Steroid Hormone-responsive Secondary Factor X Deficiency

Dear Sir,

Although more than 30 cases of secondary factor X deficiency have been reported, very few cases have been treated successfully. Most of the incidences accompanied monoclonal gammapathy and amyloidosis (1), with or without multiple myeloma. We experienced a case of factor X deficiency with monoclonal gammopathy and progressive muscle hematoma. We treated the patient successfully with prednisone; bleeding tendency and partial thromboplastin time improved without any change in the activities of coagulation factors.

A 65-year old Japanese man was admitted to our department because of back pain. He had been healthy until 3 years before admission, when he noticed gingival bleeding and subcutaneous purpura. Three months before admission, he was hospitalized for lumbago, macroscopic hematuria, and massive epistaxis. Laboratory studies at the prior hospital revealed prolonged prothrombin time (PT, 34.7 s), activated partial thromboplastin time (aPTT, 64 s) and a reduced level of coagulation factor X (4.5%). Although he was administered a total of 33 units of fresh frozen plasma and 4000 units of a plasma factor IX preparation, which includes factor X, his clinical and laboratory tests did not improve. The subcutaneous bleeding and hematoma increased, and he began to complain of severe back pain. He was referred to our department for diagnosis.

On physical examination, the patient was anemic, with two solid hepatomegaly were detected by CT. Slight splenomegaly and moderate hepatomegaly were detected by CT.

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References


Received July 3, 1998 Accepted after revision August 19, 1998

Thromb Haemost 1998; 80: 1032-3
Laboratory tests revealed the following: hemoglobin, 6.8 g/dl; hematocrit, 22%; platelets, 164,000/mm³; and leukocytes, 9000/mm³. Serum urea nitrogen, creatinine, sGPT, lactic dehydrogenase, γ-GTP, and haptoglobin were within normal limits. The alkaline phosphatase level was 623 IU/l (normal, 118-325 IU/l) and the sGOT level was 42 IU/l (normal, 13-29 IU/l). Direct Coomb’s test was negative, and C-reactive protein concentration was 6.3 mg/dl. The PT was 26.9 s (20%), and the aPTT was 61.6 s (normal: 26.2-39.3 s). Coagulation factor X activity was 12%, and the amount of factor X was less than 10% of normal; other coagulation factor (II, V, VII, VIII, IX, XI, XII) activities were not reduced. Mixing studies for circulating anticoagulant were negative, and anticoagulant antibodies could not be demonstrated. Coagulation factors in the patient’s family members were normal. Serum protein electrophoresis revealed an increase in the β- to γ-fraction. Quantitative immunoglobulin determination and immunoelectrophoresis disclosed the following: IgG, 1159 mg/dl (normal, 788-1841 mg/dl); IgA, 1801 mg/dl (normal, 77-437 mg/dl); IgM, 480 mg/dl (normal, 78-552 mg/dl). Serum immunoelectrophoresis revealed IgA κ-type M-protein and urine immunoelectrophoresis revealed κ-type Bence-Jones protein. Bone marrow aspiration disclosed hypocellular marrow with slightly increased (5%) plasma cells without monoclonality. Amyloid deposits were not detected in bone marrow aspirate, rectum, skin, gingiva, or subcutaneous fat tissue. Thus, we diagnosed the patient as having a secondary factor X deficiency with monoclonal gammopathy.

From the first hospital day, the patient was treated with prednisone 60 mg/day, which resulted in rapid improvement in the bleeding tendency. On the third hospital day, his aPTT and PT were shortened to 42.3 s and 24.4 s, respectively (Fig. 1), although the activity of all coagulation factors remained the same. C-reactive protein decreased rapidly and became normal in 2 weeks. The anemia and hematoma improved, and the prednisone was tapered. However, when the dose of prednisone was reduced to 10 mg/day, he showed gingival bleeding and aPTT prolonged to 53.5 s. The dose of prednisone was increased to 60 mg/day and the bleeding tendency, aPTT, and PT again improved. The dose of prednisone was carefully decreased over 40 days and maintained at 15 mg/day. Plasma IgA concentration gradually decreased to 1383 mg/dl and remained approximately the same thereafter. At present, the patient is under close observation as an outpatient, remains on 15 mg prednisone, and is without signs of bleeding.

Our patient developed hematoma and anemia very rapidly, and immediate treatment was required. Since the factor X complementation treatment was not effective, we treated the patient with prednisone, assuming the presence of a circulating inhibitor or antibody against factor X (2) before realizing the presence of the monoclonal gammopathy. The subsequent treatment improved the bleeding tendency; however, we could not demonstrate the inhibitor to factor X in his plasma or urine by laboratory tests such as Western blotting. The reason why aPTT and PT responded to prednisone is unknown. All the coagulation factors remained unchanged throughout the clinical course, including the low plasma factor X level, even after normalization of aPTT. This phenomenon suggests that some unknown steroid-inducible factor might exist as a component or cofactor in the blood coagulation cascade or independent from the cascade. This might explain the hypercoagulability sometimes found in steroid-treated patients. There have been several reports of secondary factor X deficiency, most of which accompany amyloidosis. Only Manabe et al. (3) have described a patient with factor X deficiency and monoclonal gammopathy, and the etiology of factor X deficiency accompanying monoclonal gammopathy has not been determined.

The therapeutic plan for our patient is still under discussion, i.e., whether to employ an additional agent such as melphalan or to treat the patient surgically (4). Fortunately, prednisone treatment did improve the bleeding tendency. However, due to the adverse effect of the treatment, the patient suffered from steroid-induced diabetes mellitus, which is now under control with insulin injection, and he is also at a high risk for osteoporosis. The prognosis in such cases is generally poor, since patients frequently develop systemic amyloidosis or multiple myeloma. Only two cases have been reported that resulted in spontaneous resolution after cessation of melphalan-prednisone therapy (5, 6). We hope that our patient’s monoclonal gammopathy improves spontaneously, and that steroid therapy can be discontinued.

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