

## Brief report

# Acquired factor X deficiency in patients with amyloid light-chain amyloidosis: incidence, bleeding manifestations, and response to high-dose chemotherapy

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**Acquired deficiency of factor X occurs in patients with systemic amyloid light-chain (AL) amyloidosis, presumably due to adsorption of factor X to amyloid fibrils. Of 368 consecutive patients with systemic AL amyloidosis evaluated at Boston Medical Center, 32 patients (8.7%) had factor X levels below 50% of normal. Eighteen of these patients (56%) had bleeding complications, which were more**

**frequent and severe in the 12 patients below 25% of normal; 2 episodes were fatal. Ten factor X-deficient patients received high-dose melphalan chemotherapy followed by autologous stem cell transplantation. Of 7 patients alive 1 year after treatment, 4 had a complete hematologic response, and all 4 experienced improvement in their factor X levels. One of 2 additional patients with**

**partial hematologic responses had improvement in factor X. Thus, aggressive treatment of the underlying plasma cell dyscrasia in AL amyloidosis can lead to the amelioration of amyloid-related factor X deficiency. (Blood. 2001;97:1885-1887)**

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## Introduction

Acquired deficiency of factor X (Stuart factor) is the most common coagulation factor deficiency that has been identified in patients with amyloid light-chain (AL) amyloidosis. This was first described in single case reports almost 30 years ago and confirmed in a series of 95 patients.<sup>1</sup> Factor X deficiency is postulated to occur via the adsorption of factor X to amyloid fibrils.<sup>2,3</sup> A total of 368 consecutive patients with systemic AL amyloidosis were screened for factor X deficiency at our institution. In this report, we describe the incidence of factor X deficiency, the frequency and severity of hemorrhagic complications in factor X-deficient patients, and the improvement of factor X levels after treatment with high-dose melphalan and autologous stem cell transplantation (HDM/ASCT).

or INR (normal values 0.86-1.13), was measured using the Innovin reagent (Dade Behring). The activated partial thromboplastin time, or aPTT (normal values 26-42 seconds), was measured using Pathromptin (Dade Behring). Patients with reduced factor X levels and clinical bleeding also had other factor levels measured in a similar fashion. A linear regression analysis was performed to determine the correlation of factor X levels with the INR, aPTT, and severity of nephrotic syndrome as measured by the amount of urine protein collected in 24 hours.

## Results and discussion

Thirty-two of the 368 patients (8.7%) had factor X levels below 50% of normal. This incidence is slightly higher than the 6.3% reported in a series of 95 patients,<sup>1</sup> but lower than the 14% reported in another large series.<sup>6</sup> Twenty-nine of the 32 patients had primary AL amyloidosis only, 2 patients had multiple myeloma with AL amyloidosis, and 1 had Waldenström's macroglobulinemia with AL amyloidosis. The median age of these 32 patients was 58 years (range 38-77); the male:female ratio was 1.5:1. The light-chain isotype was  $\lambda$  in 23 patients and  $\kappa$  in 9. The INR was elevated in 28 (87%) of the 32 patients with factor X deficiency, and a prolonged aPTT was found in 9 (28%). However, neither the INR nor aPTT correlated well with the factor X level.

Significant bleeding events occurred in 18 (56%) of the 32 patients (Table 1). Of the 20 patients with moderate factor X deficiency (25%-50% of normal), 9 had hemorrhagic complications (45%), of which 4 (20%) were classified as severe, although only 1 of the 20 (5%) required a transfusion. Subcutaneous hemorrhage was seen in 5 patients; 1 of these patients had developed an abdominal wall hematoma subsequent to a laparoscopic ovarian cystectomy and required a transfusion. The other 4

## Study design

### Patients

A total of 368 new patients with AL amyloidosis were evaluated in the Amyloidosis Research and Treatment Program at Boston Medical Center between January 1997 and May 2000. All patients had a tissue biopsy or fat aspirate demonstrating amyloid deposits and a monoclonal immunoglobulin protein in serum or urine, frequently associated with monoclonal plasma cells in the bone marrow. Suitable patients were treated on a series of clinical trials using HDM/ASCT, conducted with approval of the Institutional Review Board. Preliminary results from these trials have been reported elsewhere.<sup>4,5</sup>

### Coagulation studies

Factor X activity was measured by a standard one-stage method using single-donor factor X-deficient plasma (George King Bio-Medical, Overland Park, KS) on a Dade Behring BCS Coagulation Analyzer (Deerfield, IL). The prothrombin time, expressed as an international normalized ratio,

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**Table 1. Clinical features of 18 AL amyloidosis patients with factor X deficiency and bleeding manifestations**

