

## Acquired Factor X Deficiency in Light Chain Amyloidosis: A Report of 2 Korean Cases

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Amyloidosis is a heterogeneous group of diseases in which misfolding of extracellular proteins is the pathogenic factor. Light chain amyloidosis (AL) is the most common form of amyloidosis, and the causative proteins in AL are the immunoglobulin light chains produced by clonal plasma cells. Hemorrhagic events, ranging from mild subcutaneous hemorrhage to life-threatening bleeding, account for a significant proportion of morbidities and mortality in AL patients. Deficiency of factor X from deposition into amyloid fibrils has been reported to be the most common acquired factor deficiency in AL. We herein report 2 patients with acquired factor X deficiency in AL. A 55-yr-old woman with AL had a prolonged prothrombin time (PT) and an activated partial thromboplastin time (aPTT) of 2.51 International Normalized Ratio (INR) and 75.1 sec, respectively, which were corrected on mixing with normal plasma. Factor X activity was markedly decreased at 5%. The other patient was a 67-yr-old man with AL with a PT of 1.63 INR and an aPTT of 50.3 sec, which were corrected on mixing with normal plasma. Factor X activity was decreased at 17%. Neither of the patients had apparent hemorrhagic manifestations. Identification of acquired factor deficiency and timely coagulation tests are needed in the diagnostic workup and management in AL.

**Key Words:** Amyloidosis, Factor X deficiency, Korea

### INTRODUCTION

Amyloidosis is a heterogeneous group of diseases in which misfolding of extracellular protein is the pathogenic factor. This process produces insoluble, toxic protein aggregates that are deposited in tissues in bundles of  $\beta$ -sheet fibrillar protein [1]. The most common cause of amyloidosis is clonal plasma cells in the bone marrow producing immunoglobulins that are amyloidogenic (light chain amyloidosis or AL) [2]. Hemorrhagic events, ranging from mild subcutaneous hemorrhage to life-threatening bleeding, account for a significant proportion of morbidities and mortality in

AL. Bleeding tendency is frequently encountered in AL, and while mild subcutaneous hemorrhage is the most common manifestation, life-threatening bleeding has also been reported [3-6]. Acquired hemostatic abnormalities, including coagulation factor deficiencies, hyperfibrinolysis, and platelet dysfunction are the background of bleeding tendency [5, 6]. In particular, acquired deficiency of factor X is the most common coagulation factor deficiency in patients with AL, and it is postulated to occur via the adsorption of factor X to amyloid fibrils [3, 5-8]. We herein report 2 Korean patients with acquired factor X deficiency in association with AL.

### CASE REPORTS

#### 1. Patient 1

A 55-yr-old woman with generalized edema was diagnosed with AL on the basis of a renal biopsy. Serum and urine electrophoresis combined with immunofixation revealed M-protein of IgG/lambda type, and bone marrow analysis showed monoclonal proliferation of plasma cells. Coagulation tests revealed a prolonged prothrombin time (PT) of 2.51 International Normalized Ratio (INR) and an activated partial thromboplastin time (aPTT) of 75.1 sec

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(29.1-41.9 sec). Thrombin time was within the normal range (18.6 sec; reference interval, 15.6-20.0 sec). Complete correction of the prolonged PT and aPTT on mixing with normal plasma prompted us to proceed with factor assays, which revealed markedly decreased factor X activity at 5% (69-126%) and mildly decreased factor V activity 63% (81-160%). The patient had no apparent bleeding symptoms. The patient underwent autologous peripheral blood stem cell transplantation and achieved complete hematological remission. Follow-up coagulation tests revealed improvement of prolonged PT/aPTT (PT, 1.77 INR and aPTT, 52.5 sec) and normalization of factor V activity (136%). However, factor X activity was still decreased at 12%. Despite the improvement of coagulopathy, the patient experienced bleeding diathesis during the follow up for chronic kidney disease.

## 2. Patient 2

A 67-yr-old man with dyspnea was diagnosed with cardiac amyloidosis. Monoclonal immunoglobulins of IgG/kappa type were detected in the serum and urine, and bone marrow analysis showed an increase of monoclonal plasma cells. Coagulation tests showed prolongation of both PT (1.63 INR) and aPTT (50.3 sec), which were corrected on mixing with normal plasma. Thrombin time test was not performed. Factor assays revealed a significant decrease of factor X activity at 17%. Other coagulation factor activities were not decreased. He had no apparent bleeding manifestations. He received chemotherapy, and follow-up coagulation tests showed a normalized aPTT, but the PT was still prolonged (1.64 INR). Follow up for factor X activity was not performed.

## DISCUSSION

Acquired factor deficiency with or without bleeding symptoms is not infrequent in AL, whereas it is rare in other types of amyloidosis. Specific coagulation factor deficiencies in AL have long been recognized and have been explained by the adsorption of coagulation factors to amyloid fibrils. Evidence showing the interaction of amyloidogenic light chains with coagulation factors and anecdotal reports of improved hemostasis after removal of amyloidotic spleen support the fact that coagulation factors bind to the amyloid fibrils [5]. Both isolated coagulation factor deficiency and combined deficiencies have been reported. Factor X deficiency has been described as the most common acquired coagulation factor deficiency, affecting up to one-third of patients with AL. Deficiencies of other coagulation factors

such as II, V, VII, and IX have also been reported [5-7]. According to a previous study that evaluated a total of 368 patients with AL, 32 patients had a factor X activity below 50% of normal. Eighteen of these patients (56%) had bleeding complications, which were more severe in the 12 patients with factor X activity below 25% of normal [7]. The 2 patients with acquired factor X deficiency from AL described in the present report had no bleeding symptoms, even with the very low level of factor X activity (5%) in Patient 1. A review of the literature revealed a single case report on acquired factor X deficiency in AL patients in Korea [9]. Kim et al. [9] reported factor X deficiency in a patient with AL and nephrotic syndrome. The patient had mildly decreased factor X activity of 49% (70-120%), prolonged PT of 1.32 INR and upper normal aPTT of 39.4 sec (32-41.2 sec). Despite normal aPTT, mildly prolonged PT, and slightly decreased factor X activity, he had bleeding tendency and symptoms such as petechiae.

Previous studies reported that high-dose chemotherapy followed by autologous stem cell transplantation led to complete remission and normalization of the factor X level [7, 10, 11]. Patient 1 achieved complete remission after chemotherapy and autologous peripheral blood stem cell transplantation. The patient showed improvement of prolonged PT and aPTT (2.51 to 1.77 INR and 75.1 to 52.5 sec, respectively). However, factor X activity was still significantly decreased (12%), and the patient developed bleeding diathesis during the course of treatment. Indeed, it was reported that the baseline factor X level was not predictive of bleeding risk, and optimal management of factor X deficiency in AL is still elusive [12]. The findings in the previously reported patient [9] and the 2 patients described in the present report demonstrate the heterogeneous clinical and laboratory manifestations of factor X deficiency in Korean patients with AL.

To the best of our knowledge, this is only the second report of factor X deficiency in association with AL in Korea. Further prospective studies involving multiple institutions are needed to investigate the epidemiology and clinical implications of acquired factor X deficiency in Korean patients with AL. Appropriate coagulation workup should be conducted in patients with AL with prolonged coagulation times, and further studies are needed to obtain laboratory and clinical data to delineate the frequency and clinical implications of acquired coagulopathy in Korean patients with AL.

## Authors' Disclosures of Potential Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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