Clinical case
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Acquired hemophilia A secondary to Epstein-Barr virus infection.

Hemofilia A adquirida secundaria a infección por virus de Epstein-Barr

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Abstract

BACKGROUND: Acquired hemophilia A is a bleeding disorder that is usually presented as an idiopathic entity; nevertheless, it has been attributed to other factors, such as autoimmune, malignancy, infections, among others. The diagnosis is made when autoantibodies against epitopes of factor VIII (FVIII) are evidenced, causing the neutralization of the FVIII coagulant activity.

CLINICAL CASE: A 34-year-old female patient that presented with coagulopathy after Epstein-Barr virus (EBV) infection verified by IgG against the nuclear antigen of EBV, secondary causes, like autoimmune, pregnancy, drugs, and others were ruled out. This patient improved after receiving treatment with factor VIII, and complete remission was obtained with rituximab and steroids. After a three-year follow up there has not been any new episode of coagulopathy.

CONCLUSIONS: Acquired hemophilia A is a life-threatening entity, if not diagnosed and treated promptly it can be fatal. To the best of our knowledge, this is the first case of Epstein-Barr virus-associated acquired hemophilia A.

KEYWORDS: Hemophilia A; Epstein-Barr virus; Factor VIII.

Resumen

ANTECEDENTES: La hemofilia A adquirida es un trastorno hemorrágico que suele manifestarse como una enfermedad idiopática; sin embargo, se ha atribuido a otros factores, como autoinmunitario, malignidad, infecciones, entre otros. El diagnóstico se establece cuando se evidencian autoanticuerpos contra epítopos del factor VIII (FVIII), que provocan la neutralización de la actividad coagulante del FVIII.

CASO CLÍNICO: Paciente femenina de 34 años que tuvo coagulopatía posterior a infección por virus de Epstein-Barr (EBV) comprobada por IgG contra el antígeno nuclear de EBV; se descartaron causas secundarias, como autoinmunitaria, embarazo, fármacos, entre otras. La paciente mejoró tras recibir tratamiento con factor VIII y se obtuvo remisión completa con rituximab y esteroides. Tras tres años de seguimiento no ha habido ningún nuevo episodio de coagulopatía.

CONCLUSIONES: La hemofilia A adquirida es una afección que amenaza la vida, si no se diagnostica y trata oportunamente puede ser mortal. Hasta donde sabemos, éste es el primer caso de hemofilia A adquirida asociada con el virus de Epstein-Barr.

PALABRAS CLAVE: Hemofilia A; virus de Epstein-Barr; factor VIII.

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BACKGROUND

Acquired hemophilia A is a rare, acquired bleeding disorder due to the development of autoantibodies directed against epitopes of Factor VIII (FVIII), causing the neutralization of the FVIII coagulant activity. The autoantibodies against FVIII differ from alloantibodies against FVIII of hemophilia A (HA). In the general population, the incidence of acquired hemophilia A is 1 to 4 cases per million inhabitants and 80% of cases occur in people over 65 years of age.[1,2]

Regarding the etiology, 50% of the cases are idiopathic and the rest is distributed between autoimmune, malignancy, pregnancy, infections, drugs, monoclonal gammopathy of undetermined significance, rheumatic polymyalgia, dermatological diseases, blood products transfusion, and other disorders.[1,2]

In acquired hemophilia A pathophysiology neutralizing antibodies, IgG1 and IgG4 subclasses, are developed. These autoantibodies are mainly directed against the A2 and C2 epitopes of the FVIII molecule. It seems that global coagulation is more suppressed in acquired hemophilia A than in severe HA due to the inhibition of Factor IX activated (FIXa)-dependent factor X (FX) activation in the presence of anti-C2 autoantibodies against FVIII.[1]

The clinical picture of acquired hemophilia A is an abnormal bleeding that can be life threatening in a person without a history of coagulopathy. The bleeding predominates in the skin, muscles, soft tissues, mucosa, retroperitoneum, genitourinary system, and lung, while hemarthrosis are rare.[2] Acquired hemophilia A is suspected when a prolonged activated partial thromboplastin time (aPTT) is evidenced and that does not correct with plasma, followed by demonstration of diminished FVIII activity and the presence of autoantibodies with neutralizing activity against FVIII measured with the Bethesda Nijmegen modified assay, which allows the titration of the autoantibody in Bethesda Units/mL (BU/mL).[1,3] A Bethesda Unit (BU) is the antibody potency required to inactivate 50% of normal FVIII activity; however, antibody titers do not correlate with prognosis, differing from congenital hemophilia.[4]

Once the diagnosis of acquired hemophilia A has been made, treatment aims to control and prevent bleeding, eradicate the inhibitor through immunosuppressive treatment (IST), and treat the underlying disease when it exists.[2,5] Herein we present the case of a middle-aged woman with acquired hemophilia A that began after Epstein-Barr virus infection.