Patient no.	Factor X, %	INR	aPTT (s)	Site of bleeding*					
				Skin	Proc	GI/GU	TFN	SPL	Fatal
1	< 10	2.96	57	+	+				
2	10	1.64	41			+			
3	12	1.37	28	+					
4	13	1.56	31	+	+		+		
5	16	1.66	36	+	+		+		+
6	16	2.41	47		+	+	+		+
7	17	1.89	47				+	+	
8	17	1.79	42		+		+		
9	23	1.74	41					+	
10	29	1.12	25	+					
11	31	1.68	39			+			
12	35	1.32	33			+			
13	37	1.49	47	+	+		+		
14	38	1.49	33			+			
15	40	1.13	36	+					
16	41	1.07	23			+			
17	42	1.26	42	+					
18	47	1.07	31	+					

\*Sites of bleeding included significant subcutaneous or soft tissue hemorrhage (Skin); unusual bleeding from a central venous line placement, biopsy, or other surgical procedure (Proc); gastrointestinal bleeding or hematuria (GI/GU); bleeding that required transfusion (TFN); intrasplenic hemorrhage (SPL); or bleeding associated with or contributing to mortality (Fatal).

patients had additional evidence of gastrointestinal or genitourinary hemorrhage.

Of the 12 patients with severe factor X deficiency (< 25% of normal), 9 had hemorrhagic complications (75%). Six events were characterized as severe (50%), and 2 were fatal (17%). Five of the 12 patients (42%) required transfusion of packed red cells. Hemorrhagic complications were associated with invasive procedures in 5 patients and involved significant subcutaneous hemorrhage in 4 patients. Two patients had gastrointestinal or genitourinary bleeding, and 2 patients had subcapsular splenic hemorrhages. For 1 of these patients, this was the presenting symptom, and the diagnosis of AL amyloidosis was made after splenectomy. The second patient developed intrasplenic hemorrhage necessitating splenectomy in the posttransplantation period. Clearly, the frequency and severity of hemorrhage was worse in the patients with the lowest factor X levels. Conversely, in the nonfactor X-deficient patients, serious hemorrhagic complications were rare in this patient population, although factor X deficiency is not the only cause of hemorrhage in patients with AL amyloidosis, who also suffer from capillary fragility because of amyloid deposition in the vessel walls, dysfibrinogenemia, abnormal platelet aggregation,<sup>1,6,7</sup> and other factor deficiencies, including deficiencies of factors II, VII, IX,<sup>8</sup> and V.<sup>9</sup> Elevation of the thrombin time and Russell viper venom clotting time can be seen.<sup>10,11</sup>

Nephrotic syndrome was present in 11 of the 32 patients with factor X below 50% (24-hour urinary protein excretion ranging from 3.8 to 16.8 g). However, there was no statistical correlation between urinary protein losses and factor X levels ( $r^2 = 0.18$ ). Thus, factor X deficiency in AL amyloidosis is not a consequence of nephrotic protein losses.

Liver function abnormalities were also present in 14 of the 32 patients with factor X below 50%. However, these were primarily modest elevations in alkaline phosphatase or bilirubin, consistent with the typical intrahepatic obstructive process caused by amyloid deposition; there was no laboratory or clinical evidence of significant hepatocellular damage or liver failure in these patients. Thus, the deficiency in factor X appears to be independent of hepatic disease and is unlikely to be due to a synthetic defect. Rather, as has

been reported in the literature previously,<sup>2,3</sup> it is likely that factor X is adsorbed to amyloid fibrils and sequestered from the plasma.

Of the 32 patients with factor X deficiency, 10 were treated with HDM/ASCT (Table 2). Two of these 10 patients succumbed with bleeding complications in the peritransplant period despite attempts to maintain platelet counts above  $50 \times 10^9/L$  ( $50\,000/mm^3$ ), infusion of fresh frozen plasma, vitamin K therapy, and treatment with prothrombin concentrates. One patient (no. 5 in Tables 1 and 2) with combined deficiency of factors VII and X (52% and 16% of normal, respectively) died of sepsis and massive gastrointestinal bleeding on day 29 after transplantation. Another patient (no. 6), who had combined deficiencies of factors V and X (5% and 16% of normal, respectively), apparently died of hypoxemia due to pulmonary hemorrhage on day 15 after transplantation. A third patient (no. 16) died of a cardiac event at 6 months after transplantation.

