Informes de Caso • Case Report

ACQUIRED HEMOPHILIA:
CASE REPORT OF SEVERE HEMORRHAGIC DIATHESIS IN A 72 YEAR OLD HISPANIC
Nelson Matos-Fernández, MD; Luis Ortiz-Muñoz, MD; Armando García, MD; José Adorno-Fontánez, MD; William Caceres, MD, FACP.

ABSTRACT
A 72-year-old man with seizure disorder and hypertension developed gross hematuria. The patient was found lethargic, hypotensive, with gross hematuria and multiple hematomas. Recent seizure episodes and trauma were denied. Laboratory results showed a prolonged aPTT, normal PT, low hemoglobin and hematocrit. The patient was treated with fresh frozen plasma with minimal improvement of his bleeding and without correction of the PTT. Several blood transfusions were required for optimization of hemoglobin levels. A mixing test was done with no correction of the PTT suggesting the presence of a factor inhibitor. The activity of factor VIII was 0% and levels of factor VIII inhibitors were as high as 525.9 BU. The patient received multiple treatments with resolution of the bleeding. The patient responded to rituximab, a monoclonal antibody against CD20, and melphalan illustrating the efficacy of these medications in regulating the production of auto-antibodies.

Key words: Diathesis, Factor VIII inhibitor, Factor VIII, aPTT, PT, Acquired Hemophilia

INTRODUCTION
Severe spontaneous bleeding can be secondary to a localized pathologic process or a disorder of hemostasis. Disorders of hemostasis can be congenital like hemophilia A and B or acquired such as those associated to inhibitors or deficiencies of the coagulation factors. The inhibitors are antibodies to a variety of clotting factors that can inhibit the activity or increase the clearance of the associated clotting factor. Factor VIII inhibitor is the most common autoantibody and affects the activity of factor VIII, leading to a bleeding disorder. There is an incidence of less than 1 case per million per year. The median age is 64; except in cases related to pregnancy. This disease is more common in females and the mortality varies from 6% to 22% [1, 2, 3]. There are some disorders associated with antibodies to clotting factors like...

From: Internal Medicine Program. Veterans Affairs Medical of San Juan, Puerto Rico. Address correspondence to: Matos-Fernández, Nelson, MD; Internal Medicine Program, Veterans Affairs Hospital. 10 Casa Street. San Juan, Puerto Rico. 00921. Tel: (787) 641-7582, ext. 13191. E-mail address: matosfdz@hotmail.com.
rheumatic diseases, malignancy, clonal lymphoproliferative disorders and pregnancy. This disorder can be idiopathic in nature. Inhibitors against factors V, IX, XI, and XIII have also been identified. We report a case of a 72-year-old male Hispanic who was diagnosed with a factor VIII inhibitor during a workup for intractable bleeding. The patient was treated with multiple transfusions of blood components and other medications with no clinical improvement until the administration of rituximab and melphalan. This resulted in a complete clinical resolution of the patient's symptoms and a decrease in plasma levels of the inhibitor.

CASE REPORT

A 72-year-old Puerto Rican man with seizures treated with phenytoin (Dilantin®) and diet controlled hypertension was evaluated at the San Juan Veterans Affairs (VA) Medical Center Emergency Medicine Department after complains of hematuria for 3 days duration and multiple large hematomas in the right flank that extended to the back, right arm, left hand, wrist, right knee, and left ankle of one day of evolution. During the initial evaluation the patient was found afebrile, lethargic, hypotensive, with multiple large hematomas (Figure 4 and 5). The patient and his family denied any recent history of trauma or episodes of seizures. Laboratory values showed a hemoglobin level of 5.7 g/dl and a hematocrit of 17.2%. Coagulation parameters showed activated partial thromboplastin time (aPTT) of 90.1 secs (Figure 3), prothrombin time (PT) of 14.9 secs, and an international normalized ratio (INR) of 1.18. A mixing test was performed that was positive for circulating anticoagulant inhibitor. Several transfusions of packed red blood cell's (RBC's) and fresh frozen plasma (FFP) were given with post transfusion hemoglobin of 8.2 g/dl, and hematocrit of 24.6%. He was admitted to the hematology oncology ward for further evaluation and management.

