Case report of an acquired factor XIII inhibitor: diagnosis and management

Thomas F. Gregory, MD, and Barry Cooper, MD

A 57-year-old man presented with a spontaneous upper-extremity hematoma and compartment syndrome. The patient experienced excessive bleeding following evacuation of the hematoma, and the results of routine coagulation studies were normal. Factor XIII activity was undetectable using a photometric assay, and the presence of an inhibitor was detected with mixing studies. Bleeding was controlled with infusions of fresh frozen plasma and cryoprecipitate. Cyclophosphamide was started on the 16th hospital day, and four weekly doses of the monoclonal anti-CD20 antibody, rituximab, were begun 3 weeks later. One week after the initial dose of rituximab, the inhibitor was no longer detectable and the factor XIII level increased to 28%. After completion of the rituximab therapy, the factor XIII activity was 58% with no inhibitor present. This case illustrates the need to check for unusual defects such as factor XIII deficiency if a bleeding tendency is evident—even if routine studies are unrevealing.

Factor XIII is the final enzyme in the coagulation cascade and is responsible for catalyzing the intermolecular cross-linking of fibrin polymers, therefore increasing the mechanical rigidity of the fibrin clot (1). Hereditary deficiency of this enzyme is a rare cause of a lifelong bleeding disorder, and homozygotes for this autosomal recessive disorder have <1% factor XIII activity (2). Clinical features include recurrent soft tissue bleeding and delayed wound healing. Women with factor XIII deficiency have an increased incidence of fetal loss during pregnancy, although menorrhagia is not frequently seen. Unlike patients with hemophilia A and B, individuals with factor XIII deficiency are unlikely to develop hemarthrosis, although intracranial hemorrhage is a frequent cause of death. Since only 2% to 3% factor XIII activity is necessary to provide hemostasis and the enzyme has a half-life of 8 to 14 days, heterozygotes are asymptomatic. Transfusions of factor XIII in the form of fresh frozen plasma (FFP), cryoprecipitate, or factor XIII concentrates (fibrogammin, Hoechst) every 4 to 6 weeks is adequate therapy for congenitally deficient homozygotes.

Acquired deficiencies of factor XIII have been described in association with drugs, chronic renal failure, hepatic cirrhosis, and lymphoproliferative disorders. In most cases these acquired deficiencies are partial and do not lead to significant bleeding. The development of inhibitors to factor XIII represents a rare cause of depressed factor XIII activity. Such inhibitors have

been described in patients congenitally deficient in factor XIII treated with multiple transfusions (3), but most inhibitors are IgG antibodies and develop in patients without preexisting factor XIII deficiency (4–6).

We describe a patient presenting with an acquired factor XIII deficiency secondary to a spontaneous inhibitor. Awareness of this rare coagulopathy is important since all screening coagulation studies routinely ordered in bleeding patients will be normal, including platelet count, prothrombin time (PT), partial thromboplastin time (PTT), platelet function assays, fibrinogen, thrombin clot time, and assays for von Willebrand's disease. Specific assays for factor XIII by measuring clot solubility in dispersing agents such as 5M urea or 1% monochloroacetic acid are necessary to identify this disorder. Once the etiology was identified, infusions of cryoprecipitate controlled bleeding acutely, with the inhibitor abating 1 month later, following treatment with cyclophosphamide and the chimeric anti-CD20 monoclonal antibody, rituximab.

CASE REPORT

A 57-year-old man presented to the emergency department complaining of progressive pain and swelling in the right forearm for 10 days. There was no history of any injury. He was diagnosed with compartment syndrome and promptly taken to the operating room for a right forearm fasciotomy and evacuation of the hematoma. After the procedure, the patient continued to bleed at the surgical site in spite of an infusion of aminocaproic acid. He required blood transfusions and additional irrigation and debridement procedures in the operating room. The patient described easy bruising for the prior 6 weeks and had urologic evaluation for gross hematuria, including abdominal ultrasound, computed tomography imaging, and cystoscopy. No anatomic cause for the hematuria was identified. There was no prior history of excessive bleeding with trauma, dental procedures, or surgery, including tonsillectomy and appendectomy. The patient did not have a family history of excessive bleeding or a known coagulation disorder.

