PUERPERAL ACQUIRED FACTOR VIII INHIBITOR CAUSING A VON WILLEBRAND-LIKE SYNDROME IN A PATIENT WITH ANTI-DNA ANTIBODIES

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ABSTRACT

A 30-year-old Malay lady, with no previous or family history of bleeding, presented with severe gum bleeding 25 days post-partum. The factor VIII:c was 0.03 iu/ml with evidence of a slow-acting factor VIII inhibitor. Von Willebrand factor antigen (VWF:ag) varied from less that 0.05 to 0.17 iu/ml, and there was absent ristocetin-induced platelet aggregation. Anti-nuclear and anti-DNA antibodies were present, but there were no other features of systemic lupus erythematosus. There was some clinical response to cryoprecipitate and tranexamic acid, and slight improvement with corticosteroid. Fifteen months later, the patient has no active bleeding problem, and her VWF-ag is increasing spontaneously. However, factor VIII:c is less than 0.01 iu/ml and her factor VIII inhibitor titre is still >20 Bethesda units/ml.

Keywords: autoantibody, factor VIII, haemophilia, von Willebrand's disease, systemic lupus erythematosus

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INTRODUCTION

Acquired factor VIII inhibitors in non-haemophilic subjects have been found in various settings, such as autoimmune diseases, the puerperium, malignancy, skin diseases and drug reactions[1]. Those that occur post-partum tend to be of low titres and disappear spontaneously or after a short course of corticosteroids[1]. We describe a case that was diagnosed post-partum, but which was atypical in (a) having positive anti-DNA antibodies, (b) failing to resolve with corticosteroid therapy, and (c) having many features of acquired von Willebrand's disease.

CASE REPORT

A 30-year-old woman presented to University Hospital, Universiti Sains Malaysia, Kelantan in September 1991 with a 2-day history of spontaneous severe gum bleeding. She was then 25 days post-partum, although her pregnancy and delivery had been uncomplicated, with no excessive post-partum haemorrhage. Two previous childbirths had been uneventful and there had been no previous history of bleeding. Her menstrual bleeding had always been light. There was no family history of bleeding. She denied any history of facial rash, mouth ulceration, alopecia, arthralgia or Raynaud's phenomenon.

Physical examination revealed profuse gum bleeding and ecchymoses on the upper and lower limbs, but she was otherwise normal.

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Investigations showed the following: haemoglobin 84g/L, white blood cell count 6.9 x 10^9 /L, MCV=88fL and platelet count 155 x 10^9 /L; bleeding time was more than 15 minutes (normal range 3-7); prothrombin time 12 seconds (INR 1.2), activated partial thromboplastin time (APTT) 90 seconds (control, 32.6 seconds); fibrinogen 2.0g/L (normal range 2-4); fibrin degradation products were 6 g/L (normal range < 10). Platelet aggregation studies revealed no response to ristocetin, but normal responses to adrenaline, ADP and collagen. The factor VIII:c was 0.03 iu/mL (normal 0.5-2.0); vWF-ag, by ELISA, was 0.17 iu/mL (normal 0.5-2.0). Ristocetin cofactor activity was not measured. Factor IX level was 1.48 iu/mL (normal 0.5-2.0). A 50:50 mixture of normal and patient's plasma, tested immediately after mixing, showed correction of the activated partial thromboplastin time (mixed plasma 36.0 seconds, control 33 seconds).

The patient was given cryoprecipitate infusions (total 16 units) but the gum bleeding took 4 days to stop. The patient was then discharged, but was re-admitted four weeks later, again with spontaneous gum bleeding. Investigations were similar to the previous admission except that the patient's APTT showed failure of correction by normal plasma if the mixture was incubated for one hour before being assayed (patient 55 seconds, control 32 seconds, 50:50 mix 53 seconds). Factor VIII:c was 0.04 iu/mL and vWF:ag <0.05 iu/mL. Immunological investigations showed a positive antinuclear antibody (titre of 1:40, nucleolar pattern); double-stranded DNA antibodies were positive at a titre of 1:10. Rheumatoid factor and direct Coombs' tests were negative.