The patient continued with hematuria despite fresh frozen plasma transfusions. Antihemophilic factor VIII (Humate-P®) 2800 units intravenously every 12 hours for 2 days, and methylprednisolone 60 mg intravenously every 6 hours were given with control of the subcutaneous bleeding but persistence of gross hematuria. Factor VIII inhibitor levels were reported at 287.3 Bethesda units (BU) with a maximum increase to 525.9 BU (Figure 1). Initially factor VIII activity was measured at 2% and subsequently decreased to 0% (Figure 2). The patient was also treated with desmopressin 22 mcg intravenously once, immune globulin 28 gm intravenously once daily for 5 days, Factor VIII inhibitor bypassing (FEIBA®) 5550 unit every 12 hours for 3 days, rituximab (Rituxan®) 375 mg/m² intravenously once weekly for 4 weeks, and factor IX complex human (KONYNE®) 5000 units intravenously every 12 hours, without resolution of the hematuria. The factor VIII inhibitors started to decrease, with the subsequent increase in the factor VIII activity, but persistent elevation of aPTT. The patient was then started on melphalan (Alkeran®) 2 mg orally every day for 3 months. A work up for malignancy and autoimmune diseases was performed and reported negative. An idiopathic etiology was assessed. Although Factor VIII inhibitor, as a phenytoin adverse reaction, has not been reported, phenytoin was changed to levetiracetam (Keppra®) without the occurrence of seizures. After three months the patient was discharged home with a factor VIII inhibitor at 152.5 BU, factor VIII activity in 1%, and an aPTT at 81.2 secs without hematuria, or subcutaneous bleeding. Ten months later the patient had a Factor VIII inhibitor of 6.2 BU and a factor VIII activity of 36%, without further bleeding episodes reported.

DISCUSSION

Factor VIII inhibitors are usually IgG antibodies of polyclonal origin that do not
bind complement. The predominant subclasses are IgG1 and IgG4 heavy chain [1, 2, 3]. These autoantibodies are directed against different epitopes of the very large factor VIII: C molecule [2]. Much of these antibodies bind to the C2 domain or less often to the A2 domain of the factor VIII. The domain C2 binds to the procoagulant phospholipid phosphatidylserine on activated platelets and endothelial cells and to the von Willebrand factor [1]. Loss of this domain leads to a reduction of procoagulant activity of the intrinsic pathway of coagulation and rarely interferes with other functions of the molecule. Factor VIII inhibitor has been associated to several disorders like clonal lymphoproliferative disorders, malignancy, rheumatic disease, and pregnancy. Adenocarcinomas of the lung and prostate are the most common

**Figure 1.** Factor VIII inhibitor in Bethesda units (BU) in plasma versus time. Normal 0.4 Bethesda Units or less. Test done at Quest Diagnostic-Nichols Institute, San Juan Capistrano, California. Taken from Computerized Patient Record System from San Juan VA Medical Center.

![Graph of Factor VIII Inhibitor](image1)

**Figure 2.** Factor VIII activity in plasma versus time. Normal 50 % to 150 %. Taken from Computerized Patient Record System from San Juan VA Medical Center.

![Graph of Factor VIII Activity](image2)
**Figure 3.** aPTT in plasma versus time. Normal 22.4 secs to 38.3 secs. aPTT = activated partial thromboplastin time. Taken from Computerized Patient Record System from San Juan VA Medical Center.

**Figure 4.** Hematoma on upper back, and right shoulder.

**Figure 5.** Hematoma on right flank.
solid tumors associated. In hematologic malignancies, chronic lymphocytic leukemia is the most common one [1]. Pregnancy related factor VIII inhibitor usually occurs in the postpartum period and account for significant morbidity to young women. Rheumatic diseases related to the production of factor VIII inhibitor are rheumatoid arthritis, and systemic lupus erythematosus.

The major symptom is bleeding which is often severe. There is a difference in the nature and extent of the bleeding between the hemophiliacs and factor VIII inhibitor patients. Patients with hemophilia bleed principally into joints, muscles, and other soft tissues while patients with factor VIII inhibitors have life-threatening bleeding. They present with large hematomas, extensive ecchymoses or severe mucosal bleeding including epistaxis, gastrointestinal bleeding, or hematuria [1, 2]. The presence of any of these signs and symptoms in an elderly patient with no history of trauma or known bleeding disorder should raise the suspicion of this disorder. Coagulation parameters characteristically show a normal prothrombin time, and a prolonged activated partial thromboplastin time [1, 2]. Heparin can give these findings so one must inquire about its recent use. Other diseases that can give this pattern are deficiencies of factors XI, IX, VIII, or von Willebrand disease. To differentiate between a deficiency or an inhibitor a mixing test should be done. This test mixes equal amounts of patient’s plasma and normal plasma and then the aPTT is measured. If there is correction of the prolonged aPTT, a deficiency of the factor is suggested. If there is no correction, it suggests the presence of an inhibitor. After this mixing the aPTT should be incubated at 37° C and measured one and two hours later to detect slow factor VIII inhibitors. If the mix test suggests an inhibitor the Bethesda assay has to be performed to diagnose factor VIII inhibitors and to quantify the antibody titer. In this assay serial dilutions of patient plasma are incubated with normal plasma at 37° C for two hours. The activity of the factor VIII is measured using a clotting assay. The definition of an inhibitor unit or the Bethesda unit (BU) is the amount of inhibitor that would inactivate half of the factor VIII in the incubation mixture. The stronger the inhibitor, the greater the dilution required allowing for factor VIII activity [1, 2]. The activity of factor VIII has to be measured after the Bethesda assay.

