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CASE REPORT

Penicillin-Induced Anti-Factor VIII Antibodies: A Case Report

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ABSTRACT

Introduction: Acquired hemophilia A is very rare autoimmune disorder caused by an autoantibody to factor VIII that interferes with its coagulant function. It may be associated with a number of conditions such as lymphoproliferative disorders, drugs and solid malignancies. Hemarthrosis in Acquired hemophilia A is very rare clinical presentation and was never reported in cases induced by penicillin.

Case presentation: We report a 65-year-old male, born and living in Brazil, who presented hemorrhagic episodes complicated with joint hemarthrosis due to acquired hemophilia A caused by a commonly used drug, Benzathine penicillin.Disease management was focused on controlling bleeding, primarily with the use of factor VIII inhibition bypassing activity and eradicate the autoantibody using various immunosuppressants. The challenges in manage this case included delayed diagnosis, durable remissions, difficulty achieving hemostasis. Clinical and laboratory coagulation response has improved eight weeks after only with the administration of double immunosuppression medication: corticosteroid and cyclophosphamide.

Conclusion: This case gives us the lesson that prompt diagnosis and treatment achieved by hematologists may improve the prognosis and prevent severe bleeding. Early detection is vital to improving outcomes.

Keywords: Acquired Factor VIII Inhibitors, Acquired Hemophilia A, Benzathine Penicillin

List of Abbreviations:
AH = acquired hemophilia A
PT = prothrombin time
aPTT = activated partial thromboplastin
aPCC = activated prothrombin complex concentrate
rFVIIa = recombinant activated factor

1. INTRODUCTION

Acquired hemophilia (AH) is a rare hematological problem (incidence estimated at 1 case per 1,000,000 persons per year) that can be defined by the presence of anticoagulant antibodies - mainly factor VIII inhibitors - distributed in the body and also acting against the procoagulant function of these elements. The early recognition of this condition is fundamental for the health care team and also for the patient, taking into account that hemorrhagic manifestations emerging from this condition are very significant, presenting a high death rate (20-30%).[1]

Unlike congenital hemophilia, which is genetic, AH might be caused by a malignant neoplasm, such as in a paraneoplastic syndrome, or a viral infection. It might additionally occur in association with autoimmune diseases (AR, SLE, and Sjögren's syndrome). There are also records of the incident of this coagulation condition in puerperia and healthy senior adults, as well as after the usage of medicines such as penicillin (Table 1).[2]

Table 1: Conditions associated with AHA

Condition	Examples
Diabetes	
Pregnancy	
Infections	SARS-CoV-2, hepatitis B (HBV), C (HCV), HIV
Autoimmune disorders	Systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, Sjögren syndrome, autoimmune hemolytic anemia, Goodpasture syndrome, myasthenia gravis, Graves' disease, autoimmune hypothyroidism
Dermatologic disorders	Psoriasis, pemphigus
Hematologic malignancies	Hematologic malignancies Chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple myeloma, Waldenström macroglobulinemia, myelodysplastic syndrome, myelofibrosis, erythroleukemia
Respiratory diseases	Asthma, chronic obstructive pulmonary disease
Solid cancers	Prostate, lung, colon, pancreas, stomach, choledochus, head, neck, cervix, breast, melanoma, kidney

The medical picture of AH is comparable to a typical hemostasis defect, impacting the skin and the layers of the mucous membrane, as well as subcutaneous tissues, in the form of contusions. Anemia requiring blood transfusion may be among the clinical presentation of this pathology, however, it is rare to present hemarthroses, which may help in the differential diagnosis with hereditary hemophilia. However, the presence of hemarthroses is rare, which could aid to differentiate the diagnosis of acquired hemophilia from hereditary hemophilia. In addition, the symptoms are not associated with the levels of factor VIII.[3,4]

From the therapeutic point of view, corticoids and also immunosuppressants such as cyclosporine, vincristine, and cyclophosphamide have been used in medication with the purpose of inactivating and preventing coagulation in patients with acquired hemophilia. In addition, innovative therapies with immunoglobulin, interferon, plasmapheresis, and even rituximab have actually been attempted, although a conventional therapy has not yet been found.[5,6]

In this paper, we reported the case of an individual that acquired hemophilia after the use of benzathine penicillin for the therapy of syphilis complicated with joint hemarthrosis. Although there have been previous reports of cases of acquired hemophilia induced by penicillin with spontaneous remission or with a high complete response rate to immunosuppression with the use of corticoid alone. The uniqueness of this case is that spontaneous joint hemarthrosis was never observed in HA induced by penicillin cases. Furthermore, this case required the administration of double immunosuppression medication, with a partial laboratory response after eight weeks. This evolution diverges from published reports (Table 2).