From the Department of Oncology, Baylor Charles A. Sammons Cancer Center and Baylor University Medical Center, Dallas, Texas.

Corresponding author: Barry Cooper, MD, 3535 Worth Street, Suite 200, Dallas, Texas 75246 (e-mail: barry.cooper@usoncology.com).

Past medical history was significant for colitis, currently inactive, and Guillain-Barré syndrome several years earlier without neurologic sequelae. Medications included hyoscyamine, budesonide, mesalamine, pantoprazole, and fexofenadine.

Physical examination was significant for persistent serosanguineous drainage from the right forearm wound and a 10-cm bruise evident over the left inner thigh. Petechiae, lymphadenopathy, and splenomegaly were absent.

Laboratory results included a hematocrit of 40%, a white blood cell count of 9200/ μ L with normal differential, and a platelet count of 322,000/ μ L. Postoperatively, his PT was 11 seconds; PTT, 27 seconds; fibrinogen, 472 mg/dL; thrombin clot time, 15 seconds; and platelet function assay, normal. Results of assays for von Willebrand's disease were normal, including ristocetin cofactor (174%), factor VIII assay (208 U/dL), and von Willebrand's antigen (185 U/dL). Alpha 2-antiplasmin activity was 98%, and platelet factor 3 was present. Factor XIII activity was undetectable using a photometric assay (7). Results of an inhibitor assay were positive at a titer of >1:10.

The patient's clinical course over the ensuing 2 months is illustrated in the *Figure*. Prior medications were discontinued without improvement in factor XIII levels. On the ninth hospital day, with the diagnosis of factor XIII deficiency confirmed, the patient was transfused with FFP or cryoprecipitate intermittently. Therapy increased measurable levels of factor XIII for about 2 days. Immunosuppression with oral cyclophosphamide was started on the 16th hospital day, and the patient was discharged on every-other-day intravenous cryoprecipitate. The inhibitor was still present 2 weeks after cyclophosphamide was initiated, albeit at a lower titer of 1:2. Rituximab 375 mg/m² was started 3 weeks after cyclophosphamide with four weekly doses. One week after the initial dose of rituximab, the factor XIII activity was 28%, the inhibitor titer was negative, and no further cryoprecipitate was required. One week after the last dose of rituximab, the factor XIII level was 58%. Cyclophosphamide was continued for 5 months on a tapering schedule. Six months after treatment was initiated, the factor XIII level remained normal (67%) without evidence of recurrent bleeding.

DISCUSSION

Failure to recognize an uncommon acquired coagulation disorder can have serious consequences. The differential diagnosis of a hemorrhagic disorder with normal baseline coagulation studies (PT, PTT, thrombin clot time, fibrinogen, platelet count, platelet function assay and/or bleeding time) is limited. Von Willebrand's disease, even with a normal PTT and bleeding time, is the most common abnormality detected. Other etiologies include alpha 2-antiplasmin deficiency, platelet factor 3 deficiency, dysfibrinogenemia, and factor XIII deficiency. Ap-

Figure. Clinical course. Factor XIII activity was initially undetectable, and the inhibitor titer was >1:10. Factor XIII activity steadily increased after the initiation of cyclophosphamide and rituximab, with a corresponding decrease in inhibitor titer. FFP indicates fresh frozen plasma.

propriate studies in our case confirmed factor XIII deficiency due to an inhibitor, presumably acquired.

According to the classification of Lorand, inhibitors can interfere with factor XIII activity by preventing activation of factor XIII, interfering with the function of factor XIIIa, or altering the reactivity of the fibrin substrate (8, 9). Most cases of acquired factor XIII inhibitors are idiopathic or associated with prolonged drug ingestion, most commonly isoniazid (10, 11). Other drugs associated with acquired factor XIII inhibitors include penicillin (12), phenytoin (13), and practolol (14). Patients with acquired factor XIII inhibitors usually present with severe subcutaneous and retroperitoneal bleeding that is often difficult to control, resulting in a high mortality rate. If an offending drug is suspected, the medication should be discontinued. Prompt clinical improvement may occur, but excessive bleeding will often persist for a period of weeks or months.

