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Acquired Factor XI Deficiency in a Child With Membranoproliferative Glomerulonephritis

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Abstract

We describe a 7-year-old male with membranoproliferative glomerulonephritis who presented with nephrotic syndrome and subsequently developed factor XI (fXI) deficiency. An association between these conditions has not been described previously. In this case, fXI deficiency was caused by an antibody to fXI that enhanced clearance of the protein from plasma. Loss of fXI in the urine did not appear to be involved. Antibody-mediated clearance of prothrombin or factor X can cause acquired deficiencies of these proteins. This is the first report, to our knowledge, of an antibody that causes fXI deficiency by this mechanism.

Keywords

antibody; epistaxis; factor XI deficiency; nephrotic syndrome

INTRODUCTION

Factor XI (fXI) is a plasma protein that is required for hemostasis primarily in tissues with high fibrinolytic activity, such as the oropharynx and urinary tract [1]. Bleeding in congenital fXI deficiency occurs mainly after surgery or trauma involving those tissues. Alloantibodies that inhibit fXI activity develop relatively frequently after replacement therapy in patients with the severest form of deficiency (<1% normal fXI level) [2]. However, acquired deficiency due to an antibody in the absence of congenital deficiency is rare, having been reported with autoimmune disorders (systemic lupus erythematosus, rheumatoid arthritis, Crohn disease) [1,3], or malignancies (chronic myelomonocytic or lymphocytic leukemias, and gastrointestinal adenocarcinoma) [1]. Membranoproliferative

glomerulonephritis (MPGN) is an uncommon disorder diagnosed primarily in children and young adults presenting with nephrotic or nephritic syndrome [4]. The pathogenesis is not well understood, but appears to involve immune complex deposition in glomeruli, with subsequent activation of the classical (type I MPGN) or alternative (type II MPGN) complement pathways leading to tissue damage [4].

CASE REPORT

A 15-month-old previously well male presented with edema, hematuria, and proteinuria and was diagnosed with nephrotic syndrome. His partial thromboplastin time (PTT) was normal (24 seconds, refer to Table I for laboratory data), and there was no family history of renal or hematologic disease. A kidney biopsy was uncomplicated by bleeding, and revealed MPGN, which was treated intermittently over the subsequent 5 years with corticosteroids. At age 31 months the patient was evaluated for recurrent epistaxis. The prothrombin time (PT, 9.2 seconds) and PTT (35 seconds) were normal. Nosebleeds continued, requiring cautery on several occasions, and he was reevaluated at 59 months of age after his PTT was found to be slightly prolonged (39 seconds). Factor VIII (104%), factor IX (97%), fibrinogen (324 mg/dl), and von Willebrand factor antigen (127%) levels were normal. Two and 6 months later, his PTT was significantly prolonged (67 and 69 seconds, respectively), with markedly reduced fXI activity (2% of normal). Mixing patient and normal plasma (1:1) corrected the PTT, consistent with a factor deficiency, and a Bethesda assay for fXI inhibitory antibodies was negative. Studies performed at Vanderbilt University confirmed that the prolonged PTT corrected on 1:1 mixing with normal plasma, with a fXI activity of 4% of normal and no evidence of an inhibitor. Levels of fXII (130%, normal 50–150%) and anti-thrombin (125%, normal 60–120%) were normal.

At 67 months of age, the patient underwent tonsillectomy and adenoidectomy. The pre-operative fXI activity and antigen levels were markedly reduced (1% and 5%, respectively). After fresh frozen plasma (FFP) infusion (10 ml/kg), the fXI activity increased to 16% (PTT 38 seconds) and remained stable over 28 hours with no immediate post-operative bleeding. This was the patient's first exposure to plasma. Twelve days after surgery, he developed severe bleeding from the operative site. The PTT was 121 seconds with a normal PT. FFP (10 ml/kg) was administered twice, without correction of the PTT. Cautery was required to stop the bleeding. The post-infusion fXI level was 4% of normal. A mixing study showed a substantial, but incomplete, correction from a PTT of 75.5 seconds (Vanderbilt) down to 40.0 seconds (normal 22–34 seconds), suggesting a factor deficiency with a modest component of inhibitory activity. An inhibitor assay now revealed a low titer (2 Bethesda units) fXI inhibitor.

A Western blot of patient plasma at 65 months of age confirmed reduced fXI cross-reactive material (Fig. 1A). Little cross-reactive material was present in the patient's plasma prior to pre-operative FFP infusion at age 79 months (Fig. 1B), but was detectable after the first FFP infusion, consistent with the rise in fXI activity to 16% of normal (Table I). In contrast, on post-operative day 13, no fXI antigen was detectable after FFP infusion.

Given the acquired nature of the patient's deficiency, we postulated that his situation was due either to loss of fXI in the urine, or clearance by an antibody with weak inhibitory properties. There was a trace of fXI antigen in control and patient urine by ELISA, but fXI was not demonstrable by Western blot, even with immunoprecipitation of concentrated samples (Fig. 1C). A solid-phase binding assay using immobilized fXI indicated the presence of an anti-fXI IgG in patient plasma prior to FFP exposure. Using this plasma as a primary antibody in Western blots (Fig. 1D), an anti-fXI IgG was confirmed in the patient prior to FFP exposure. A faint signal was also detected with patient plasma collected at age 65 months. The signal was markedly stronger 13 days post-FFP exposure (post-operative day 13).