Of the 7 patients who survived more than 1 year, 4 achieved a hematologic complete response (CR; defined as absence of evidence of plasma cell dyscrasia or monoclonal gammopathy), 2 achieved a hematologic partial response (PR), and 1 patient had no improvement with treatment (no response, or NR). All of the 4 patients achieving a CR were found to have increased levels of

**Table 2. Response of 10 patients with factor X deficiency to HDM/ASCT<sup>1,2</sup>**

Patient no.	Response	Melphalan, mg/m <sup>2</sup>	Factor X,	
			pre-HDM/ASCT, %	Factor X, post-HDM/ASCT, %
4	CR	140	13	42
5*	Expired	200	16	
6*	Expired	200	16	
7	PR	200	17	15
10	CR	140	29	41
14	NR	140	38	39
15	CR	200	40	104
16*	Expired	200	41	
18	PR	140	47	96
19	CR	200	19	86

\*Patient 5 expired at day 29 post-HDM/ASCT, patient 6 expired at day 15, and patient 16 at 6 months.

factor X after treatment and experienced no further clinical bleeding; 1 patient achieving a hematologic PR experienced a normalization of the factor X level, while the other 2 patients (1 PR, 1 NR) had no improvement in factor X (Table 2). There are reports of isolated cases of AL amyloidosis in which resolution of acquired factor X deficiency occurs spontaneously,<sup>12</sup> after treatment with oral melphalan,<sup>13,14</sup> or after splenectomy.<sup>15,16</sup> This series is the first in which the salutary impact of high-dose chemotherapy and stem cell transplantation upon factor X levels has been reported.

In conclusion, our data suggest that all systemic AL amyloidosis patients should be screened for reduced factor X levels, because this occurs in a significant proportion of these patients and is associated with an increased hemorrhagic morbidity. High-dose melphalan chemotherapy can result in amelioration of the factor X

deficiency; however, the risk of life-threatening peritransplant bleeding is high, particularly in patients with severe factor X deficiency or concomitant deficiency of other factors.

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## References

- Greipp PR, Kyle RA, Bowie EJ. Factor-X deficiency in amyloidosis: a critical review. *Am J Hematol.* 1981;11:443-450.
- Girmann G, Wilker D, Stadie H, Scheurlen PG. Acquired isolated factor X deficiency associated with systemic amyloidosis. Case report and review of literature. *Klin Wochenschr.* 1980;58:859-862.
- Furie B, Voo L, McAdam KP, Furie BC. Mechanism of factor X deficiency in systemic amyloidosis. *N Engl J Med.* 1981;304:827-830.
- Comenzo RL, Vosburgh E, Falk RH, et al. Dose-intensive melphalan with blood stem-cell support for the treatment of AL (amyloid light-chain) amyloidosis: survival and responses in 25 patients. *Blood.* 1998;91:3662-3670.
- Comenzo RL, Vosburgh E, Simms RW, et al. Dose-intensive melphalan with blood stem cell support for the treatment of AL amyloidosis: one-year follow-up in five patients. *Blood.* 1996;88:2801-2806.
- Mumford AD, O'Donnell J, Gillmore JD, et al. Bleeding symptoms and coagulation abnormalities in 337 patients with AL-amyloidosis. *Brit J Haem.* 2000;110:454-460.
- Hoshino Y, Hatake K, Muroi K, et al. Bleeding tendency caused by the deposit of amyloid substance in the perivascular region. *Intern Med.* 1993;32:879-881.
- McPherson RA, Onstad JW, Ugoretz RJ, Wolf PL. Coagulopathy in amyloidosis: combined deficiency of factors IX and X. *Am J Hematol.* 1977;3:225-235.
- Gatel A, Cacoub P, Piette JC. AL amyloidosis combined with acquired factor V deficiency [letter]. *Ann Intern Med.* 1998;128:604-605.
- Gamba G, Montani N, Anesi E, et al. Clotting alterations in primary systemic amyloidosis. *Haematologica.* 2000;85:289-292.
- Gastineau DA, Gertz MA, Daniels TM, Kyle RA, Bowie EJ. Inhibitor of the thrombin time in systemic amyloidosis: a common coagulation abnormality. *Blood.* 1991;77:2637-2640.
- le Quellec A, Sotto A, Ciurana AJ. Spontaneous resolution of acquired factor X deficiency in amyloidosis. *J Intern Med.* 1993;234:329-330.
- Camoriano JK, Greipp PR, Bayer GK, Bowie EJ. Resolution of acquired factor X deficiency and amyloidosis with melphalan and prednisone therapy. *N Engl J Med.* 1987;316:1133-1135.
- Schwarzinger I, Stain-Kos M, Bettelheim P, et al. Recurrent, isolated factor X deficiency in myeloma: repeated normalization of factor X levels after cytostatic chemotherapy followed by late treatment failure associated with the development of systemic amyloidosis. *Thromb Haemost.* 1992;68:648-651.
- Greipp PR, Kyle RA, Bowie EJ. Factor X deficiency in primary amyloidosis: resolution after splenectomy. *N Engl J Med.* 1979;301:1050-1051.
- Rosenstein ED, Itzkowitz SH, Penziner AS, Cohen JI, Mornaghi RA. Resolution of factor X deficiency in primary amyloidosis following splenectomy. *Arch Intern Med.* 1983;143:597-599.