Acquired hemophilia associated with rheumatoid arthritis

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ABSTRACT

The occurrence of the antibody against factor VIII is a well-known phenomenon in hemophilia A, occuring in 5 to 15% of the hemophilic patients in the United States, England, Sweden and France. The development of factor VIII in non-hemophilic patients is rare and may occur in healthy individuals, mostly elderly and women in postpartum period, and in patients with malignant neoplasia or autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome.

We described the case of a 64-year-old female patient who has had seropositive rheumatoid arthritis for 23 years and presented with a ten-day history of progressive ecchymosis. Therapy with methylprednisolone, intravenous cyclophosphamide, immunoglobulin and factor VIII reposition was instituted, resulting in a remission of the bleeding and negativity for antibodies against factor VIII titers.

We concluded that, despite its rarity, the presence of acquired factor VIII inhibitors should be investigated when patients with autoimmune diseases develop bleeding manifestations.

Keywords: rheumatoid arthritis, factor VIII inhibitor, acquired hemophilia A.

INTRODUCTION

Acquired hemophilia A is a rare change of blood coagulation featured by the occurrence of antibody against the procoagulating activity of factor VIII.[1] This condition may occur associated with autoimmune diseases, such as rheumatoid arthritis (RA),[1-8] systemic lupus erythematosus (SLE),[2,3] and Sjögren's syndrome.[9] It has also been reported in healthy elderly,[7,8] postpartum period,[8] patients with malignant neoplasia,[2] and related with the use of some drugs, such as penicillin.[3,8]

Several therapies, including corticosteroid, cyclophosphamide, cyclosporine or vincristine, have been used to reduce or remove factor VIII inhibitors. Treatments with high doses of immunoglobulin, interferon and plasmapheresis have been reported, although today there is no gold standard therapy defined.[4,5,10] The most used treatment plan, when it is associated with autoimmune diseases, is a combination of methylprednisolone and cyclophosphamide.[4,5,7,10,11] During the last years, rituximab has been said to possibly be a valuable agent in the treatment of acquired hemophilia.[11]

We describe the case of a female patient with RA who presented with a severe bleeding case history and was diagnosed with acquired Hemophilia A.

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CASE REPORT

A 64-year-old mulatto woman, widow, who was born in the city of Ibiá (state of Minas Gerais) and came from the city of Frutal (state of Minas Gerais), with a history of progressive ecchymosis and hematomas spread all over her body for 10 days. She was first admitted at Hospital Escola da Universidade Federal do Triângulo Mineiro (UFTM) in April, 2005. She has presented with a diagnosis of RA for 23 years and had used prednisone 5 mg/day since the beginning of the disease, as a facultative follow-up. During physical examination, we found large hematomas and ecchymosis in her lower limbs (Figures 1 and 2), chest and vulva, and also hands with ulnar deviation of fingers and a synovial thickening in the metacarpophalangeal joints.

Laboratory exams showed 2,370,000/mm^3 erythrocytes, 7.4 g/dL hemoglobin, 22.4% hematocrit, 340,000/mm^3 blood platelets, 23.3 mg/dL C reactive protein, 1.0 g/dL acid α1-glycoprotein, 50 mm erythrocyte sedimentation rate speed during the first hour, activation time of prothrombin (ATP) with 78% of activity and time of activated partial thromboplastin (ActTP) with 3.45 patient-test ratio (normal between 0.9 and 1.25). Doses of rheumatoid factor were 51.6 UI/mL (reference value < 10 UI/mL). Factor VIII dosing was 4.3% (reference value – 50 to 150%), and factor VIII inhibitor dosing was higher than 10 UI Bethesda. Facing the enlargement of activated partial thromboplastin, the reduction of factor VIII dosing and the presence of antibody against factor VIII, acquired Hemophilia A diagnosis was performed (moderate intensity = factor VIII level between 1 and 5%).

Treatment during hospitalization consisted of three cycles, intravenously, of methylprednisolone 700 mg/day, two cycles of immunoglobulin 25 g, cyclophosphamide 500 mg, with a 21-day interval between them and reposition of prothrombinic complex (factor VIII 1250 UI 12/12 hours for 15 days).

