Life-Threatening Intracranial Bleeding Associated With the Presence of an Antifactor VII Autoantibody

By Alain Delmer, Marie-Hélène Horellou, Georges Andreu, Thomas Lecompte, Françoise Rossi, Michel D. Kazatchkine, Meyer Samama, and Robert Zittoun

This is a report of a 62-year-old male patient who had a bleeding disorder due to the presence of a factor VII (proconvertin) inhibitor. After treatment with a high-dose intravenous (IV) immunoglobulin failed and a life-threatening intracranial hemorrhage occurred, plasma exchanges were performed and immunosuppressive therapy was given.

A MONG acquired inhibitors of blood coagulation factors, the most common is antifactor VIII antibody. Inhibitors against factors II, V, IX, X, XI, XIII, and in one report, against factor VII (proconvertin) have also been described. In the present report we describe a case of bleeding diathesis associated with the onset of severe intracranial bleeding caused by an acquired inhibitor to factor VII.

CASE REPORT

A 62-year-old white man was referred to our institution on May 15, 1987 because of a severe bleeding tendency associated with an isolated prolonged prothrombin time (PT). He had no previous personal or family history of unusual bleeding and had not received a transfusion of blood product. The patient's current medications included furosemide, spironolactone, digoxin, and isosorbide dinitrate because of a left cardiac failure due to the rupture of a papillary muscle 3 years earlier. Coagulation tests performed at that time were normal. Twenty days before being referred, he was admitted to another institution because of gross hematuria. Radiographic examinations failed to prove an organic lesion. The PT was 16.5 seconds (control 11.5), and the factor VII activity was 0.11 IU/mL (Table 1). Large spontaneous bruises and rectal bleeding developed within a few days, and the patient received 2 units of fresh frozen plasma twice. The results of the coagulation tests remained unchanged. The patient was afebrile, and the clinical examination showed no other abnormality than large echymotic areas on upper and lower limbs. Hematocrit was 38.4%. WBC count was 8,200/μL with normal differential, and ESR was 40 mm/h. Results of the coagulation tests are shown in Table 1 (Column 2), and the investigations described in one report, against factor VII (proconvertin) have also been described. In the present report we describe a case of bleeding diathesis associated with the onset of severe intracranial bleeding caused by an acquired inhibitor to factor VII.

<table>
<thead>
<tr>
<th>Table 1. Patient’s Hemostatic Data at Presentation and After Therapy</th>
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<td>Platelet count (x 10^5/L)</td>
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<td>Activated PTT (sec)</td>
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<td>PT (sec)</td>
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<td>Factor V activity (IU/mL)</td>
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<td>Factor II activity</td>
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<td>Thrombin time (sec)</td>
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<td>Fibrinogen (mg/dL)</td>
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The concentration of fibrinogen-fibrin degradation products was differential, and ESR excluded a monoclonal component.

High-dose IV immunoglobulins (IV Ig; Sandoglobulin, Sandoz, Basel, Switzerland, 0.4 g/kg/d) were administered for five consecutive days from May 21, 1987 on; no improvement in the coagulation tests was seen even after eight days from the beginning of IV Ig (Table 2), and cutaneous hemorrhages worsened. Therefore, immunosuppressive therapy was started on May 28, 1987, including cyclophosphamide (1.5 g in bolus IV infusion for one day) and corticosteroids (bolus IV methylprednisolone 500 mg/d for two days followed by prednisolone given orally 100 mg/d). Twenty-four hours later, CNS hemorrhage was suspected based on the abrupt onset of neurologic symptoms. Plasma exchanges (PE) were performed for three consecutive days with successive removal of 3,170 mL, 6,250 mL, and 3,400 mL of plasma and replaced with equivalent volumes of fresh frozen plasma (FFP). High-dose (80 IU/kg) factor VII concentrate (25 IU/mL, Biotransfusion, Lille, France) was infused with antithrombin III (35 IU/kg) before the first PE to allow safe femoral catheterization and did not induce any change in coagulation tests. Plasma inhibitor was not detected when assayed six hours following the first PE. PT and factor VII level progressively became normal (on the seventh and ninth days, respectively, from the beginning of PE). Neurologic abnormalities improved within a few days and an MRI scan confirmed their hemorrhagic origin. Ten days after the last PE, bilateral iliac deep-vein thrombosis occurred and was confirmed by phlebography. It required heparin treatment. The dose of administered prednisolone was progressively decreased until January 1988. One month later a systematic biological control revealed a relapse (TP 12.3 seconds, factor VII 0.5 IU/mL), but no plasma inhibitory activity was evidenced at that time. Immunosuppressive therapy (prednisolone 0.5 mg/kg/d and azathioprine 100 mg/d) was administered again and resulted in a prompt normalization of coagulation tests (Fig 1).

METHODS

Blood collection, routine coagulation tests, and assays for specific coagulation factors were performed using standard methods. Factor VII activity was measured by using deficient factor VII (Diagnostica Stago, Asnières, France) and factor VII antigen by a commercial enzyme-linked immunosorbent assay (ELISA) (Asserachrom VII:Ag, Diagnostica Stago, Asnières, France).