CASE REPORT

A 34-year-old female patient with odynophagia history treated as bacterial pharyngitis with tetracycline, azithromycin, ceftriaxone, and dexamethasone for two weeks. At which time edema and ecchymosis were added in the pelvic limbs, vasculitis was suspected, and azathioprine and steroid were administered at unspecified doses without response. Two weeks later, she was admitted to the intensive care unit due to hemorrhagic hypovolemic shock, mechanical ventilation was required. She had extensive ecchymosis in limbs with secondary edema (**Figure 1**), without evidence of gastrointestinal, lung, or urinary bleeding. She presented bleed-

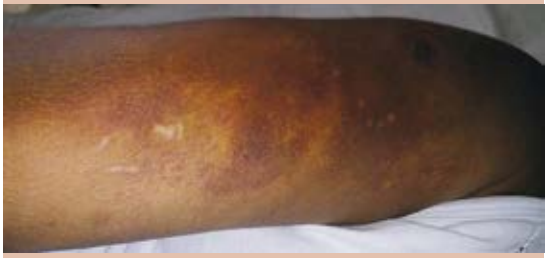

Figure 1. Ecchymosis on the patient's left arm.

ing at radial arterial puncture sites; with control of bleeding with physical means which subsequently ulcerated and healed (**Figure 2**). Her laboratory tests showed prolonged aPTT, anemia, and high levels of creatinine kinase without kidney damage (**Table 1**). Erythrocytes packs and a single dose of 3000 U of factor eight inhibitor bypassing activity (FEIBA) were administered. Once hemodynamic stability was achieved and mechanical ventilation was withdrawn, a coagulopathy approach was started. A decrease in FVIII activity and inhibitor against FVIII were found (**Table 1**), concluding the diagnosis of acquired hemophilia A. Soft tissue ultrasound demonstrated intramuscular and subcutaneous hematomas (**Figure 3**). Underlying immunological and neoplastic diseases were ruled out. Due to upper respiratory infection history, antibodies against the Epstein-Barr virus (EBV) were requested with a report of IgG 60.43 (positive > 1.0), IgM 0.38 (positive >1.0), and IgG against the nuclear antigen of EBV 20.67 (positive > 1.0), negative heterophile antibodies, indicative of EBV infection history. We concluded EBV-associated acquired hemophilia A.

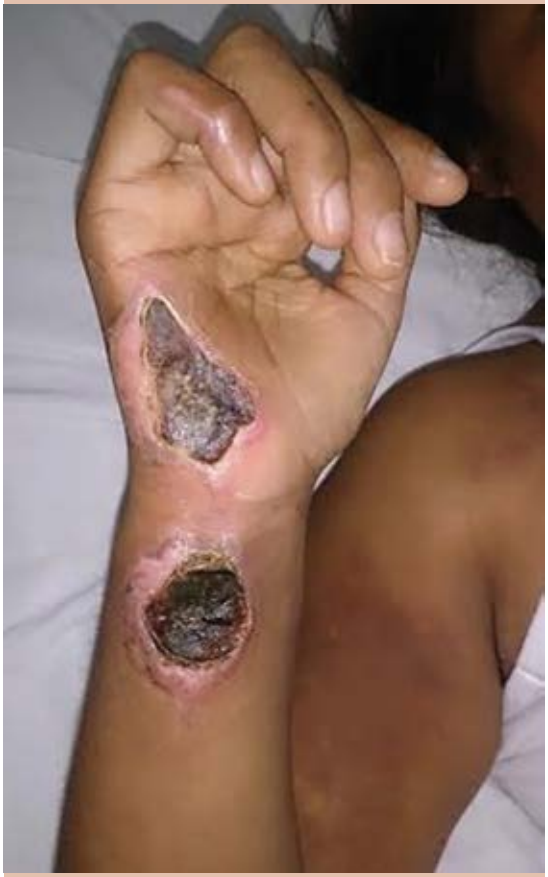

Figure 2. Scars in radial artery puncture sites with bleeding history and control of it with physical means.

Treatment was given with four weekly doses of rituximab 375 mg/m^2 body surface plus prednisone 1 mg/kg/day (four weeks with subsequent gradual dose reduction). The patient achieved complete remission at 9 months of follow-up. During the three-year medical follow-up, there was no evidence of relapse or development of autoimmune or neoplastic disease.

DISCUSSION

We present the case of a woman, without personal or family history of bleeding disorders, with unexplained severe bleeding and aPTT prolongation in which acquired hemophilia A was concluded. The initial diagnostic approach consists of ruling out the presence of heparin and lupus anticoagulant; subsequently, mixing studies must be performed with dilution in plasma and if there is no correction of aPTT, the presence of an acquired inhibitor against any of the coagulation factors should be considered.[4] Once the diagnosis of acquired hemophilia A has been made, it should be investigated whether there is an associated cause.[3] This case, to our knowledge, could correspond to the first case of Epstein-Barr virus-associated acquired hemophilia A.