Table 2: Penicillin-induced anti-FVIII antibodies: analysis of the literature data.

Study, year [ref.]	Age (years)	Sex	Associated drug	Symptoms at diagnosis	FVIII level* (IU/ml)	FVIII inhibitor* titer (BU/ml)	Anti- Outcome hemorrhagic	Immunosuppressive	Outcome
Morrison,1993	44	M	Penicillin	Thigh hematoma	0.01	230	PFVIII	Not indicated	Not indicated
	33	M	Penicillin	Hematoma, compartment syndrome	0.01	30	PFVIII	Not indicated	Not indicated
Bossi,1998	26	F	Ampicillin	Ecchimoses,hematoma, hematúria, hemoptysis, hemothorax	0.02	32	PFVIII	Corticosteroids	Complete remission

CASE PRESENTATION

A 65-year-old male who lives alone was admitted in other health service with discomfort, swelling, and also ecchymosis on the right upper leg. The individual had actually been feeling healthy until seven days before admission, after waking up from rest with swelling and discoloration of the skin of the right thigh, over the knee. There was no background of upper leg injury. Over the following five days, the swelling and discoloration spread to the knee and swelling with pain developed. The patient went to the emergency division of a medical facility and received medication, being subsequently referred to this service called Fundação de Hematologia de Pernambuco for further evaluation.

In the examination on admission this health center, the patient presented a temperature of 36.5 ° C, blood pressure of 134/75 mm Hg, heart rate of 76 beats per minute, the respiratory rate of 17 breaths per minute, and oxygen saturation of 99% while breathing ambient air. The ecchymosis expanded from the knee to the right iliac crest, with the patient presenting discomfort with palpation of the knee. The femoral pulse and the range of motion in the right knee were normal. Radiographs of the thigh revealed no fractures or bone lesions. Blood levels of electrolytes and glucose were normal, as well as the results of the examinations of the kidney function; various other outcomes of laboratory examination are shown in Table 3. There was no numbness or prickling in the upper leg or history of hemarthrosis or long-term blood loss with oral treatments. The case history of the patient included hypertension, dyslipidemia, vascular disease, and therapy for syphilis using benzathine penicillin a month ago. The day-to-day medication prescribed to the patient included losartan (100mg) and hydrochlorothiazide (25mg).

Table 3: Laboratory Data.

Variable	Reference Range	On Admission
Hematocrit (%)	34–45	30.1
Hemoglobin (g/dl)	11–16	9.4
White-cell count (per µl)	4000–11,000	9.760
Differential count (%)		
Neutrophils	40–75	74
Lymphocytes	15–54	13.4
Monocytes	4–13	10.6
Eosinophils	0–7	2
Basophils	0–1	0
Platelet count (per µl)	150,000–450,000	212,000
Mean corpuscular volume (fl)	80–11	92.0
Lactic acid (mmol/liter)†	0.5–2.0	1.3
Creatine kinase (U/liter)		0.9
International normalized ratio	1.00–1.30	0.98
Activated partial-thromboplastin time	0.80 - 1.20	3.38

The computed tomography (CT) of the right knee showed joint hemarthrosis in the right knee and a disproportionate augmentation of the rectus femoris muscle, suggesting intramuscular hematoma. Hyperdense stranding was observed in the subcutaneous fat centered over the right knee as well as in the upper leg, which is a finding consistent with hemorrhage. The CT angiography of the arteries revealed no indicators of hemorrhage or findings that could lead to localization of an arterial injury, such as pseudoaneurysm or arterial breakdown. Additionally, a mixing study failed to correct the prolonged activated partial thromboplastin time and Factor VIII level was low at 0.4% (normal53%-196%). The autoimmune workup was negative for antithyroid peroxidase (anti-TPO) antibodies, antinuclear antibodies, rheumatoid factor, antineutrophil cytoplasmic antibodies, perinuclear anti-neutrophil cytoplasmic antibodies, anti-Ro and anti-La antibodies (SS-A, SS-B), histone antibodies, anti-cardiolipin antibodies (IgM and IgG), beta 2 glycoprotein antibodies, Jo-1 antibodies, double-stranded DNA antibodies, and liver/kidney microsomal antibodies.