DISCUSSION

We conclude that the patient had a fXI autoantibody with weak inhibitory properties that facilitated fXI clearance from plasma. The antibody titer clearly increased after factor replacement, as has been observed with some factor VIII autoantibodies.

Nephrotic syndrome is associated with changes in plasma coagulation factors and regulatory proteins [5]. Acquired deficiencies of factor XII (fXII) and anti-thrombin (AT) are well-documented [5,6]. Green et al. [7] observed low fXII levels in a patient with an inherited membranous glomerulopathy, and determined that reduced clotting activity was due to loss in the urine. Viziri et al. [8] also measured substantial amounts of fXII in the urine of nephrotic syndrome patients. Similarly, AT loss in the urine has been described, with AT correlating well with albumin levels [9,10]. In contrast, Hruby et al. [11] detected fXII in the urine of only 1 of 13 children with nephrotic syndrome, and noted that plasma fXII antigen was substantially greater than activity. Work by Thompson [6] and Saito et al. [12] also support the premise that urinary loss does not explain fXII deficiency in many cases of nephrotic syndrome, suggesting the presence of an interfering substance that reduces plasma fXII activity. It is likely that the mechanism differs from patient to patient, and may be influenced by the nature of the underlying disease process.

Acquired fXI deficiency has not been reported in nephrotic syndrome. Nakamura et al. [13], while noting reduced fXII levels in the early phases of disease prior to treatment, did not see an effect on fXI levels, while Ueda et al. [14] reported increased fXI levels in treated and untreated nephrotic syndrome patients. Our patient clearly had reduced plasma fXI activity and antigen that could not be accounted for by urinary loss. Indeed, his fXII and AT levels were normal, suggesting proteinuria was not significant at 65 months of age, when his fXI level was 2–4% of normal. The presence of an IgG antibody to fXI prior to exposure to exogenous protein is consistent with an autoantibody that may be related to MPGN. The antibody is not a particularly strong neutralizer of fXI activity as measured by Bethesda assay, even after the titer increased post-FFP administration. Given the low fXI antigen level in plasma, the IgG most likely facilitates fXI clearance, although we cannot rule out that reduced fXI synthesis is contributing. Clearance of prothrombin from plasma by nonneutralizing prothrombin antibodies is occasionally seen in patients with lupus anticoagulants [15], and acquired factor X deficiency has been reported in primary amyloidosis [16], with factor X specifically binding to amyloid fibrils made of

immunoglobulin. Our findings emphasize the importance of considering immune-mediated clearance as a cause for a coagulation factor deficiency in patients with autoimmune disorders.

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Fig. 1.

A: Western blots of 2 μ l samples of plasma size-fractionated on a 7.5% SDS-polyacrylamide gel. The primary antibody was biotinylated anti-fXI IgG 14E11.[17] Detection was with streptavidin-HRP and chemiluminescence. FXI deficient plasma (XI-), normal plasma (N), or patient plasma (P). Positive control (+C) is purified human fXI. The position of the fXI homodimer is indicated at the right of the panel. **B:** Normal (N) or FXI deficient (XI-) control plasmas are compared to patient plasma prior to FFP (Pre-FFP) and 4–6 hours after administration of 10 ml/kg FFP on POD #0 (10/7) and POD #13 (10/20). **C:** Urine samples were dialyzed against Tris-HCl pH 7.4, 100 mM NaCl (TBS) to remove urea. FXI was immunoprecipitated from 1 ml of urine with anti-fXI IgG O1A6 linked to agarose beads. Beads were eluted with SDS-non-reducing sample buffer, and size-fractionated on a 7.5% SDS-polyacrylamide gel. Western blots were developed as in panels A,B. TBS was used as a negative control (-C), TBS containing 1 μ g/ml human fXI was a positive control (+C), normal control urine (N), and patient urine (P). **D:** Western blots of purified human fXI size fractionated on a 7.5% SDS-polyacrylamide gel. The primary antibody in lanes 1, 2, and 3, are 1:10 dilutions of patient plasma from (1) 65 months of age. (2) 79 months of age, POD #0, and (3) POD #12. In the negative control (-C) a 1:10 dilution of normal human plasma was used as primary antibody, while in the positive control (+C), antibody 14E11 was used. For all panels, positions of molecular mass standards in kilodaltons are shown to the left of each blot.

TABLE I

Table of Clinical Data

Age (months)	POD	Time of Day (military time in hours:minutes)	PT ¹ (seconds)	PT ² (seconds)	PTT ¹ (seconds)	PTT ² (seconds)	fXI ¹ (%)	fXI ² (%)	Comments
15					24 (23–39)				
31			9.2 (9–11.5)		35 (23–39)				
59			10.4		39 (22–34)				
61					67				
65			10.1	12.8 (12–15)	69	44.6 (22–34)	2	4	Mix corrects ^{1,2}
79	0	8:00		12.2		68.6		1	Pre-FFP
	0	14:30		13.0	38	40.0		16	Post-FFP
	0	21:00		12.5	39	37.7		11	
79	1	10:57		12.3	36	35.5		15	
79	12	23:00	9.4		121				Mix partially corrects ²
79	13	3:36		12.4	123	72.3		4	Post-FFP
	13	13:41			118				Post-FFP
	13	19:15			124				

¹ Table shows prothrombin times (PT), partial thromboplastin times (PTT), and fXI activity (fXI) for studies performed at ¹AI duPont Hospital for Children and

² Vanderbilt University Medical Center. Post-operative day (POD) indicated following the patient's adenoidectomy and tonsillectomy.