short report
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SPONTANEOUS APPEARANCE OF HUMAN AND PORCINE FACTOR VIII INHIBITORS: WHICH THERAPEUTIC APPROACH ?

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ABSTRACT

An 82-year-old woman presented with severe bleeding due to antibodies inactivating both human and porcine factor VIII. Treatment with porcine factor VIII was successful in correcting the hemorrhagic manifestations, despite the fact that subsequent studies showed that the baseline porcine inhibitor titer was greater than the human inhibitor titer. Anamnestic response to porcine factor VIII did not allow us to use it longer; immunosuppressive therapy, however, was successful in long-term control of the anti-factor VIII antibody titer and in preventing further bleeding.

Key words: factorVIII, anti-human factor VIII antibodies, anti-porcine factor VIII antibodies, therapy

The acquired spontaneous appearance of anti-human factor VIII autoantibodies in non-hemophiliac subjects is extremely rare. These antibodies have been observed in patients affected by collagenopathies or by neoplasia, ulcerative colitis, chronic bronchiectasic bronchopathy and lymphoproliferative diseases, multiple myeloma and Waldenstrom's macroglobulinemia.[1]

Specific immunoglobulins against human factor VIII can also be present in dermatologic diseases, in pregnant women and during *post-partum*, as well as in apparently healthy elderly subjects. Lastly, the appearance of inhibitors can also occur during allergic reactions to drugs like penicillin, sulfonamide and phenytoin.[2-4] The etiopathogenesis is still completely unknown and the appropriate treatment is debated.[1, 5-8] We wish to describe a case of coagulopathy caused by the spontaneous appearance of anti-human and anti-porcine factor VIII inhibitors in an elderly, non-hemophilic patient suffering from chronic bronchiectasic bronchopathy.

Case report

R.F. is an 82-year-old female suffering from chronic bronchiectasic bronchopathy and arterial hypertension.

Signs of coagulopathy appeared on September 15, 1992, and the patient was admitted to the Bronchopulmonary Division with a fever and slight dyspnea. Laboratory tests revealed: activated thromboplastin time (APTT) 62"; prothrombin activity (PA) 70%; fibrinogen 700 mg/dL; positive plasma fibrogen-derived proteins (FDP) and negative urinary FDP; thrombin time 13 sec; haptoglobin 181 mg/mL; circulating immunocomplexes (CIC) IgG 200, IgM 286; sedimentation rate 86; WBC 11×10^9/L, RBC 334×10^{12}/L, Hb 9.7 g/dL, Plt 308×10^9/L. Other blood tests were normal.

The patient was treated with cyprophloxacine and the fever subsided after two days; this was followed by a rapid and progressive anemia (Hb 8.5 g/dL) associated with spontaneous ecchymoses. Red blood cell concentrates and vitamin K were administered. On October 15, a spontaneous hematoma appeared in the upper right dental arch. Hb was stable at about 8.5 g/dL and APTT was 50 sec. New ecchymoses subsequently developed and a large hematoma extended from the left side of the neck to the left breast and to the entire posterior left hemithorax.

On October 21, the patient was transferred to our Division. Porcine factor VIII (Hyate:C

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Speywood, UK) was begun at a dose of 4,000 units (10 vials slow drip i.v.) and prednisone 40 mg i.v. Owing to arterial hypertension, DDAVP was considered too dangerous for the patient; however, prompt control of bleeding was not achieved by IVIg. On the same day, a sample of blood was sent to the Hemophilia Center of Florence. Some days later the parameters were as follows: factor VIII:C (one-stage method) 14.5%; anti-human factor VIII inhibitor 2 B.U.; anti-porcine factor VIII inhibitor 4.4 B.U.; ratio anti-human factor VIII/anti-porcine factor VIII antibodies: 0.45; lupus anticoagulant absent; fibrinogen (Clauss) 180 mg/dL; bleeding time 121sec (Ivi).

On November 13, the patient reported melena caused by iatrogenic erosive gastropathy: Hb was 8.2 g/dL and total bilirubinemia was 3.5 mg/dL with 50% indirect; both anti-human and anti-porcine antibodies were negative. Corticosteroid treatment was interrupted, antacids and H2 antagonists were intensified, and somatostatin infusions were administered. Due to persisting melena and an APTT of 42 sec, porcine factor VIII was administered at a dose of 4,000 units/day for 20 days. Anti-human factor VIII antibodies were negative, while the anti-porcine factor VIII ones were increased to 2B.U. Human factor VIII was initiated at a dose of 1,000 units, later decreasing to 500 units, and cyclophosphamide treatment was begun at 50 mg/day for six months. All tests and investigations autoimmune disorders were negative.

The patient was treated with corticosteroids (prednisone 8 mg) and cyclophosphamide (50 mg a day) and enjoyed good health until November 1993.

In December 1993 blood tests were: APTT 44.7 sec; PA 85.1%; human factor VIII 26%; factor VIII:C inhibitors 1; porcine factor VIII inhibitors absent. A month later the patient was operated on for cataract. Then low doses of prednisone (4 mg/day) were continued and she remains in good health as of this writing (November 1994).

Discussion

Coagulopathies caused by human and porcine factor VIII inhibitors can be extremely serious. Our case presented a dramatic onset and the porcine factor VIII inhibitor was nearly always higher than that of human factor VIII. In most of the previously reported cases the cross reactivity of anti-human antibodies with porcine factor VIII ranged from 10 to 80%. This is the reason why we started therapy with porcine factor VIII concentrate even before the results of the specific assay were obtained.

Multiple causes are responsible for the production of autoantibodies in general, and for those involved in hemostasis in particular, e.g. antiphospholipid antibodies.[9]

Recent developments in the pathophysiology of B cells, however, may be helpful in understanding the pathogenesis of autoimmune diseases.[10] Our patient persistently showed low levels of factor VIII:C and evidence of specific autoantibodies, but had no evidence of coagulopathy after clinical onset.

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