In terms of cancer workup, cancer screening was negative. The CT scan of the patient's chest, abdomen, and pelvis did not revealed malignancy. The serological workup for malignancy was negative for carcinoembryonic antigen, free light chain kappa/lambda ratio, alpha-fetoprotein, prostate-specific antigen. The infectious workup was negative for blood and urine cultures. The patient was also negative for HIV and hepatitis B and C, cytomegalovirus, Epstein-Barr virus and other virus.

The patient evolved with a new episode of macroscopic hematuria and an aPTT of 83.4 seconds. Therapy with desmopressin was attempted to treat bleeding without success after three days of use. There was no significant decrease in hemoglobin levels and blood transfusion requirements. Immunosuppressive treatment with prednisone 1 mg/kg/day and intravenous cyclophosphamide 500 mg every 21 days was started concomitantly with desmopressin. There was improvement in hematuria one week after the start of treatment. One month after the use of corticosteroids and the first dose of cyclophosphamide, the aPTT decreased to 60.2 seconds, presenting complete symptomatic improvement.

After eight weeks of daily prednisone treatment and after two infusions of cyclophosphamide, the patient presented an aPTT of 56.4 seconds. The patient suspended medications by himself after this period of time, with recurrence of hematomas and worsening of aPTT to 111.2 seconds 20 days after the discontinuation of medication. At the time, the patient presented factor VIII of 6.4% and inhibitor concentration of 147.2 UB/mL.

Corticosteroid was reintroduced at the same dose and a third dose of cyclophosphamide was applied with clinical and laboratory response, with a new aPTT of 58 seconds after three weeks of the resumption of treatment. Currently, approximately one year after the onset of symptoms and after six months of irregular treatment, the patient is weaning from prednisone and has undergone four infusions of cyclophosphamide, with a schedule of six doses in total. The patient currently has an aPTT of 49.5 seconds and is asymptomatic.

2. DISCUSSION

2.1 Differential Diagnosis and Etiology

It is feasible that the ecchymosis of the patient had been triggered by repeated episodes of minor injury that he might not recall. However, the patient presented a single ecchymotic stain, which suggests a single event instead of repeated distressing episodes over time. The ecchymosis of this patient is associated with the rectus femoris hematoma observed on CT. This patient had both leg raising pain and a large contusion, which suggests that he most likely had actually mixed hematoma, with both intramuscular and intermuscular bleeding.

The mixed hematoma can either be caused by an injury or occur automatically. Traumatic hematoma, which is associated with sports or various other injuries, is quite more common. [6]However, this patient did not report participation in sporting activities, besides not presenting a background of a fall or injury. Other crucial consideration is that a reason for hematoma in older patients is the experience of some type of elderly abuse (Table 4). However, the patient lives alone.

Table 4: Differential diagnosis of AHA in elderly.

Antiphospholipid syndrome	Although antiphospholipid antibodies cause aPTT prolongation in vitro, they act in vivo to produce a hypercoagulable state due to activation of phospholipid-dependent coagulation pathways. Manifests with venous or arterial thrombosis or obstetric failures. Often accompanied by decreased PLT and haemolytic anaemia. Presence of antiphospholipid antibodies, lupus anticoagulant
Laboratory errors	Factors causing prolongation of aPTT mimicking AHA: – Haematocrit > 55%, haemolysis, hyperbilirubinemia, hyperlipidaemia – Traumatic venipuncture – Storage conditions prior to testing, spin of samples – Type of reagent – Type of recording device coagulation – Pre-incubation time with the activator – Presence of air bubbles in the sample Multiple performance measurement to exclude laboratory error
Mild-moderate hereditary haemophilia diagnosed after the age of 60 years	Congenital deficiency of factor XI; Congenital deficiency of factor VIII or IX;
Bleeding complications of anticoagulant treatments	Medicines: – Heparin (mainly unfractionated) – Direct inhibitors of coagulation Inhibitors of individual coagulation factors: – VIII, V, IX, X
Abuse of NSAIDs	
Trauma	
Multifactorial disorders	Other acquired bleeding disorders (acquired von Willebrand disease, acquired platelet dysfunctions, uremia, and liver cirrhosis)