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Detection and measurement of factor VII inhibitor were performed by assay of the residual factor VII activity and antigen before and after a two-hour incubation at 37°C of the mixture of normal plasma with successive dilutions of the patient's plasma. The higher dilution of patient's plasma for which an inhibitory effect was evidenced, defined the titer of factor VII inhibitor.

The IgG fraction was prepared from patient's serum by ammonium sulfate precipitation and chromatography on diethyl aminoethyl (DEAE) Trisacryl (IBF, Villeneuve la Garenne, France). F(ab')2 fragments were prepared from patient's IgG by pepsin (Sigma Chemical Co, St Louis) digestion (2% wt/wt) for 18 hours at 37°C at pH 4.1, dialysis against phosphate-buffered saline (PBS) pH 7.4, and chromatography on protein A sepharose (Pharmacia Fine Chemicals, Uppsala, Sweden). The F(ab')2 preparation contained no Fc, as assessed by an ELISA using a monospecific antihuman Fc gamma antibody (Cappel, Cochranville, PA). IgG and F(ab')2 preparations were dialyzed against PBS. The inhibitory activity of these preparations was assessed in a similar manner as total plasma.

RESULTS

Coagulation tests demonstrated an isolated prolonged PT that was not corrected when the patient's plasma was mixed with an equal volume of normal plasma. Factor VII activity and antigen were <0.01 IU/mL and 0.05 IU/mL, respectively, at the time when a factor VII inhibitor was detected. The inhibitory activity of the patient's plasma increased with prolonged incubation time with a normal plasma. The kinetics of the factor VII/inhibitor reaction demonstrated that the factor VII activity decreased until a plateau was reached at 45 minutes (Fig 2). A similar inhibition of factor VII activity and antigen was observed (Fig 3). Plasma inhibitory activity was heat stable at 56°C for 30 minutes. The titer of the inhibitor progressively increased within a few days, and an inhibitory activity was detected up to a 1/8 dilution of the patient's plasma (Table 2).

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The IgG nature of the inhibitor was suggested by the disappearance of antifactor VII activity after absorption of the patient's plasma on staphylococcal protein A. The finding of anti-VII activity in the IgG fraction and the F(ab')2 fragments prepared from the patient's plasma confirmed the IgG nature of the antibody. Antifactor VII activity was measured in the patient's plasma (7.5 mg IgG/mL), the patient's IgG fraction (9 mg IgG/mL), and F(ab')2 frag-
mements prepared from IgG fraction (3.2 mg IgG/mL); ie, 5 × 10⁻³ mol/L IgG, 6 × 10⁻³ mol/L and 3.37 × 10⁻³ mol/L, respectively. A similar inhibition of factor VII activity was observed in the presence of the patient's plasma, which contained 0.31 × 10⁻³ mol/L IgG, 1.5 × 10⁻³ mol/L of the patient's purified IgG, and 0.45 × 10⁻³ mol/L of the patient's F(ab')₂ fragments. Antifactor VII activity was not found in the normal IgG prepared from a healthy individual or in the control F(ab')₂ fragments.

DISCUSSION

Only one case of acquired inhibitor to factor VII has been previously published in a patient with bronchogenic carcinoma. The inhibitor was proved to be an IgG autoantibody and was associated with mild bleeding symptoms. The clinical course in our patient was marked by a severe bleeding tendency with a life-threatening intracranial hemorrhage, which appeared at a time when factor VII was below 0.01 IU/mL. The limiting concentration of factor VII required for intact hemostasis has not been determined with certainty; although some authors have suggested that the threshold of 0.05 IU/mL is sufficient for hemostasis, CNS hemorrhage has occurred at a higher level in patients with hereditary factor VII deficiency. Factor VIII inhibitors in nonhemophilic patients and other acquired inhibitors of coagulation factors are associated in half the cases with underlying disorders such as immune diseases, monoclonal gammopathies, carcinoma, and lymphoproliferative syndromes, or are occasionally related to drug sensitivity. No such condition was detected in our patient after 17 months of follow-up. In patients with antifactor VIII autoantibodies, immunosuppressive therapy may induce a fall in titer or a disappearance of inhibitor within a few weeks, but the antibody may also disappear spontaneously after several months.

Management of life-threatening bleeding episodes in factor VIII inhibitors is difficult. In some patients high-dose IV polyclonal immunoglobulins (IV Ig) have resulted in a rapid decrease of inhibitor titer within 24 to 48 hours. It was suggested that IV Ig may act through idiotypic/anti-idiotypic interactions between F(ab')₂ fragments contained in IV Ig preparations and antifactor VIII antibodies and/or through a long-term alteration of the immune repertoire. The lack of biological improvement and the worsening bleeding symptoms by the ninth day from the beginning of IV Ig led us to
consider an alternate therapy. Experience of PE is restricted to anti-VIII antibody in life-threatening circumstances or for imminent surgery, usually in combination with the infusion of the deficient factor and sometimes immunosuppressive therapy. In the present case plasma inhibitory activity was not observed after the first PE. However, PT and factor VII levels became normal within a few days. This delay to PT and factor VII normalization, as well as the occurrence of relapse while steroids were discontinued, underlines the importance of associated immunosuppressive therapy in our patient. The responsibility of high-dose factor VII infusion preceding the first PE for inducing iliac venous thrombosis remains unclear.

REFERENCES

Life-threatening intracranial bleeding associated with the presence of an antifactor VII autoantibody

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