Replacement therapy with cryoprecipitate or FFP has not always proven successful. Factor XIII concentrate has been used in patients with congenital factor XIII deficiency, but its use in patients with acquired factor XIII inhibitors is limited and the product is not yet commercially available. Nakamura et al reported that infusions of factor XIII concentrate controlled acute bleeding in a patient with an acquired inhibitor (5). Plasmapheresis may reduce inhibitor titers and result in clinical improvement, and immunosuppression with cyclophosphamide may reduce inhibitor titers and restore factor XIII activity. Cyclophosphamide has well-established immunosuppressive properties and is effective therapy for a variety of autoimmune hematologic disorders including chronic immune thrombocytopenia (ITP), autoimmune hemolytic anemia, and acquired factor VIII inhibitors.

Rituximab is a chimeric, human IgG1 kappa monoclonal antibody specific for the CD20 antigen expressed on the surface of B lymphocytes. The antibody is known to induce rapid in vivo depletion of both normal B lymphocytes and lymphoma B cells. Mechanisms of action include complement-mediated cytotoxicity, antibody-dependent cytotoxicity, inhibition of B-cell

proliferation, and induction of apoptosis (15). Rituximab has demonstrated clinical efficacy in the treatment of B-cell lymphoproliferative disorders expressing the CD20 antigen. The drug's limited toxicity has led to the recent use of rituximab for the treatment of autoimmune disorders, anticipating a decrease in antibody production by CD20⁺ B cells. Examples include ITP, autoimmune hemolytic anemia, and acquired hemophilia A.

Rituximab has been shown to diminish hemolysis in children with autoimmune hemolytic anemia. Zecca et al reported that 13 of 15 pediatric patients previously treated with two or more immunosuppressive agents responded to treatment with rituximab with a median increase in hemoglobin levels of 4 g/dL. Ten patients demonstrated a sustained response, not requiring additional treatment (16).

Rituximab has efficacy in treating refractory chronic ITP. Twenty-five percent to 30% of patients with ITP will develop a chronic course, being refractory to corticosteroids, intravenous immunoglobulin, and splenectomy. In a series reported by Stasi et al, 25 patients with ITP resistant to conventional therapy were treated with rituximab, including eight patients who had relapsed following splenectomy. Ten patients (40%) obtained at least partial response (platelet count >50,000/ μ L). Seven of these patients had a response duration longer than 7 months (17).

Acquired hemophilia is a rare disorder characterized by the development of autoantibodies against factor VIII. Immunosuppressive treatment with corticosteroids and cytotoxic drugs alone or in combination is regarded as the mainstay of treatment. Wiestner et al reported that four patients with acquired factor VIII inhibitors responded to immunosuppressive regimens including rituximab (18). Recently, Stasi et al noted that eight of ten patients with acquired hemophilia and clinically significant bleeding experienced rapid clinical improvement following administration of rituximab, including normalization of factor VIII levels and disappearance of the inhibitor. Three patients relapsed within 20 weeks but responded to retreatment (19).

Our patient presented with severe, spontaneous bleeding due to the presence of an acquired factor XIII inhibitor. Bleeding was initially controlled with infusion of FFP and cryoprecipitate, but this therapy produced only a transient increase in factor XIII activity. Cyclophosphamide was started 6 days after the diagnosis was established, and rituximab was added 3 weeks later. The normalization of factor XIII activity and disappearance of the inhibitor was likely related to the combination of cyclophosphamide and rituximab. The inhibitor titer had started to decrease after 3 weeks of cyclophosphamide therapy before rituximab was initiated. One week after rituximab therapy was started, the factor XIII level was 28% with a negative inhibitor titer.

In conclusion, our case illustrates that patients presenting with acquired bleeding disorders can have normal routine

coagulation test results. Studies for unusual, predominantly hereditary defects, such as factor XIII deficiency, should be included in the hemostatic evaluation if routine studies are unrevealing and a bleeding diathesis seems evident.