As the prospected resources of trauma have been ruled out and imaging researches also did not present a muscular tissue irregularity or aneurysm, this patient's muscle hematoma can be considered as spontaneous. The patient had a number of risk factors for spontaneous muscular hematoma, including age and a history of hypertension. [7]However, he did not have one the most typical risk factors, such as the usage of therapeutic anticoagulation with warfarin or heparin derivatives, as well as the usage of more recent oral anticoagulant agents. In addition, spontaneous muscular hematoma has a tendency to occur in the following three muscle groups: the external stomach muscles, internal stomach muscles, and also gluteal muscles. This is due to the fact that the blood supplies to these muscle groups are vulnerable to adjustments in abdominal movement and also shearing forces.[6,7]

Furthermore, the bleeding proceeded for seven days, as well as spreading down the thigh, what shows an issue with the development of embolism. Primary hemostasis, or the development of preliminary embolisms, includes platelets and capillaries, as well as outcomes of this disorder, such as mucocutaneous bleeding and petechiae. Secondary hemostasis, or fibrin-based clot formation, includes thickening factors, and this disorder might also result in hematomas in the muscles and joints. The platelets of this patient were typical, so the ecchymosis, as well as the hematoma, were related to the hemostatic dysfunction along with the long activated partial-thromboplastin time (aPTT).[8]

This patient had no case history of tingling or numbness in the upper leg or history of hemarthrosis or prolonged bleeding with dental procedures. Thus, it was presumed that the reason for the prolonged aPTT was acquired instead of inherited. There are four feasible causes for acquired prolonged aPTT acquired inhibitor of factor VIII, IX, XI, or XII, lupus anticoagulant therapeutic anticoagulation and an acquired von Willebrand factor deficiency. This patient was not getting

therapeutic anticoagulation. An extended aPTT caused by the lupus anticoagulant is usually related to clotting compared with blood loss. Additionally, the antiphospholipid antibody syndrome can be related with hemorrhage, as well as there are no reports of an association with spontaneous muscle bleeding. Therefore, the existence of lupus anticoagulant is a not likely medical diagnosis in this case.[9,10]

The Von Willebrand factor is mainly observed in hemostasis and platelets, also protecting the factor VIII. In addition, the von Willebrand factor level is directly associated with the factor VIII level. An extended aPTT does not normally occur until the factor VIII level is at 20 to 30% of the typical level. If the von Willebrand factor level had decreased so sharply in this situation, the patient would have mucocutaneous bleeding, which did not occur. Furthermore, a low level of acquired von Willebrand factor is associated with lymphoproliferative conditions, autoimmune problems, and also heart conditions, none of which were observed in this papering. Generally, low level of acquired von Willebrand factor is unlikely to clarify this patient's presentation.[11]

The remaining possibility is the presence of an acquired inhibitor of factors VIII, IX, XI or XII. The acquired factor IX deficiency is unusual, and case reports typically involve postpartum females. The acquired factor XI and XII deficiencies are possibly not related with blood loss. The acquired factor VIII deficiency is the most likely reason for the extended aPTT presented by the patient. This unusual type of acquired hemophilia A is uncommon due to the growth of autoantibodies versus aspect VIII, becoming evident over weeks to months. The incidence increases with age, with a median age at diagnosis of 78 years. Bleeding can be severe and intramuscular blood loss can occur. The problem is frequently associated with cancer cells and autoimmune conditions, although more than 50% of cases have an unidentified reason. The visible symptoms of acquired factor VIII would involve a spontaneous hematoma and also the development of hemorrhage over a 7-day period, besides matching the symptoms with the patient's clinical profile. In opposite to congenital hemophilia, it is very rare find spontaneous joint hemarthrosis in AHA cases.

Nevertheless, this patient presented joint hemarthrosis in the right knee what is in contrast to congenital hemophilia, spontaneous joint hemarthrosis is rarely observed in AHA cases and never was reported by AHA penicillin-induced case. This joint hemarthrosis can be the result of severe prolonged aPTT and weight load, what does not make a specific sign of congenital hemophilia.

Acquired factor VIII deficiency, also recognized as acquired hemophilia A, is an uncommon autoimmune disorder with 1.5 to 2.0 cases per million people yearly and is due to inhibitory autoantibodies against coagulation factor VIII activity. It frequently impacts older populations, with a mean age of 75-78 years, and is related with autoimmune diseases, infection, and also malignancy. In this patient, all serologies were unfavorable and the display for neoplasia was also adverse. The medical diagnosis of acquired hemophilia caused by the usage of penicillin benzathine, which was administered as a therapy for syphilis, is a particular problem of this medication.