Treatment of this disorder should be started as soon as the result of the mixing test is received because the most common cause of this disorder is the factor VIII inhibitor and a delay in the treatment can be fatal. The treatment goals are: controlling the bleeding and then eliminating the inhibitor. To control the bleeding, desmopressin, human or porcine factor VIII concentrate, or recombinant human factor VIIIa can be used. To eliminate the inhibitor, immunosuppressive drugs, such as cyclosporine, cyclophosphamide, cladribine, and intravenous immune globulin, are used. Plasmapheresis can be performed as the last resource in combination with the immunosuppressive drugs as describe by Fischer et al [5].

Rituximab is an anti-CD20 monoclonal antibody that eliminates most circulating B cells. The CD20 surface marker is present on greater than 95% of mature B cells in peripheral blood and lymphoid organs. This molecule function as a membrane ion channel that is important in B cell development. The CD19 and CD20 are the most often used markers to enumerate B cells in flow cytometry [5]. Rituximab is efficacious in immune disorders resulting from autoantibody formation. It is approved for the use in B-cell non-Hodgkin’s lymphoma. It has been used in autoantibody-mediated diseases like immune thrombocytopenia and auto-
immune hemolytic anemia. Wiestner et al reported that rituximab appears to be effective and safe in treating patients with factor VIII inhibitors [5]. The dose is the same used in patients with lymphoma, 375 mg/m² intravenously once a week for 4 to 8 weeks. The most common adverse reactions are fever, nausea, headache, leucopenia, pruritus, rash, hypotension, urticaria, hypotension, and dizziness. The most serious associated adverse reactions are arrhythmias, angioedema, hypersensitivity reactions, cardiogenic shock, Stevens-Johnson syndrome, toxic epidermal necrolisis, lymphopenia, and acute pneumonitis.

Melphalan or L-sarcolysin is a L-phenylalanine mustard that is a derivative of nitrogen mustard. It is an alkylating agent that cross-links the DNA and probably binds to the N⁷ position of guanine. It is approved for the treatment of multiple myeloma and some solids tumors like ovary, testis, and breast [7]. It is active against both resting and rapidly dividing tumor cells like plasma cells. In view that the plasma cells in the bone marrow constitute the principal source of serum IgG [4], this drug was used to decrease the formation of the autoantibodies against the Factor VIII.

CONCLUSION

Acquired hemophilia is an uncommon but treatable coagulopathy. Management includes control of bleeding with factor replacement and immunosuppression with cytotoxic drugs. The internist must be aware of this condition for proper management and better outcomes. We have presented a case of severe acquired hemophilia and its complex management. This is the second case of acquired hemophilia at Veterans Affairs Hospital, in San Juan, PR, that was treated with rituximab and melphalan with an excellent long-term outcome and minimal adverse effects. Rituximab, an antiCD20 monoclonal antibody approved for B-cell lymphomas, has also shown efficacy in immune regulation and control in the production of autoantibodies for several conditions including acquired hemophilia secondary to factor VIII inhibitors. Melphalan, an alkylating agent approved for multiple myeloma can be used to control the production of autoantibodies by the plasma cells. These medications can be added to the armamentarium of the internist in the management of immune diseases.

RESUMEN

Varón puertorriqueño de 72 años de edad con hipertensión y convulsiones tratadas con fenitoína que desarrolló hematuria de tres días de duración asociado a múltiples hematomas en el cuerpo. Al momento de la evaluación inicial el paciente se encontraba letárgico, hipotenso, con hematuria franca y múltiples hematomas en el flanco derecho, hombro derecho, rodilla derecha, ambas manos, muñeca izquierda y tobillo izquierdo. Los miembros de la familia negaron trauma o convulsiones recientes. Los laboratorios demostraron un aPTT prolongado, un PT normal, hemoglobina y hematocrito bajo. El paciente fue tratado con múltiples transfusiones de plasma con una mejoría mínima del sangrado y sin la corrección del PTT. Se requirieron varias transfusiones de sangre para la optimización de los niveles de la hemoglobina. La prueba de corrección de aPTT con plasma sin la corrección del PTT sugiere la presencia de un inhibidor del factor VIII. La actividad del factor VIII estaba baja en 0% y los niveles de los inhibidores del factor VIII en plasma eran altos en 525.9 BU. El paciente respondió a rituximab, un anticuerpo monoclonal contra CD20, y melphalan un agente alquilante, ilustrando el uso de estos medicamentos en la regulación de la producción de autoanticuerpos.
REFERENCES
14. Computerized Patient Record System from San Juan VA Medical Center.