1. Sakata Y, Aoki N. Cross-linking of alpha 2-plasmin inhibitor to fibrin-stabilizing factor. *J Clin Invest* 1980;65(2):290-297.
2. Ratnoff OD, Steinberg AG. Fibrin cross-linking and heredity. *Ann N Y Acad Sci* 1972;202:186-189.
3. Henriksson P, McDonagh J, Villa M. Type I autoimmune inhibitor of factor XIII in a patient with congenital factor XII deficiency [abstract]. *Thromb Haemost* 1983;50(1):272.
4. Fiore PA, Ellis LD, Dameshek HL, Lewis JH. XIII inhibitor and antituberculosis therapy [abstract]. *Clin Res* 1971;19:418.
5. Nakamura S, Kato A, Sakata Y, Aoki N. Bleeding tendency caused by IgG inhibitor to factor XIII, treated successfully by cyclophosphamide. *Br J Haematol* 1988;68(3):313-319.
6. Graham JE, Yount WJ, Roberts HR. Immunochemical characterization of a human antibody to factor XIII. *Blood* 1973;41(5):661-669.
7. Fickenscher K, Aab A, Stuber W. A photometric assay for blood coagulation factor XIII. *Thromb Haemost* 1991;65(5):535-540.
8. Lorand L. Fibrinolytic: the fibrin-stabilizing factor system of blood plasma. *Ann N Y Acad Sci* 1972;202:6-30.
9. Lorand L. Hemorrhagic disorders of fibrin stabilization. In Ogston D, Bennett B, eds. *Hemostasis: Biochemistry, Physiology and Pathology*. London: John Wiley & Sons Ltd, 1977:405-423.
10. Otis PT, Feinstein DI, Rapaport SI, Patch MJ. An acquired inhibitor of fibrin stabilization associated with isoniazid therapy: clinical and biochemical observations. *Blood* 1974;44(6):771-781.
11. Krumdieck R, Shaw DR, Huang ST, Poon MC, Rustagi PK. Hemorrhagic disorder due to an isoniazid-associated acquired factor XIII inhibitor in a patient with Waldenström's macroglobulinemia. *Am J Med* 1991;90(5):639-645.
12. Lopaciuk S, Bykowska K, McDonagh JM, McDonagh RP, Yount WJ, Fuller CR, Cooperstein L, Gray A Jr, Lorand L. Difference between type I autoimmune inhibitors of fibrin stabilization in two patients with severe hemorrhagic disorder. *J Clin Invest* 1978;61(5):1196-1203.
13. McDevitt NB, McDonagh J, Taylor HL, Roberts HR. An acquired inhibitor to factor XIII. *Arch Intern Med* 1972;130(5):772-777.
14. Milner GR, Holt PJ, Bottomley J, Maciver JE. Proctol therapy associated with a systemic lupus erythematosus-like syndrome and an inhibitor to factor XIII. *J Clin Pathol* 1977;30(8):770-773.
15. Reff ME, Carner K, Chambers KS, Chinn PC, Leonard JE, Raab R, Newman RA, Hanna N, Anderson DR. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood* 1994;83(2):435-445.
16. Zecca M, Nobili B, Ramenghi U, Perrotta S, Amendola G, Rosito P, Jankovic M, Pierani P, De Stefano P, Bonora MR, Locatelli F. Rituximab for the treatment of refractory autoimmune hemolytic anemia in children. *Blood* 2003;101(10):3857-3861.
17. Stasi R, Pagano A, Stipa E, Amadori S. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. *Blood* 2001;98(4):952-957.
18. Wiestner A, Cho HJ, Asch AS, Michelis MA, Zeller JA, Peerschke EI, Weksler BB, Schechter GP. Rituximab in the treatment of acquired factor VIII inhibitors. *Blood* 2002;100(9):3426-3428.
19. Stasi R, Brunetti M, Stipa E, Amadori S. Selective B-cell depletion with rituximab for the treatment of patients with acquired hemophilia. *Blood* 2004;103(12):4424-4428.