2.2 Laboratory Diagnosis

The thrombin time can be gauged or an anti-factor Xa assay can be executed to discover heparin. The anti-factor Xa assay can also be used to discover rivaroxaban, apixaban, fondaparinux, and low-molecular-weight heparin. The anti-factor Xa assay was carried out in this patient and the presence of these anticoagulants was not found.

If an anticoagulant is not present or if the aPTT remains extended after eliminating heparin, the next action is to execute a mixing study of aPTT, which includes mixing individual plasma with regular plasma in a 1:1 ratio and then obtaining the aPTT. A typical aPTT after mixing suggests a deficiency of factor VIII, IX, XI or XII, given that the normal plasma can provide any type of factor that could be missing in the individual plasma. Extended aPTT after mixing suggests the existence of inhibition, as this inhibition in the plasma would certainly influence the normal plasma. One of the most usual inhibitions is the lupus anticoagulant, yet uncommon possibilities include a variable IX or XI inhibitor. The existence of a factor VIII inhibitor is related with distinct outcomes on this assay; the aPTT is typical or near normal at first. However, after a 2-hour incubation period, the aPTT ends up being extended again. In this patient, the aPTT results after a mixing study recommended the existence of factor VIII inhibition. The patient's factor VIII level was substantially reduced, at 0.2% (with the recommendation ranging from 50 to 200%). Other aPTT-based assays for elements IX, XI, and XII presented normal outcomes. Root causes for an unnaturally low factor VIII level - including a clotted specimen, extreme von Willebrand factor deficiency, as well as lupus anticoagulant - were ruled out due to the existence of factor VIII inhibition; the hexagonal phase phospholipid neutralization assay was unfavorable for confirmation, and the lupus anticoagulant screening test had an incorrect positive outcome. A chromogenic assay that is not affected by lupus

anticoagulant obtained a factor VIII level of 0.2%, giving additional proof that the reduced factor VIII level was not related with lupus anticoagulant.[4,12]
The last step is to quantify the factor VIII inhibitor with a Bethesda assay, which successively dilutes the patient's plasma until the inhibition no more acts against dimensioning factor VIII activity. The inhibitor titer is expressed in Bethesda units (BU), which show the amount of inhibition that neutralizes 50% of the expected factor VIII activity in the mix of the assay. In this case, the evaluation of dilution suggested that the patient had an inhibition titer of 198.4 BU, proving the diagnosis of acquired factor VIII deficiency.

2.3 The Pathophysiology

Factor VIII inhibitory activity in a specific penicillin antibody is shown through the dose-related absorption of Factor VIII clotting. The mechanism of this induction of intolerance is not completely understood, although platelet aggregation studies with ristocetin suggested that the inhibitor was specific for the coagulant activity of factor VIII and did not influence Von Willebrand factor activity. Penicillin may have had a hapten-carrier relationship to the large Factor VIII molecule. Penicillins are small molecules that have been shown to covalently bind to the Factor VIII molecule in plasma and create hapten–carrier complexes. The beta-lactam ring binds to lysine residues in serum proteins, and creates the major antigenic determinant penicilloyl-polylysine when binding to a polylysine matrix. Haptenation from covalent binding to carboxyl and thiol groups leads to the creation of several minor determinants. The hapten/prohapten model is applied to immediate or antibody-mediated penicillin hypersensitivity (Gell–Coombs type I, II, and III reactions). As a primary response after the first exposure to hapten–FVIII complex, this protein which is internalized by antigen-presenting cells or dendritic cells; then the protein is presented to naive CD4+ T cells, resulting in its activation in the presence of costimulatory signals. The activated T cell activates naive B cells that are expanded and differentiated into FVIII plasma cells, it secretes anti-FVIII IgM or FVIII memory B cells (Figure 1). [6,13]

Therapy

The management of AH induced by penicillin is basically to establish the hemostasis using a bypass the critical obstruction in the clotting cascade, administering immunosuppressive agents to remove the inhibition and also establishing the underlying cause. In patients with low inhibitor titers, factor VIII supplementation with the usage of desmopressin to to release endogenous stores or with transfusion of factor VIII focuses may be sufficient to develop hemostasis. In patients with titers greater than > 5 BU or with continuous blood loss in spite of conservative administration (as in this situation), the usage of bypassing representatives, such as recombinant factor VIIa or FEIBA (factor VIII inhibition bypassing activity) is required (Table 5).[2,14,15,16]

