Acquired Hemophilia in a Patient With Myeloma

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ABNORMAL BLEEDING IS frequently associated with dysproteinemias. Abnormalities that account for the bleeding tendency in patients with these disorders include thrombocytopenia, impaired platelet function, and the hyperviscosity syndrome. Abnormally low rates of synthesis of specific plasma coagulation factors, or the genesis of inhibitors to these factors, are also involved. A single patient may have more than one coagulation abnormality.[1-3] The following case is the first reported association of a factor VIII inhibitor with the λ-light-chain form of myeloma.

Report of a Case

The patient, a 58-year-old woman, had weakness, fatigue, and anorexia for three weeks. Since the age of 20, she had smoked about 40 cigarettes and drunk 9 fl oz (266 ml) of whiskey a day. She had been taking fenoprofen calcium for many years for knee pain. Examination revealed orthostatic changes in blood pressure—from 130/60 mm of mercury supine to 100/50 mm of mercury standing—obesity, a grade I/VI systolic ejection murmur heard over the left sternal border, a skin rash in the left inguinal region with mild excoriation and drainage, clubbing of the fingernails, external hemorrhoids, and occult blood in the stool. The other physical findings were normal.

On admission, the hemoglobin level was 58 grams per liter (5.8 grams per dl), the mean corpuscular volume was 65.5 fl (65.5 μm^3), the leukocyte count was 9 × 10^9 per liter (9,000 per mm^3) with a normal differential cell count, and the platelet count was 276 × 10^9 per liter (276 × 10^3 per mm^3). The reticulocyte fraction was 5 × 10^{-3} (0.5%), and a peripheral smear showed microcytic, hypochromic, and target erythrocytes. A prothrombin time and an activated partial thromboplastin time (aPTT) were within normal limits. Abnormal blood chemistry and urine values are shown in Table 1.

Serum protein electrophoretic analysis showed a low albumin level of 27 grams per liter (2.7 grams per dl) (normal, 32 to 50), a γ-globulin level of 11 grams per liter (1.1 grams per dl) (normal, 7 to 15), and a small monoclonal spike in the γ-globulin region. Immunoelec-

TABLE 1.—*Abnormal Laboratory Values at Initial Presentation*

Substance	SI Units	Patient Values (Conventional Units)	Normal Values*
Blood Chemistry			
Urea nitrogen, mmol/liter (mg/dl)	22.1	(62)	1.8 to 8.9
Creatinine, μmol/liter (mg/dl)	260	(4.1)	45 to 120
Uric acid, μmol/liter (mg/dl)	1,250	(21)	130 to 460
Calcium, mmol/liter (mg/dl)	1.90	(7.6)	2.12 to 6.62
Phosphorus, mmol/liter (mg/dl)	1.75	(5.4)	0.80 to 1.45
Alkaline phosphatase, U/liter (IU/liter)	155	(155)	50 to 136
Total protein, grams/liter (grams/dl)	52	(5.2)	60 to 85
Urine			
Protein reaction	4+		
Creatinine clearance, ml/sec (ml/min)†	0.40	(22)	1.18 to 1.92
Total protein, grams/d (mg/24 hr)†	5.90	(5,900)	0.70

SI = Système International

*Normal values are given in SI units.
†Based on a 24-hour collection.

trophoresis showed a free λ-light-chain monoclonal gammopathy with suppression of all other components of the immune globulin system.

Urine protein electrophoretic analysis revealed a large monoclonal spike in the mid-γ-globulin region and an elevated total protein level of 2.6 grams per liter (260 mg per dl) (normal < 0.30) composed of 5% albumin and 95% γ-globulin. Immunoelectrophoresis demonstrated a massive excretion of free λ-light chain-type Bence Jones protein; the particular analysis indicated a total value for reactive protein of 1.77 grams per day (1,765 mg per 24-hour specimen) (normal < 0.2), of which 96% was γ-globulin.

A bone marrow examination revealed increased cellularity, normoblastic erythroid hyperplasia, moderate plasmacytosis (22%), and no stainable iron stores. X-ray films of the long bones and pelvis showed no osteolytic lesions. A lytic lesion in the lateral end of the left clavicle was noted on a chest film. A colonoscopy was normal. Esophagogastroduodenoscopy revealed a partially healed benign gastric ulcer.

