Spontaneously Developing Autoantibody To Factor VIII In An Elderly Woman : Diagnostic And Therapeutic Challenges

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Abstract

An elderly woman with a continuously bleeding small wound was investigated for the presence of antibodies to FVIII using activated partial time-based screening and confirmatory tests. A late acting coagulation factor inhibitor was detected. The same was characterised to be a low titre antibody against FVIII (5.2 Bethesda units). Cryoprecipitate infusions, corticosteroids and topical desmopressin were unsuccessful in controlling the bleeding. Addition of cyclophosphamide brought about stoppage of bleeding and disappearance of the autoantibody.

INTRODUCTION

Acquired autoantibodies to coagulation factor VIII though rare (0.2 to 1 in 1 million), can pose major problems in the diagnosis and treatment. Alloantibodies to factor VIII develop in 5-20% of hemophilia A patients following infusion of cryoprecipitate or pure factor VIII. Autoantibodies to factor VIII in nonhemophilic patients on the other hand, could be encountered in a wide variety of autoimmune disorders, e.g. in women in peri-partum period, in association with hematologic and other malignancies, following administration of drugs (e.g. penicillin, sulfa drugs, chloramphenicol and phenytoin) or it could develop spontaneously (idiopathic), especially in older persons. 1-3

We describe here a case of autoantibody to factor VIII in an elderly woman who was successfully managed with immunomodulation and cryoprecipitate infusions.

CASE HISTORY

A 65-year-old woman was admitted with continuous bleeding from an incised wound on the right abdominal wall which had developed following pressure at that site from a tight dress. The wound was cauterised, debrided and stitched on many occasions at another hospital. However, it didn’t heal and kept oozing blood. She developed progressive anemia and was given multiple packed red cell transfusions to correct it. She also received small doses of cryoprecipitate and fresh frozen plasma outside on several occasions without much avail. The patient had mild hepatosplenomegaly (ultrasonographically) but no lymphadenopathy. No other abnormality was found on physical examination and on imaging except for a pseudoaneurysm (hematoma) in the right femoral space which appeared to have resulted from an attempted catheterization of the femoral artery at another hospital. Investigations revealed anemia (hemoglobin 7.7g/dl, hematocrit 22.8%) normal total and differential leucocyte counts and normal platelet count (318 x 10^9/l). Renal and liver parameters were normal. Activated partial thromboplastin time (APTT) was prolonged (60 seconds/control 30.3 seconds), prothrombin time was normal (9.3 seconds/control 8.8 seconds; international normalized ratio (INR) = 1.05) and so was bleeding time (6.5 minutes/normal 2.5 - 9.5 minute). Although the abnormal APTT got almost fully corrected in the laboratory on addition of normal pooled plasma (36.1 seconds/30.6 seconds), on further incubation of the mixture at 37°C for one hour and two hours APTT became prolonged again suggesting the presence of a slow acting inhibitor. The inhibitor was identified as factor VIII antibody and was quantitated to be 5.2 Bethesda units. Factor VIII level was low (5.8%; normal = 50-150%). Factor IX level was normal (81.9%; normal = 50-150%). Platelet aggregation response to adenosine diphosphate (ADP) (both low and high concentrations), epinephrine, collagen and ristocetin was normal. Antinuclear antibody and antibody to neutrophil cytoplasmic antigen were absent.

The patient was managed initially with daily cryoprecipitate infusions, tablet prednisolone 40 mg daily and desmopressin nasal spray. Since the oozing from the wound did not stop following these medications, she was given intravenous (IV) immunoglobulin (Ig) 20mg/kg/day for 5 days in addition to cryoprecipitate and prednisolone. Following this the bleeding decreased, although APTT at this time was still around 60 secs. Cryoprecipitate and
prednisolone were continued. However, five days after stopping IV Ig, the patient developed a spontaneous hematoma in the left calf muscle. The dose of cryoprecipitate was increased to six units 12-hourly and IV methyl prednisolone was given at a dose of 1.5 mg/kg/day for 5 days. The average APTT remained high during this period but the calf hematoma stabilized and no other fresh sites of bleeding appeared. The patient was switched over to oral prednisolone (1 mg/kg/day) and tablet cyclophosphamide was added (2mg/kg/day). In ten days’ time the patient showed remarkable improvement. The bleeding stopped completely, the wound healed and the calf hematoma started resolving. APTT came down to around 40 seconds. The patient was discharged on tablet prednisolone and tablet cyclophosphamide. Follow up studies carried out one month later showed normal coagulation parameters. Tablet prednisolone and tablet cyclophosphamide were gradually withdrawn. The patient has since fully recovered and the femoral pseudoaneurysm (hematoma) also has disappeared.