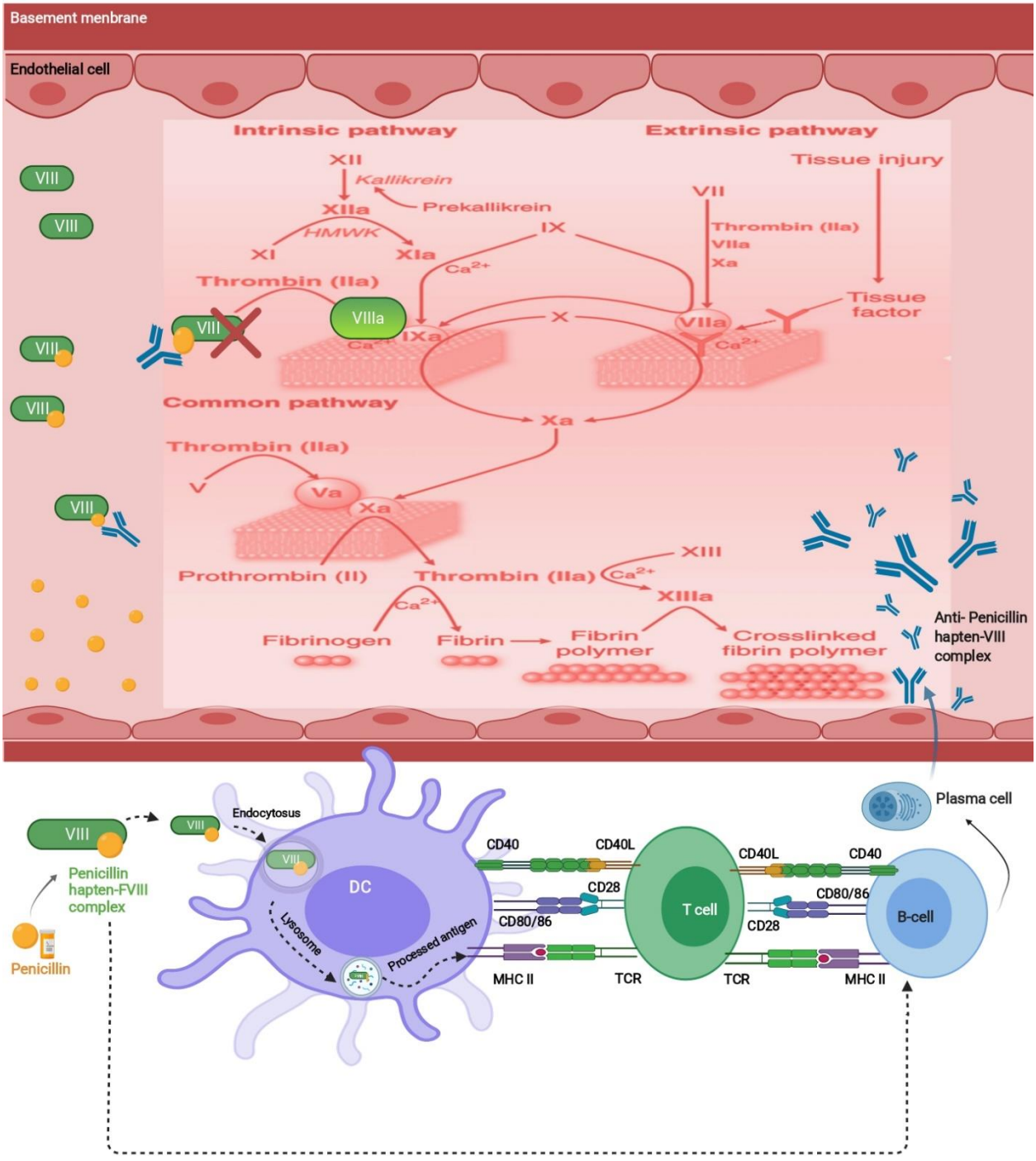

Figure 1: Primary response: after being exposed to FVIII for the first time, DCs or other APCs internalize the protein; the protein is subsequently given to naive CD4+ T cells that activate with the presence of costimulatory signals. The activated T cell causes naive B cells to proliferate and develop into FVIII plasma cells, which secrete anti-FVIII IgM antibodies, or FVIII memory B cells. B,

