and rare disorder linked with bleeding complications. As a result, rapid diagnosis is crucial because promptly initiating the correct treatment to manage bleeding and eliminate inhibitors through immunosuppressive therapy significantly impacts survival. Further randomized clinical trials are essential to elaborate our understanding of AHA management; however, due to the infrequency nature of AHA and random complications associated with it, conducting randomized controlled trials may be difficult to coordinate.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest is to be disclosed.

Statement of informed consent

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. The patient's privacy has been protected, and identifying information has been anonymized.

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