CASE REPORT

High Titer Inhibitor-Acquired Hemophilia A Treated With Human FVIII Concentrate in Limited Resource: A Case Report

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ABSTRACT

Acquired hemophilia A (AHA) is a rare condition that affects one in a million people each year, and there are not many diagnostics or therapeutic agents available for treatment due to its rarity. This is a case report of a 61-year-old woman who presented with a spontaneous subcutaneous hematoma and multiple extensive bruises in her extremities. There was no prior history of bleeding disorders, and the laboratory results showed an isolated aPTT prolongation with no correction after mixing studies, and a reduction in FVIII activity level along with a high FVIII inhibitor titer (928BU). Furthermore, the diagnosis of idiopathic AHA was made after other secondary causes had been ruled out, and the patient received human FVIII concentrate instead of bypassing agents due to its availability. The patient still experienced clinical improvement despite using this alternative. AHA is currently managed using both hemostasis agents and inhibitor eradication, and they come with several limitations. Human FVIII concentrate therapy is still an option in situations with limited resources, even though it is not recommended in patients with high inhibitor titer levels.
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INTRODUCTION

Acquired hemophilia A (AHA) is a rare condition where autoantibodies are developed to factor VIII in people who have never experienced hemophilia A (1). This condition is currently managed using hemostasis agents and inhibitor eradication, which have several limitations. Many bypassing agents are unavailable to control hemostasis because of their scarcity and unpredictable response. Furthermore, morbidity and mortality are associated with treatment complications, particularly infections caused by immunosuppressive agents (2).

We report a case of high titer inhibitor-AHA in a 61-year-old woman accompanied by mucocutaneous bleeding that was controlled using human FVIII concentrate and conservative management. The human FVIII concentrate was used despite its low success rate in patients with high titer inhibitor due to a lack of bypassing agents.

CASE REPORT

A 61-year-old woman presented to the emergency room complaining of painful right thigh swelling (Wong-Baker scale of 8) for one week and multiple spontaneous bruises in her extremities for six months, which had worsened in the two weeks before admission. Anemia symptoms (pallor and palpitations) were discovered, although weight loss, abdominal enlargement, fever, and other bleeding symptoms, such as gastrointestinal bleeding, hematuria, and joint bleeding, were not identified. Additionally, there was no evidence of joint pain, swelling, or stiffness, as well as a prior history of asthma, liver disease, diabetes, thyroid disorder, and hematology disorder. There was no history of hematological disorders among the male relatives and no prior drug history other than a prescribed analgesic.

Vital signs were unremarkable, and the significant observations during the physical examination included an anemic conjunctival, a 15x5 cm subcutaneous hematoma on the right thigh, as well as multiple extensive bruises on both arms, hands, legs, and feet. The two knee joints were normal in size and mobility, and there were no signs of gastrointestinal bleeding or

hematuria.

Laboratory results showed low hemoglobin and a prolonged aPTT, along with a normal PT and platelet count, which is shown in Table I. There was an incomplete correction of aPTT in the mixing study after undergoing 2 hours of incubation with evidence of reduced FVIII level. The patient was initially diagnosed with AHA, accompanied by subcutaneous hematoma and anemia. Subsequently, human FVIII concentrates, packed red cell transfusions, and analgesics were administered to the patient, and RICE (rest, ice, compression, and elevation) was specifically prescribed for the right thigh.

The FVIII inhibitor Bethesda assay revealed a high titer inhibitor of 928 BU the next day, indicating that AHA was the cause of the problem, but there was neither a bypassing agent nor rpFVIII available due to resource limitations. However, a loading dose of 60 U/kg human FVIII concentrates followed by a daily dose of 60 U/kg for seven days eventually helped with the swelling and pain. Furthermore, intravenous steroids (prednisone 1 mg/kg/day) were initially administered but were discontinued on the second day due to elevated blood pressure and blood glucose. There was a reduction in the size of the subcutaneous hematoma on the right thigh from 15 x 5 cm to 8 x 3 cm, as well as multiple extensive bruises on both arms, hands, and feet. The pain was also reduced from an 8 to a 4 on the Wong-Baker scale. There was no further decrease in hemoglobin (11.2 g/dL). Other immunosuppressive therapy was avoided due to the risk of infection and its low effectiveness in high titer inhibitors.