The patient evolved with major improvement of her case history, normalization of ActTP and diminishing of antibody against factor VIII in 1 month of treatment. She was discharged from using prednisone 100 mg/day and she has undergone to three more monthly intravenous cycles of cyclophosphamide 500 mg at Ambulatório de Reumatologia. In August, 2005, cyclophosphamide was discontinued, and the patient was followed up at outpatient room with favorable evolution.

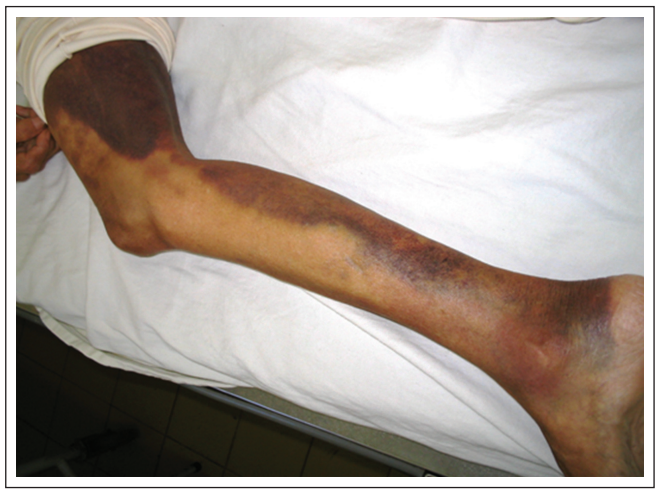

Figure 1. Hematoma and extense ecchimosis of a lower limb.

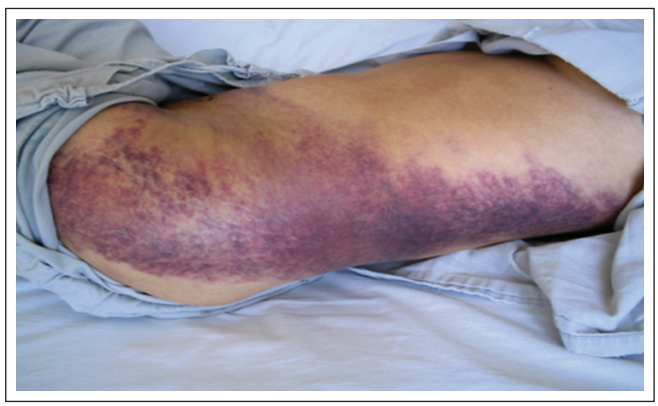

Figure 2. Lower limb ecchimosis.

DISCUSSION

This case report shows a female patient with autoimmune disease who has developed acquired hemophilia and has been successfully treated with a combination of methylprednisolone, immunoglobulin, factor VIII reposition/prothrombinic complex, and intravenous cyclophosphamide.

The differential diagnosis of ecchymosis and/or hematoma with ActTP enlargement, reduction of factor VIII dosing and presence of factor VIII inhibitor featuring acquired Hemophilia includes neoplasia or autoimmune diseases, such as RA, SLE and Sjögren's syndrome, use of drugs like penicillin, women during postpartum period and healthy elderly.

RA association with seric anti-factor VIII antibody is rare. Factor VIII inhibitors in non-hemophilic patients are generally associated with severe bleeding and may cause death in more than 20% of the cases.[1,4] The main objective in the acquired hemophilia treatment is to eradicate factor VIII antibody[10], additionally to controlling hemorrhage.

Type, extension and severity of hemorrhage in patients with autoantibodies (acquired hemophilia) differ from that observed in patients with hemophilia A and who develop inhibitors. In those patients, bleedings start in childhood and appear in joints, muscles and soft tissues, and the presence of factor VIII inhibitors do not increase the frequency of bleeding episodes, however, it makes it difficult to control such events. Patients with acquired hemophilia usually are adults with sudden, more severe bleeding in skin, subcutaneous tissue and muscles; hemarthroses are less common.[10,11]

The fact that anti-factor VIII antibody production is not associated with the disease activity, as observed in case reported, suggests the importance of monitoring blood coagulation in patients in clinic remission and with bleeding manifestations. An early diagnosis is extremely important, because, although it is a rare condition, it is also extremely severe and has high mortality.[3,4,6]

By presenting this case, we concluded that the presence of acquired factor VIII inhibitors should be investigated when patients with autoimmune diseases develop bleeding manifestations during prolonged ActTP with ATP and normal blood platelet number.

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