The treatment is aimed to control and prevent bleeding, avoid any invasive procedure, eradicate the inhibitor by IST, and treat the underlying

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Table 1. Blood tests

	Before immunosuppressive treatment	After immunosuppressive treatment	Reference parameters
Hemoglobin, g/dL	6.7	14.2	12-18
Leucocytes, K/mL	29.4	7.6	4.5-10.0
Platelets, K/mL	259	400	150-450
Reticulocytes, %	25	1	0.5-2.5
Creatinine kinase, U/L	7250	80	50-150
Creatinine, mg/dL	1.07	0.8	0.7-1.3
PT, seconds	14	13	11-15
aPTT, seconds	80	32	25-35
Factor VIII, %	2	52	50 -150
FVIII inhibitor, BU/mL	53	0	0

PT: prothrombin time; aPTT: activated partial thromboplastin time; BU: Bethesda unit.

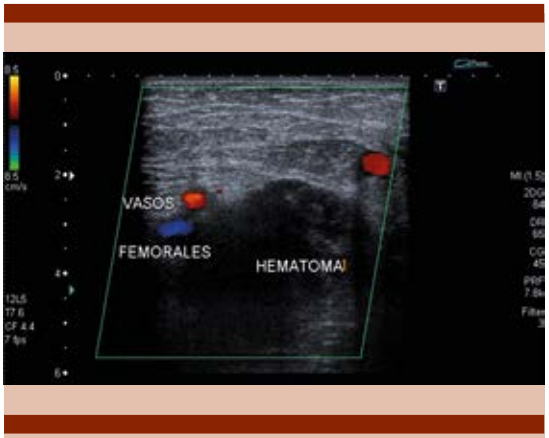

Figure 3. Soft tissue ultrasound demonstrating subcutaneous bruising.

disease.[5,6,7] We controlled acute bleeding with bridging therapy or bypassing the inhibitor activity using activated prothrombin complex concentrates (APCC). The FEIBA is the most used among the APCC.[3,7,8] In the case of our patient, we used a single dose of 3000 U FEIBA.

First-line IST includes steroids and cyclophosphamide, whereas rituximab, azathioprine, cyclosporine, mycophenolate, vincristine, immunoadsorption, and plasmapheresis are second-line IST.[7] Aggarwal et al. proposed an algorithm that incorporates rituximab based on inhibitor titers: 1) for patients with mild bleeding and inhibitor titers of <5 BU, monotherapy with steroids is warranted; 2) for patients with severe bleeding and low to intermediate titers (< 30 BU) or an inadequate response to prednisone as monotherapy, rituximab is added. 3) For patients with titers ≥ 30 BU, multiple approaches including rituximab, cyclophosphamide, and prednisone are used.[8] Nowadays, there are three accepted IST regimens: steroids alone, steroids plus cyclophosphamide, and rituximab with or without steroids.[5]

With IST, patients are expected to achieve a partial remission (PR) or complete remission (CR). The PR is defined as restored FVIII > 50 IU/dL and the absence of active bleeding after stopping any hemostatic treatment for more than 24 hours. CR involves PR associated with the absence of inhibitor detection, use of prednisone < 15 mg/day, and discontinuation of any other immunosuppressive drug. Good prognostic factors to achieve PR are FVIII > 1 IU/dL and inhibitor titers < 20 BU/mL. Poor prognostic factors to achieve PR are FVIII < 1 IU/dL, inhibitor titers > 20 BU/

mL, and anti-FVIII autoantibodies type IgA.[6] Furthermore, a score of ≥ 2 on the World Health Organization scale, presence of neoplasms, and age > 65 years are associated with low survival.[5]

The acquired hemophilia A remission is expected in 60-80% of patients in 5-6 weeks with IST. A PR is expected in less than three weeks with steroid monotherapy if exist good prognostic factors, although this response may be faster and in high percentage, if they are combined with cyclophosphamide (50% vs 80%). If there is no response (inhibitor does not decrease or FVIII does not increase) after 3-5 weeks with first-line IST, a second-line treatment may be considered; the most widely used is rituximab. Initial monotherapy with rituximab achieves CR in 42% of cases and when is combined with a steroid, or with cyclophosphamide plus steroid, this remission rises to 67%. The rituximab can achieve CR in patients who have not responded to first-line treatment, especially in those with high inhibitor titers (> 100-200 BU/mL).[5-11]

After achieving remission, relapses have been reported in 18% of patients treated with steroids, 12% of those treated with steroids plus cyclophosphamide, and < 3% of those treated with rituximab-based regimens. There are no specific treatment regimens for relapses; however, rituximab has been proposed as maintenance therapy.[6,8,11] The estimated mortality of acquired hemophilia is > 20% in patients older than 65 years and in those with underlying malignancy.[5]

CONCLUSIONS

Our patient had not only life-threatening bleeding but also had high levels of inhibitors, which is why management with rituximab and steroids was considered from the beginning, according to the scheme proposed by Aggarwal et al. Our patient achieved a complete response at the 9-month follow-up. Acquired hemophilia A is a life-threatening entity if not diagnosed and treated promptly it can be fatal. To the best of our knowledge, this is the first case of Epstein-Barr virus-associated acquired hemophilia A.

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