The patient was discharged and planned for outpatient treatment of 60 U/kg FVIII three times a week, but she attended the nearest hospital, where she was administered 30 U/kg FVIII two times a week. Unfortunately, the patient couldn't afford to have her FVIII levels monitored due to financial and logistical issues caused by her rural location and COVID-19 travel restrictions. Consequently, the patient was only observed clinically, and no bleeding symptoms were reported one month after discharge, but she visited the nearest hospital two months after discharge due to a recurrence of subcutaneous hematoma in her lower extremities. The patient, however, was not referred to tertiary healthcare.

DISCUSSION

Acquired hemophilia A (AHA) is a rare condition with an annual incidence of about 1 per million people and a mortality rate of more than 3 - 9% compared to a previous 20% rate. The advancement of therapy is the likely possibility for this significant drop in the mortality rate (3). The diagnosis of AHA should be considered in cases of new-onset bleeding, especially if there is presence of isolated aPTT prolongation and there is no improvement with mixing studies. Additionally, the majority of cases are biphasically distributed, with small peaks between the ages of 20 and 40 years (due to the emergence of postpartum inhibitors) and large peaks at the ages of 65 years and older (3).

AHA can be associated with the peripartum period, autoimmune diseases (Systemic lupus erythematosus, rheumatoid arthritis, thyroid disorder), hematologic malignancy, infection, respiratory disorder, vaccination, or drug use in nearly half of the cases(1). The antinuclear antibody (ANA) and thyroid function tests showed normal results in the patient, and there were no signs or symptoms of rheumatoid arthritis (RA). Furthermore, there were no further workup for hematologic malignancy because the CBC and peripheral blood smear revealed only normochromic normocytic anemia. A solid tumor was ruled out based on a negative anamnesis and physical examination. There were no signs of a respiratory disorder. Common infections responsible for AHA, such as hepatitis B and hepatitis C, were also ruled out based on the presence of a normal hepatitis marker. The patient denied having received any vaccinations or having a history of drug use (antibiotics).

Table I: Laboratory findings during hospitalization

Lab test	Admission	Normal range*	Lab test	Day 2	Normal range*
Hb	8.5 g/dL	11.0-14.7 g/dL	Blood urine	Negative	Negative
Hct	26.10%	35.2-46.7 %	FOBT	Negative	Negative
MCV	92.6 fL	86.7-102.3 fL	Bleeding Time (BT)	2 minutes	1-3 min
MCH	30.1 pg	27.1-32.4 pg	Clotting Time (CT)	40 minutes	9-15 min
MCHC	32.6 g/dL	29.7-33.1 g/dL	FVIII:C	1%	60-150%
Platelet	317.10^3/uL	150-450.10^3/uL	FIX	80%	60-150%
PT	10.8 s	9-12 s	Factor von Wilebrand	242%	50-160%
APTT	69 s	23-33 s	ANA test	26 AU/ml	<40 AU/ml
anti HCV	Non-reactive	Non-reactive	FBG (day 1)	98 mg/dL	<100 mg/dL
HbsAg	Non-reactive	Non-reactive	Predinner blood glucose (day 2)	250 mg/dL	<100 mg/dL

*based on local reference range
ANA=anti nuclear antibody, anti-HCV=anti hepatitis C virus, APTT=activated partial thromboplastin time, FBG=fasting blood glucose, FOBT=fecal occult blood test, Hb=hemoglobin, Hct=hematocrit, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, MCV=Mean Cell Volume, PT=prothrombin time.

The symptoms that are commonly found in AHA are spontaneous or provoked bleeding in patients without a family history of coagulopathy. AHA bleeding usually appears as a spontaneous subcutaneous hematoma and extensive bruising in contrast to the typical joint bleeding of congenital hemophilia A, but muscle bleeding, hematuria, epistaxis, gastrointestinal bleeding, and even intracranial hemorrhage can occur. It remains unknown why the bleeding symptoms in AHA differ from those of congenital hemophilia A (4). The primary complaint of the patient in this report was a right thigh subcutaneous hematoma.