Table 5: Options for first-line therapy agents in AHA

Treatment	Clinical recommendations and recommended dose
Treatment of acute bleeding:	
Bypassing therapy	
Activated prothrombin complex concentrate (aPCC)	50-100 IU/kg iv every 8-12 hours until clinical response. Do not exceed 200 U/kg/d.
Recombinant FVII activated (rFVIIa)	90-120 g/kg iv every 2-3 hours until hemostasis achieved.
Replacement therapy	
Recombinant porcine FVIII (rpFVIII)	If no anti-porcine FVIII inhibitora: 50–100 U/kg initially then monitor every 2–3 h with FVIII activity and redose as needed. If detectable anti-porcine FVIII inhibitora: 200 U/kg initially for severe bleeding 50–100 U/kg for less severe bleeding. Monitor and redose as above. However, it is not Not currently available for routine clinical use.
Desmopressin	Patients with inhibitor titer 5BU and minor bleeding episodes: 0.3g/kg iv/sc
Human FVIII concentrates	Patients with inhibitor titer 5 BU: 20 IU/kg iv for each BU of inhibitor plus 40 IU/Kg iv
Inhibitor eradication:	
Prednisone plus cyclophosphamide	Prednisone (1 mg/kg per day) plus cyclophosphamide (1-2 mg/kg per day) po for at least 5 weeks
High-dose intravenous immunoglobulin	0.4 g/kg per day for 5 days or 1.0 g/kg per day for 2 days in association with other treatments (steroids, immunoadsorption, IT regimens)

A newer addition to the repertoire of treatments is the recombinant porcine factor VIII, which is an adequately homologous alternative to the human enzyme function but distinct enough in its amino acid sequence to avoid being recognized by many acquired inhibitors. This representative has the mechanistic advantage of direct replacement of inhibited or non-active human factor VIII, along with the logistic advantage of being simple to track using aPTT normalization. Another treatment, which is related to full avoidance of immune recognition, is by using emicizumab, an engineered bispecific antibody that can bind factors IX and X all at once, reproducing the biochemical function of factor VIII while being structurally unique. Emicizumab was originally established to treat inherited hemophilia A with inhibitions, has confirmed to be beneficial for extending the half-life prophylaxis for inherited hemophilia A without inhibitors, and has been currently studied in the context of acquired preventions.[12,13,17,18]

Immunosuppressive approaches for patients with acquired clotting-factor inhibitions have been built on the foundation of glucocorticoid treatment. The enhancement of cyclophosphamide (as in this case) has actually been connected with faster feedbacks and also significantly higher rates of full remission after first-line immunosuppression. Rituximab has also been used in this context, although the first-line responses with the enhancement of rituximab resemble those found when using glucocorticoids alone (Table 6). Nevertheless, the uniqueness of this case is that it required double immunosuppression with a partial laboratory response after eight weeks. This evolution diverges from previously published reports, in which there were cases with spontaneous remission or with a high rate of complete response to immunosuppression with just corticoid alone, suggesting that in some patients, anti-penicillin hapten- factor VIII complex memory B cells can be developed.[12,13,19,20]

Table 6: Inhibitor eradication options for second-line agents in AHA

Immunosuppressive Therapy	Recommended Dose
Cyclosporine	200-300 mg/day alone or in association with prednisone.
Rituximab	375 mg/m2 weekly for 4 weeks in association with steroids
Plasma exchange	

3 CONCLUSION

This record sums up the treatment of a patient with acquired hemophilia A, which is a rare hematologic condition that can frequently go undiscovered. Individuals with acquired inhibitors do not usually have personal or family history of bleeding tendency, and this condition is related with considerable morbidity as well as mortality due to its life-threatening condition and extreme blood loss. There are no randomized scientific tests to lead the monitoring of bleeding and inhibition eradication as a result this being a rare disease. Administration is primarily based on reports, retrospective researches, and unchecked tests.

4 ACKNOWLEDGMENTS

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5 AVAILABILITY OF DATA AND MATERIALS

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

6 AUTHOR CONTRIBUTIONS

All authors were major contributors in writing the manuscript, conceptualization of work, analyzed and interpreted the patient data, helped in data interpretation and reference checking, conceptualization of work. All authors read and approved the final manuscript.

7 DECLARATIONS

7.1 Ethics approval and patient consent

Not applicable

7.2 Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

7.3 Conflicting interests

The authors declare no conflicts of interest.

7.4 Funding

The authors have no support or funding for the reporting.

7.5 Data Availability Statement

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

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