Nephrotic Syndrome as a Complication of Immune Tolerance in Hemophilia B

To the Editor:

Inhibitors to factor IX (fIX) develop in approximately 1.5% to 3% of persons with severe hemophilia B and are commonly associated with the complete absence of fIX antigen due to large gene deletions or nonsense mutations. The occurrence of high-titer inhibitors severely compromises the management of acute hemorrhage because therapeutic levels of fIX are not achieved even with the use of large quantities of fIX concentrates. Therapeutic options are further limited by the development of allergic reactions to fIX in a sizable subset of patients. Although both standard and activated prothrombin complex concentrates (PCC and aPCC) can often provide an adequate degree of hemostasis, these products are not effective in all patients and in all clinical situations. Moreover, the use of PCC or aPCC is problematic in patients with severe allergic reactions to fIX. Recombinant factor VIIIa (Novo Nordisk, Denmark) may be the only logical alternative treatment in these settings, but this product is not licensed in the United States and its use is highly restricted. For these reasons it is generally advantageous to attempt to eliminate the inhibiting antibody. Although no standard methodology to induce immune tolerance (IT) has thus far been defined, all regimens include frequent and large doses of intravenously (IV) administered fIX over an extended period of time. Additional immune modulation is often attempted at the initiation of therapy through the use of IV gammaglobulin (IVIG), cyclophosphamide, and plasmapheresis with a staphylococcal protein A column, when available. We describe herein three cases in which nephrotic syndrome developed in association with IT in severe hemophilia B patients with high-titer inhibitors and a history of allergic reactions to fIX.

CASE 1

A 2-year-old boy with a family history of hemophilia B associated with a large gene deletion was similarly diagnosed at birth. At 10 months of age, a computed tomography (CT) scan performed following mild head trauma showed a chronic subdural hemorrhage and ventriculomegaly. He began treatment with monoclonal factor VIIa (Mononine; Centeon L.L.C., Kankakee, IL), 100 U/kg every other day. After 2 weeks of intensive replacement with fIX, a specific inhibitor was noted with a titer of 47 Bethesda units (BU). Concomitantly, the patient developed an urticarial rash after fIX administration. A positive skin test to three different fIX preparations and a positive RAST to fIX were also noted at that time. Soon afterward the patient developed a life-threatening anaphylactic reaction to FEIBA (Immuno-U.S., Inc, Rochester, MI), an aPCC that contains fIX. At 14 months of age, the patient developed an acute expanding subdural right parietal hemorrhage and underwent neurosurgical decompression under coverage with recombinant factor VIIa. After recovery from surgery, he began antigen desensitization and IT with cyclophosphamide, IVIG, and Mononine, 100 U/kg/d. Because of the history of allergic manifestations, the daily dose of fIX concentrate was initially administered over several hours and required premedication with diphenhydramine. The patient was placed on daily doses of Mononine, 100 U/kg, and remained clinically stable with inhibitor titers fluctuating between 1 and 8 BU.

Nine months after the initiation of the IT regimen, the patient presented with edema and oliguria. His serum albumin was 0.6 g/dL. Serum blood urea nitrogen (BUN) and creatinine were normal. Urinalysis revealed 4+ protein, 20 to 50 red blood cells, and no casts, and he was diagnosed with nephrotic syndrome. Human immunodeficiency virus (HIV), hepatitis C, and hepatitis B serologies were negative and complement C3 and C4 levels remained normal. He was begun on prednisone 2 mg/kg/d. After 6 weeks of treatment without clinical improvement, a renal biopsy was performed that revealed membranous glomerulonephritis (GN) with electron microscopic findings of subepithelial, subendothelial, and mesangial deposits. Immunohistochemical staining by monoclonal antibodies to human factor IX was negative. The dose of Mononine was reduced to 25 U/kg every other day and the corticosteroid treatment was continued. The proteinuria slowly resolved and his current inhibitor titer is 1 BU.

CASE 2

A 4.5-year-old boy with severe hemophilia B was treated exclusively with Mononine until the development of an inhibitor at age 21 months. This inhibitor reached a maximum titer of 40 BU and was associated with allergic symptoms that restricted the use of aPCC. IT was initiated with cyclophosphamide, IV, and a factor IX concentrate (Bebulin; Immuno-U.S.) at a dose of 100 U/kg/d. A reduction of the inhibitor titer to 8 BU was achieved approximately 8 months after the initiation of IT. At that time, the patient developed generalized edema, proteinuria, and hypoalbuminemia and a clinical diagnosis of nephrotic syndrome was made. Serum BUN and creatinine remained normal. The patient was treated empirically with prednisone at a starting dose of 3 mg/kg/d followed by a gradual taper but was largely unresponsive. Treatment with fIX concentrate was interrupted briefly because of an increase in infusion-associated allergic reactions but was resumed later with Bebulin at a dose of 100 U/kg three times per week following premedication with hydroxyzine. He currently exhibits mild-moderate proteinuria and a serum albumin of 2.6 g/dL. His most recent inhibitor titer is 6 BU.