The presence of FVIII inhibitor (INH) reported in Bethesda units (BU) in conjunction with low FVIII level confirms the diagnosis of AHA since its underlying pathophysiology is development of autoantibodies against autologous factor VIII. Furthermore, prolonged aPTT can be caused by several factors, including low levels of factors VIII, IX, XI, XII, high molecular weight kininogens, or prekallikrein. This aPPT is also affected by the presence of anticoagulants, such as heparin, lupus anticoagulants, or clotting factor inhibitors. Therefore, the recommendation suggests ruling out the possibility of lupus anticoagulants (LA) in a patient with normal FVIII: C or a non-bleeding patient (2). The LA was not evaluated in this case because FVIII: C was low with evidence of a high titer inhibitor, and the patient presented with bleeding symptoms rather than thrombosis.

The saturation of antigen (factor VIII) is difficult to achieve because the AHA autoantibody has a type 2 kinetic, non-linear inactivation pattern. The bleeding risk and treatment adequacy cannot be measured solely by residual FVIII levels or INH titers in this case due to the inaccurate representation of "in vivo" inhibitor potency in the Bethesda assay (1).

AHA therapy is divided into two parts, namely antibody eradication and effective hemostasis, which occur during bleeding episodes. Usually, patients with minor bleeding and no vital organ involvement, particularly those with low titer inhibitors, may not require hemostatic therapy. However, close monitoring is vital to determine when a hemostatic agent is required. Routine therapy includes the avoidance of invasive procedures and, if possible, the discontinuation of any therapy that may worsen bleeding, including antiplatelet or anticoagulant drugs (3). The bleeding in this patient was minor but significant enough to cause anemia and immobility. The laboratory results further revealed a high titer inhibitor, prompting the immediate start of the hemostasis treatment using the available agent.

First-line therapy for hemostasis employs bypassing agents, which include recombinant factor VIIa (rFVIIa, NovoSeven®) and active prothrombin complex concentrates (aPCC, FEIBA®) in patients with high inhibitor titers (> 5 BU) or antifibrinolytics, 1-diamino-8-D-arginine vasopressin (DDAVP), and human FVIII concentrates in patients with low inhibitor titers (3). However, not all of these hemostasis therapies work as predicted. The bypassing agents are expensive and not always available. The international AHA recommendation suggests the use of human FVIII concentrate in the absence of bypassing agents, which is what occurred in this case (2). According to a study by Bossi et al., 6 out of 9 (66.7%) AHA patients with high titer inhibitors who were treated using human FVIII inhibitors achieved complete remission in a month, with 16.7% receiving only steroids as immunosuppressive therapy. Unfortunately, one patient who received a combination of steroids and cyclophosphamide died from sepsis (5).

The aim of eradicating inhibitor is to achieve AHA remission, hence, recurrent bleeding episodes did not occur. The antibody eradication protocol includes immunoadsorption, immunosuppression, and immune tolerance induction (ITI). Furthermore, the administration of Prednisone (1 mg/kg/day) alone or in combination with oral cyclophosphamide (50-100 mg/day) for 4-6 weeks is currently recommended as the first-line treatment for autoantibody eradication(2). The medications which can be used in place of cyclophosphophamide for cytotoxic therapy include Azathioprine, 6-mercaptopurine, and vincristine (3). However, complete response (CR), which is an undetectable inhibitor (0.6 BU) and normal FVIII level (> 50%), was only achieved in 48% of patients who received steroids alone and 70% of those who received combination therapy. The survival and sustained remission of AHA was similar for both regimens(4). There was no other immunosuppressive therapy used to treat the patient besides steroids because a low FVIII level at baseline (3) and a high inhibitor titer (2) are predictors of a lower CR, and infection-related mortality is increasing (2). Furthermore, other immunosuppressive therapies for AHA were not covered by the healthcare policy.

According to Tiede et al., the monitoring of treatment effectiveness is primarily based on clinical judgment. The physical examination of the bleeding site, patient-reported pain changes, and serial blood count evaluation are sufficient. Furthermore, clinical effectiveness does not always correlate with FVIIIc levels, even though the measurement of FVIIIc levels in patients receiving FVIII treatment can be beneficial (2). However, the FVIIIC evaluation was not performed in this case for specific and financial reasons, but the clinical improvement was observed.

CONCLUSION

This case report described a rare condition of AHA in low-resource areas and the presence of an autologous FVIII inhibitor as a requirement for diagnosis. Hemostasis and antibody eradication are critical aspects in managing

this condition, but neither has predictable effectiveness. Consequently, the therapy employed in this report was tailored-fit to the patient's clinical setting, inhibitor titer levels, benefit-risk profile, and limitations. The human FVIII concentrate is currently an option in situations where bypassing agents are unavailable.

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