The patient was hydrated and treated with packed red blood cell transfusions and ferrous sulfate. Because λ-light-chain myeloma was clearly present, chemotherapy was initiated with melphalan, 0.25 mg per kg of body weight orally daily for five days, and prednisone, 1.0 mg per kg orally daily for five days, and this regimen was repeated every four weeks. After six cycles of chemotherapy, the patient's condition improved with the urine protein excretion decreasing to 0.15 grams per day (150

ABBREVIATIONS USED IN TEXT

aPTT = activated partial thromboplastin time
Ig = immunoglobulin

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mg per 24 hours); the hemoglobin level becoming stable at 105 grams per liter without transfusions; and renal function improving, with a decline in the creatinine level to 130 μmol per liter (1.5 mg per dl). She was stable without further chemotherapy at this time and refused further diagnostic tests or regular follow-up.

The patient returned at age 62 because she had coffee-ground emesis. Physical examination on admission to the hospital revealed that she was moderately obese but in no apparent distress. The liver was palpated 2 cm below the right costal margin, and stool was positive for occult blood. Initial laboratory data included a hemoglobin level of 73 grams per liter (7.3 grams per dl), a leukocyte count of 5.1 × 10⁹ per liter (5,100 per mm³), with a normal differential cell count, a platelet count of 225 × 10⁹ per liter (225 × 10³ per mm³), a prothrombin time of 12.9 seconds (control, 12.0), aPTT 64.7 seconds (control, 30.6), blood urea nitrogen 6.4 mmol per liter (18 mg per dl), and creatinine 97 μmol per liter (1.1 mg per dl). Urine protein electrophoresis showed a monoclonal spike in the γ-globulin region (71.4% of total protein) with a total urinary protein level of 0.535 grams per day (535 mg per 24 hours). Urine immunoelectrophoresis demonstrated excretion of a large quantity of monoclonal λ-light chains.

Esophagogastroduodenoscopy showed six gastric ulcers, so ranitidine was administered. The patient also received transfusions with packed red blood cells and whole blood. Her gastrointestinal bleeding ceased. Because of a lack of accessible peripheral sites, specimens for initial blood tests were obtained by left femoral venipuncture, and on the fourth day thereafter a small hematoma was noted in the left groin. Over the next 24 hours the patient had palatal oozing, and the inguinal hematoma expanded despite tamponade of the area. Pulses of her left leg were palpable, but the hemoglobin level decreased to 68 grams per liter. A hematologic consultation was obtained. Additional coagulation tests were recommended, and these revealed an Ivy bleeding time of 6 minutes (normal, 2.3 to 9.5), a platelet count of 134 × 10⁹ per liter, an aPTT of 73.9 seconds (control, 30.9) that decreased to 40 seconds in an immediate 1:1 mix with normal plasma but increased to 57 seconds after 60 minutes of incubation. Factor VIII activity was 8.2% of normal, and a factor VIII inhibitor titer of 36 Bethesda units per ml was obtained.

Immunosuppressive therapy with oral prednisone, 100 mg per day, and oral cyclophosphamide, 100 mg per day, was initiated. In addition, human factor VIII (antihemophilic factor) concentrate was administered intravenously at the rate of 43 units per kg every six hours. The palatal bleeding ceased, and the inguinal hematoma became stable. Coagulation test results gave indications of improvement, with an increase in the apparent plasma

factor VIII activity to 25% and a decrease in the factor VIII inhibitor titer to 2.0 Bethesda units per ml. On day 9, however, the inguinal hematoma dramatically increased in size, and there was evidence of superficial skin necrosis. The factor VIII inhibitor titer increased again to almost pretreatment levels (14 Bethesda units per ml). Human factor VIII therapy was discontinued, and porcine factor VIII (Hyate:C, Porton Products Ltd, Van Nuys, California) was administered by intravenous infusion at an initial rate of 100 units per kg, followed by 57 units per kg every six hours. This therapy resulted in the cessation of bleeding and correction of the coagulation abnormalities with factor VIII activity of 89.3%. The next day a surgical procedure was done without complications to evacuate the inguinal clot and debride the wound. Cyclophosphamide and prednisone were discontinued to reduce the risks of infection and impaired wound healing after the operation. She continued to receive intravenous hydrocortisone and diphenhydramine hydrochloride before porcine factor VIII transfusions to reduce the risk of anaphylaxis.