CASE 3

A 2-year-old boy with severe hemophilia B received Mononine after sustaining a traumatic intracranial hemorrhage at age 11 months. On the 14th day of treatment he began to experience severe allergic reactions, which became progressively worse despite treatment with antihistamines and steroids. An inhibitor titer, which was zero before the intracranial hemorrhage, was measured to be 30 BU. He was placed on a desensitization regimen of gradually increasing amounts of fIX concentrate after pretreatment with antihistamines. After desensitization, he was started on an IT regimen of daily infusions of fIX concentrate (Mononine), 100 U/kg.

After 8 months on IT, the inhibitor titer decreased to 2.1 BU, there was improved recovery of infused fIX, and an amelioration of allergic symptoms. Following an intercurrent febrile illness, he was noted to have mild blepharedema bilaterally. The serum albumin was 2.6 g/dL. Urinalysis revealed 4+ protein, 5 to 10 red blood...
cells, and no casts, and a diagnosis of nephrotic syndrome was made. Serum BUN and creatinine concentrations remained normal. Coincident with the development of nephrotic syndrome, the inhibitor titer increased to 9.5 BU and allergic reactions to FIX were again noted. IT was discontinued. Proteinuria has persisted but the patient remains asymptomatic with a serum albumin of 2.9 g/dL and a total serum protein of 5.2 g/dL.

DISCUSSION

The development of nephrotic syndrome may represent a new and serious complication of IT induction in hemophilia B patients with high-titer inhibitors. It is interesting to note that in each case nephrotic syndrome developed 8 to 9 months after the commencement of the IT regimen and in patients in whom IT was at least partially successful. Because of the lower prevalence of hemophilia B and the small fraction of patients with this disorder who develop high-titer inhibitors, there is only limited experience with IT in this population. Although a direct causal relationship between the IT regimens used and the development of nephrotic syndrome cannot be established at this time, the occurrence of these three cases, along with two recent preliminary reports of similar patients in Germany, is unlikely to be the result of chance alone. Moreover, membranous GN, the form diagnosed in case 1, is relatively rare in this age group and is principally seen in association with other disease processes.7

The immunologic events that underlie successful induction of IT are not well understood. The presence of circulating anti-factor VIII or factor IX antibodies that lack coagulation inhibitory activity have been detected in hemophilia A and B patients after a tolerant state was achieved. In hemophilia A patients, IT has also been associated with the development of anti-idiotypic antibodies, IgG that neutralize the inhibitory capacity of the anti-FVIII antibodies.8

To our knowledge, nephrotic syndrome has not been reported in hemophilia A patients undergoing IT despite the vastly larger clinical experience in this population (D.D., unpublished observations). Although the reasons for this difference are not known at this time, at least two plausible hypotheses can be advanced. First, factor IX, with a molecular mass of 55,000, distributes to both the intravascular and extravascular spaces, while factor VIII circulates as high-molecular-weight complexes with von Willebrand factor and is confined to the intravascular compartment. Second, hemophilia B patients undergoing IT are routinely exposed to much larger amounts of exogenous protein than are patients with hemophilia A. The normal plasma concentrations of factor VIII and factor IX are 0.1 and 5 μg/mL, respectively.11 Thus, at the standard IT dose of 100 U/kg, hemophilia B patients will receive 500 μg of factor IX protein. In contrast, hemophilia A patients undergoing IT will only be exposed to 10 μg of factor VIII. Thus, differences may exist in both the quantity and tissue distribution of the immune complexes produced in hemophilia A and B patients undergoing IT regimens.

Based on these case reports, a reassessment of the risks and benefits associated with IT in hemophilia B patients is warranted, especially in persons with a history of allergic reactions to FIX products.

REFERENCES

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Transient Increase of Leukocytes After Transplantation of Expanded and Nonexpanded Allogeneic CD34+ Blood Cells Is of Host Origin

To the Editor:

Profound neutropenia bearing an increased risk of infections represents one of the cardinal problems after myeloablative and high-dose chemotherapy. In two recent reports we showed stable engraftment in patients transplanted with selected allogeneic CD34+ blood cells alone1 or in combination with bone marrow (BM).2 All patients experienced neutropenia less than 100 neutrophils/μL, lasting for 1 to 11 days. Interestingly, a transient increase of leukocyte counts was observed in some of the patients immediately after transplantation (days 1-3). The highest increase over 10,000/μL occurred in patients receiving unmanipulated BM combined with CD34+...
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B.M. Ewenstein, C. Takemoto, I. Warrier, J. Lusher, P. Saidi, J. Eisele, L. J. Ettinger and D. DiMichele