Brief Communication

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Development of Factor VIII:C Inhibitors Following Vaccination

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Acquired inhibitors against factor VIII:C (FVIII:C) in nonhemophilic patients are associated with various conditions, including autoimmune diseases (mainly rheumatoid arthritis and systemic lupus erythematosus), malignancies, the postpartum state, drug reactions, and dermatological disorders [1-4]. One case of circulating inhibitor associated with viral infection has also been described [5].

In this report, we describe the case of a 57-year-old male, diagnosed with lichenoid dermatosis, who developed severe hemorrhagic manifestations due to the appearance of inhibitors against FVIII:C following vaccination with BCG and a pool of various strains of live attenuated corynebacteria.

A 57-year-old male was admitted to our hospital in August 1989 with severe fatigue, bleeding from the gums, macroscopic hematuria, and spontaneous leg and forearm pain. He had no family or past history of a tendency to bleed. In September 1988, a lichenoid dermatosis of the scalp was diagnosed. Because of worsening of the skin lesions, vaccine therapy with BCG and a pool of various strains of live attenuated corynebacteria was advised, and was started in June 1989 in a private clinic, after the patient had given his informed consent. This therapeutic approach was adopted on the basis of preliminary unpublished results showing the efficacy of nonspecific immunotherapy in lichenoid dermatosis. The vaccine was administered monthly by subcutaneous injection. Following the second booster, the hemorrhagic manifestations occurred. On examination, the patient appeared in poor general condition. Swelling of both calves and of the right forearm were present, due to the presence of hematomas. The liver and spleen were palpable 2 and 1 cm below the costal margin, respectively. Laboratory investigations revealed Hb 12.7 g/dl, WBC $5.2 \times 10^9/l$ (72% neutrophils, 26% lymphocytes, 1 % monocytes, and 1 % eosinophils), platelets $229 \times 10^9/l$ and ESR 80 mm in 1 h. Macroscopic hematuria was present. Liver enzymes, serum creatinine, and blood urea nitrogen were normal.

Tests for VDRL, rheumatoid factors and antinuclear antibodies were negative. The prothrombin time (PT), the activated partial thromboplastin time (aPTT), and the quantification of fibrinogen

plasma levels were evaluated according to standard procedures. The PT was normal (12 s), whereas the aPTT was prolonged (60 s; normal range 24-34 s).

The plasma concentrations of factors II, V, VII, VIII, IX, X, and XI were measured utilizing deficient plasmas obtained from Behring (Scoppito, Italy) according to standard procedures. The presence of FVIII:C inhibitors was assessed according to the Bethesda method and levels were expressed as Bethesda units (BU) [6].

FVIII:C was markedly reduced (12%; normal range 80-120%) and the presence of an inhibitor of FVIII:C was demonstrated (32 BU; fig. 1). Factors II, V, VII, X, XI, fibrinogen, and serum fibrin degradation products were normal.

There was no evidence of lupus anticoagulant activity, evaluated by dilute Russell's viper venom time [7], and both IgG and IgM anti-cardiolipin antibodies, measured by a standardized and validated ELISA [8], were negative. The administration of the vaccine was then stopped and the patient treated with intravenous fluids, prednisone (80 mg/day), FVIII:C concentrates (Emoclot, Aima Castelveccchio Pascoli, Lucca, Italy; a bolus of 50 U/kg followed by an infusion of 72 U/kg/day for 5 days), and desmopressin (1-desamino-8-D-arginine vasopressin, DDAVP; 0.3 µg/kg/day in 50 ml of saline for 3 days). The prednisone dose was tapered once the patient's condition improved and stopped after 1 month.

The patient's status improved markedly and a progressive reduction of the FVIII:C inhibitor together with normalization of the FVIII:C plasma level were documented (fig. 1).

The patient has been followed carefully for the last 5 years and no other bleeding episode has occurred. FVIII:C levels have remained in the normal range and FVIII:C inhibitors have not been detected (fig. 1). The skin lesions remain unchanged.

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In this report, we describe the development of an inhibitor to FVIII:C in a patient with lichenoid dermatosis who had been vaccinated with BCG and a pool of various strains of live attenuated corynebacteria.

The occurrence of spontaneous hematoma formation and bleeding gums is unusual with FVIII:C levels of 12%, but perhaps the patient's FVIII:C was lower prior to hospitalization.

The presence of inhibitors against FVIII:C in patients without hemophilia has been reported in different conditions, including dermatologic disorders (e.g. psoriasis, pemphigus, exfoliative dermatitis, and erythema annulare centrifugum) [1, 3]. Thus, the possibility that in the case described here the development of inhibitors against FVIII:C was associated with lichenoid dermatosis cannot be formally excluded.

However, the clinical history of our patient is more consistent with a vaccine-induced development of FVIII:C inhibitors. In this respect, the close relationship between the vaccine injection and the onset of the hemorrhagic manifestations must be noted.

No recurrence of bleeding or of the FVIII:C inhibitor was found during the 5-year follow-up, even though the patient still continues to be affected by lichenoid dermatosis.

The development of autoantibodies following vaccination is not surprising. These autoantibodies, however, are rarely associated with the clinical manifestation of auto-Vaccine injections 40- HI

Fig. 1. Behavior of FVIII:C levels (○) and FVIII:C inhibitors (●) during 5 years follow-up. The arrows represent the three injections of vaccine with BCG and a pool of various strains of live attenuated corynebacteria.

immunity. For instance, Huang et al. have described the production of anti-dsDNA antibodies in response to influenza vaccination in healthy older women [9].

In the case we describe, the vaccine-induced development of autoantibodies (i.e. FVIII:C inhibitors) was associated with a severe clinical picture.

This, to our knowledge, is the first report of the development of FVIII:C inhibitors following vaccination.

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