The patient had an uneventful postoperative course until day 16, when acute abdominal pain developed. An abdominal film revealed free intraperitoneal air. During an exploratory laparotomy, a perforation of the cecum with peritonitis was found, and the patient underwent a right hemicolectomy and ileostomy. Examination of the surgical specimens revealed acute and chronic hemorrhagic colitis and pericolitis with perforation involving the cecum, diffuse colonic mucosal hemorrhages consistent with a bleeding diathesis, acute and chronic peritonitis, and diffuse mucosal hemosiderosis. After the operation the patient required mechanical ventilation support, and cefoxitin was administered for the treatment of the peritonitis. Porcine factor VIII therapy was continued, and no further bleeding was noted.

On day 24 wound dehiscence and evisceration developed, and the patient returned to surgery for repair of the evisceration. At the time of reexploration, no abscess was noted and the peritonitis had cleared. Porcine factor VIII therapy was discontinued because plasma factor VIII activity had declined to 10.3% of normal, and an inhibitor to porcine factor VIII had developed with a level of 2.75 Bethesda units per ml. She had thrombocytopenia with platelet counts as low as 16 × 10⁹ per liter and a prolonged prothrombin time of 16.6 seconds (control, 11.0). Factor IX complex human concentrate (Konȳne-HT Cutter Biologics/Miles, West Haven, Connecticut) transfusions were administered, initially at 55 units per kg followed by 109 units per 24 hours in four divided doses, which shortened the prothrombin time. The platelet counts increased after platelet transfusions.

The rest of the hospital course was one of progressive generalized deterioration. Intra-abdominal bleeding and renal insufficiency developed with elevations of the creatinine level to 390 μmol per liter (4.4 mg per dl) and the blood urea nitrogen to 34.6 mmol per liter (97 mg per dl). Progressive respiratory failure ensued, and the patient died on the 28th hospital day.

Discussion

Acquired inhibitors of blood coagulation, also known as circulating anticoagulants, are endogenously produced pathologic substances, usually immunoglobulins, that either react directly with clotting factors or inhibit their reactions.[3] In patients without hemophilia, a circulating antibody against the factor VIII coagulant protein is a rare finding, occurring in 1 of 5 million people,[4] but it is the most common cause of spontaneous acquired inhibition against a clotting factor.[5] Factor VIII inhibitors have most often been associated with collagen vascular diseases, drug allergy, skin disorders, malignant neoplasms, and in the postpartum period.[5-7] In some cases acquired factor VIII inhibitor is the primary cause of illness; in one survey 46% of patients with this disorder were otherwise healthy, usually elderly persons.[7] Circulating anticoagulants against factor VIII have occasionally been reported with plasma cell dyscrasias, occurring with immunoglobulin (Ig) A myeloma,[8] Waldenström's macroglobulinemia,[9] amyloidosis,[10] and in a patient with an IgM paraprotein in whom chronic lymphocytic leukemia later developed.[11] This case is the first reported of a factor VIII inhibitor associated with λ-light-chain myeloma.

Autoantibodies against factor VIII are predominantly IgG, frequently from the IgG4 subclass, and have a preponderance of κ-light chains.[4] Alternatively, the factor VIII antibodies associated with plasma cell dyscrasias have been monoclonal IgA[8,10] and IgM,[9] with monoclonal λ[9] and κ[10] light chains. Antibodies inhibit or neutralize factor VIII activity by blocking functional epitopes or antigenic sites on the factor VIII protein.[4] Deletion mapping studies using recombinant DNA methods have indicated considerable epitope heterogenicity among factor VIII inhibitor antibodies, but most share one or both antigenic determinants in two regions of the factor VIII protein.[12] Although the factor VIII autoantibody in the present case has not been isolated, we speculate that the patient's monoclonal λ-light chain had activity against specific epitopes on the factor VIII molecule. Factor VIII inhibitors are characteristically time and temperature dependent in laboratory assays; for example, the incubation of inhibitor plasma mixed with equivolume normal plasma at 37°C for two hours or longer enhances the expression of factor VIII autoantibodies.[4] The patient's inhibitor in this report followed this characteristic pattern.