**DISCUSSION**

Acquired autoantibody to factor VIII is an extremely rare entity. Antibodies developing spontaneously in older persons constitute an important subgroup among these cases, although rarely antibodies can develop in younger adults. The cause and the pathogenesis of development of antibody in these cases are not well understood. The occurrence of hemophilia-like bleeding first time in old age should raise this possibility necessitating urgent measures since in the absence of prompt and appropriate treatment bleeding could prove fatal. Our patient posed several diagnostic and treatment problems. Eventhough prolonged APTT and old age of the patient prima facie pointed to the possibility of an acquired antibody to coagulation factors, almost complete correction of the patients APTT by normal pooled plasma initially suggested a factor deficiency instead of an inhibitor. The possibility of an inhibitor was suspected only following prolongation of APTT on further incubation of the plasma mixture, thereby emphasizing the need to look for slow acting inhibitors by incubating the plasma mixture for a longer time even when the initial screening suggests the absence of an (immediate acting) inhibitor. The significance of this approach lies in the fact that such patients could be mistaken for factor deficiency and treated accordingly with disastrous outcome on many occasions.

Most of the cases of spontaneous development of acquired autoantibodies to factor VIII are idiopathic and the bleeding manifestations in these cases are often similar to those in hemophilia A except hemarthrosis which is uncommon in the former. These cases need to be distinguished also from those of autoantibodies to factor VIII developing in association with autoimmune and chronic inflammatory disorders, with pregnancy and puerperium and with hematologic malignancies. Cases of autoantibodies to factor VIII associated with pregnancy and puerperium have good prognosis. Our patient had none of these associations and appeared to be a case of spontaneously developing autoantibody to factor VIII.

The therapeutic goals in these patients are two, (a) to control and prevent bleeding by increasing endogenous production of factor VIII or through infusions of coagulation factors and (b) to suppress the production of the inhibitors. The first goal is achieved by administering drugs like desmopressin and epsilon aminocaproic acid or by infusing cryoprecipitate or purified factors VIII or prothrombin complex concentrate (PCC). If human factor VIII fails to reverse the hemostatic defect, porcine factor VIII is used. The selection of the exact modality of therapy is determined by the severity of bleeding, the residual factor VIII activity and the titre of factor VIII inhibitors. Immunomodulation with the help of steroids, IV Ig infusions and cytotoxic drugs is aimed at reducing the titre of the inhibitor, thereby achieving the second therapeutic goal.

The high cost of factor VIII concentrate and non-availability of prothrombin complex concentrate compelled us to use cryoprecipitate in our patient resulting in slow response. Other publications on this subject from this subcontinent have also emphasised the difficulties in the management of these patients due to the paucity of therapeutic options and the high cost of therapy. However, major bleeding complications were rare in this case except for the development of calf hematoma during the course of her treatment, possibly due to the fact that the antibody titre (5.2 Bethesda units) was not high and that the residual factor VIII activity was above 5%. Both the parameters are considered important determinants of the nature and severity of bleeding in patients with autoantibodies to factor VIII.

This case also emphasises the role of immunomodulation in the management of acquired autoantibodies to coagulation factors. Cryoprecipitate (or even factor VIII concentrate) alone is usually unable to control the bleeding in these cases, a fact amply demonstrated in this patient. Although cryoprecipitate was administered daily over a long period of time, it was only following the administration of IV Ig, steroid and cyclophosphamide that the bleeding came under control and APTT showed improvement.

**REFERENCES**