A provisional diagnosis of acquired von Willebrand's disease (vWD) was made. The possibility of subsequent development of systemic lupus erythematosus (SLE) was considered. She was treated with cryoprecipitate and tranexamic acid mouth-washes, and the bleeding settled after 24 hours.

Three months later (January 1992), she presented with a large spontaneous haematoma of the right hand. She was given cryoprecipitate infusions, and started on 60 mg of prednisolone daily. In the fifth week of steroid therapy the APTT was 86 seconds, and factor VIII:C 0.03 iu/mL. The patient reported less bruising and no new episodes of gum bleeding, but she refused to continue with the prednisolone because of facial puffiness. Cyclophosphamide was not used because the patient was breast-feeding.

When last seen, in December 1992, she was well with no recent bleeding and no excessive bruising. She was still breast-feeding and menstruation had not yet recommenced.

Investigations showed: APTT 88 seconds (50:50 mix with normal plasma 82 seconds), factor VIII:c 0.008 iu/mL, vWF:ag 0.58 iu/mL, factor VIII inhibitor activity: 20.8 Bethesda units/mL.

Coagulation studies on her parents gave results within the normal range (father; mother, respectively): APTT (31.2, 28.6 seconds), INR (0.94, 0.95), Factor VIII:c (1.12 iu/mL, 1.66 iu/mL), vWF:ag (1.50 iu/mL, 0.76 iu/mL).

DISCUSSION

The clinical and laboratory features of this case (severe spontaneous bleeding and exceptionally low levels of FVIII:c and vWF:ag, in a patient with no family or previous personal bleeding history) suggest an acquired bleeding disorder with many of the characteristics of severe vWD. No immediate-acting factor VIII inhibitor was apparent in the initial mixing tests, but subsequently a time-dependent inhibitor was detected and quantitated at 21 Bethesda units/mL. Specific inhibitors to vWF are notoriously difficult to detect, and no attempt was made to do so here.

The patient's recent delivery of a child and the presence of antinuclear antibodies are both possible aetiological factors in the development of her coagulation inhibitor[1]. The latter may be more likely as the majority of puerperal inhibitors resolve spontaneously or relatively easily with corticosteroid therapy[1]. The diagnostic dilemma was whether the inhibitor was directed against factor VIII or vWF. Acquired vWD has been reported in a number of settings[2], but never in the puerperium and only rarely with SLE[3-7]. Factor VIII inhibitors follow one of two main patterns[8]. With the commonest, Type I, the antibody neutralises factor VIII:c in a linear fashion and only when all the inhibitor is used up can residual factor VIII:c be detected. Such antibodies usually react with an epitope close to the functionally active site of factor VIII and may develop in haemophiliacs following treatment with factor VIII. Type 2 inhibitors, more common in acquired haemophilia, have a complex action and residual functional factor VIII remains even in the presence of free antibody. This may be due to the low affinity of the antibody or because the antibody reacts with an epitope some distance from the functionally active site. If the epitope is close to the vWF binding site of factor VIII, vWF may lose its functional properties, leading to an acquired vWD-type disorder as seen in this case. There were also low levels of vWF antigen in this patient, so in vivo the antibody must also have led to the removal of vWF molecule from plasma.

Although the aetiology of the inhibitor remains obscure in this case (puerperium, SLE, or others), from the therapeutic standpoint, the patient needed to be regarded as a case of acquired vWD and initially received cryoprecipitate (the conventional treatment for vWD in Malaysia) for bleeding episodes. Immunosuppression with corticosteroids has been shown to be beneficial[5], and prednisolone was administered to our patient for a short period. Some clinical improvement was noted, although there was no appreciable effect on factor VIII:c levels. The vWF:ag levels have now risen to a low normal level, and so future therapy for bleeding episodes will be directed to correcting the factor VIII:c deficiency. The patient will also monitored carefully for symptoms and signs of full-blown SLE.

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