The clinical presentation of the patient in this report is consistent with that of other patients with acquired hemophilia who may have spontaneous hemorrhage into muscles or joints, ecchymoses, hematuria, melena, intracranial and retroperitoneal hemorrhage, intractable epistaxis, or persistent bleeding after an operation or minor trauma. In one survey, 87% of the patients had major bleeding, and death was attributed, directly or indirectly, to the presence of the inhibitor in 22% of the cases.[7]

The optimum management of patients with acquired factor VIII inhibitors who have an acute hemorrhage is not well established. Various therapeutic options have been tried, including high doses of human factor VIII concentrate to neutralize the inhibitor and provide a plasma factor VIII level of at least 0.3 U per ml (30%),[13] plasmapheresis to remove the antibody,[13] and prothrombin complex concentrate and activated prothrombin complex concentrate to provide procoagulant activity that bypasses the factor VIII-dependent clotting reactions.[14] 1-Deamino-8-D-arginine vasopressin use has also been recommended as a beneficial and less expensive treatment of patients with acquired factor VIII inhibitors.[15] These treatment methods may be successful in certain instances, but the failure rate is high.[13]

A more recently introduced and effective therapy involves transfusion with porcine factor VIII. The rationale for its use in patients in whom factor VIII circulating anticoagulants develop is based on the reduced cross-reactivity of the inhibitors for porcine factor VIII compared with human factor VIII.[16] One study reported good or excellent responses with regard to pain relief and a reduced number of hemorrhagic sites in 82% of patients with acquired hemophilia who received porcine factor VIII. Two patients, however, generated porcine inhibitors to levels in excess of 10 Bethesda units per ml.[17] This study and others supported the use of porcine factor VIII as safe and clinically effective in the treatment of hemorrhage due to factor VIII inhibitors.[18,19] The patient in this report also had an excellent clinical response to porcine factor VIII with a pronounced rise in plasma factor VIII activity and the cessation of bleeding; later, however, an inhibitor to the porcine factor VIII developed that rendered it ineffective. Another limitation in the use of porcine factor VIII is the development of thrombocytopenia, which may be the result of increased platelet aggregation demonstrated by platelet clumps on peripheral blood smear.[20] The absence of platelet clumps on the peripheral smear of this patient suggests that the thrombocytopenia was not due to porcine factor VIII; therapy with antibiotics and cyclophosphamide and the presence of peritonitis are other possible causes.

Early, largely anecdotal reports recommended immunosuppressive therapy for factor VIII inhibitors with the intent of eliminating or suppressing the cell clone responsible for inhibitor synthesis. Preliminary results from a controlled, prospective, randomized trial to evaluate the therapeutic effects and side effects of cyclophosphamide and prednisone alone or in combination in eliminating or decreasing the titer of factor VIII autoantibodies indicate that even patients with titers greater than 5 Bethesda units per ml may respond to immunosuppressive therapy, but more studies are needed to determine the optimal treatment of various clinical categories.[21] Although ineffective in the treatment of inhibitors associated with hemophilia, another therapeutic approach aimed at suppressing the production of the inhibitor with varying results in patients with acquired hemophilia is the administration of high doses of intravenous immune globulin G.[22] Our patient had a temporary response to immunosuppressive therapy and human factor VIII transfusion.

Although factor VIII inhibitors in association with dysproteinemias are relatively rare, they are of consider-

able clinical import because of the dramatic clinical presentations and the need for early and accurate diagnoses. The advanced age of most of these patients further increases the morbidity and mortality. Recent therapies have improved the results for some patients. The rarity of the disease limits the opportunity for clinical trials and necessitates the report of individual cases until better guidelines for treatment can be formulated.

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