Acquired Factor X Deficiency Associated with Atypical AL-amyloidosis

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Abstract

We herein describe the case of a 77-year-old woman with acquired factor X deficiency that was likely caused by atypical amyloidosis. The patient developed severe gastrointestinal bleeding as a result of a significant decrease of factor X activity. Neither proteinuria nor diarrhea was observed as an initial manifestation. Although a bone marrow examination revealed direct fast scarlet-positive extracellular deposits, they did not exhibit red-to-green dichroism under polarized light. Immunofluorescence microscopy showed that the fibrillar proteins were positive for CD138 but negative for \textbeta{}\textsubscript{2}-microglobulin or amyloid A antibodies. These atypical pathological features of immunoglobulin light chain-amyloidosis in this patient might be related to its unique clinical presentation.

Key words: acquired factor X deficiency, atypical amyloidosis, nephrotic syndrome, AL-amyloidosis

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Introduction

Amyloidosis represents a heterogeneous group of disorders characterized by the local or generalized extracellular deposition of fibrillar proteins in various tissues or organs (1-3). Bleeding complications, including coagulation factor deficiency, is frequently encountered in amyloidosis; in particular, acquired deficiency of factor X is the most common coagulation factor deficiency among patients with immunoglobulin light chain (AL) amyloidosis (4-7). We herein describe an atypical case of AL-amyloidosis that presented as severe nephrotic syndrome associated with diarrhea 8 months after the initial bleeding complications due to an acquired factor X deficiency.

Case Report

A 77-year-old woman was referred for the hematological evaluation of a prolongation of both the prothrombin time (PT) and partial thromboplastin time (PTT) in July 2012. Although the patient complained of gastrointestinal bleeding, no obvious cardiac, renal, hepatic, or neurological symptoms were observed at the time. The patient had a long history of erythema nodosum induced by colchicine treatment, but her symptoms had been well controlled over the preceding two years. She did not have a history of either antplatelet or anticoagulant therapy, and there was no family history of abnormal bleeding. The laboratory findings demonstrated a white blood cell count of 4,500/\mu{}L, a red blood cell count of 389\times{}10\textsuperscript{4}/\mu{}L, a hemoglobin level of 10.2 g/dL, and a platelet count of 19.1\times{}10\textsuperscript{4}/\mu{}L. Her total protein was 7.2 g/dL, her albumin level was 4.2 g/dL, and liver function...
The patient underwent a detailed examination, including a physical exam, mammography, gastrofiberscopy, colonoscopic screening, whole-body computed tomography (CT) scanning, and bone marrow aspiration. Bone marrow plasma cells accounted for 10% of the specimen (Fig. 2A) with immunohistochemical staining for IgA-λ (data not shown). A Hematoxylin and Eosin staining section contained multiple foci of homogenous eosinophilic deposits in the interstitium, which were positive for Congo red and direct fast scarlet (DFS) (Fig. 2B), but red-to-green dichroism under polarized light was not observed. Immunohistochemistry demonstrated nonspecific staining of the deposits for both immunoglobulin light chains κ and λ. These deposits were positive for CD138 (data not shown) but negative for β2-microglobulin and amyloid A antibody (data not shown). Moreover, electron microscopy of tissue from a paraffin-embedded block revealed the ultrastructural appearance of randomly arranged fibrils 11-17-nm in external diameter (Fig. 2C). These pathological features did not definitively establish a diagnosis of AL-amyloidosis. Therefore, the initial diagnostic assessments could not completely exclude the possibility of monoclonal gammopathy, so we did not reduce the light chain production by chemotherapy or immunosuppressive agents. The patient was given fresh frozen plasma (FFP) or substitution of the prothrombin complex concentrate (PCC, PPSB® Nihon Pharmaceutical, Tokyo, Japan), which slightly improved her bleeding symptoms but did not improve her laboratory abnormalities, such as the factor X activity, PT, or aPTT. The patient also repeatedly developed painful intra-articular bleeding (Fig. 3).

Eight months later, the patient suddenly presented with nephrotic syndrome (proteinuria up to 9 g/day) and severe diarrhea. Because other causes of proteinuria, such as diabetes mellitus, uncontrolled hypertension, or autoimmunity, were excluded, a second diagnostic evaluation for potential amyloidosis was performed. A rectal mucosal biopsy re-
Figure 2. Photomicrographs of the bone marrow. A: Bone marrow deposition of hyaline material. Bone marrow plasma cell infiltration comprised 10% of the specimen (Hematoxylin and Eosin staining, ×200). B: The deposited hyaline material was weakly positive (DFS stain, ×200). C: Electron microscopy revealed that the hyaline material consisted of randomly dispersed, nonbranching, 11-17-nm-diameter fibrils of varying lengths.

A

B

C

revealed essentially the same pathological features observed in the bone marrow (Fig. 4). The patient’s condition progressively deteriorated with severe watery diarrhea, and she died 10 months after the initial diagnosis of acquired factor X deficiency. We assessed the factor X activity at the time of admission and both five and seven months later, but it remained unchanged (<0.3%).

Discussion

According to recent reviews, acquired factor X deficiency is the most common coagulation factor deficiency in patients with AL-amyloidosis, occurring in from 8.7% to 14% of patients (4-7). Because factor X deficiency in amyloidosis has only been observed in AL-amyloidosis, it is assumed that factor X binds with high affinity to the highly organized β-pleated fibrillar structures that are characteristic of AL-amyloidosis (4). However, it is still unclear by what mechanism factor X interacts with amyloid and why some patients with AL-amyloidosis develop a deficiency while others do not (8). In a series of 32 cases of acquired factor deficiency due to AL-amyloidosis, Choufani et al. found that significant bleeding events occurred in 18 patients (56%). Nephrotic syndrome and liver dysfunction were observed in 11 patients (34%) and 14 patients (44%), respectively (6). The authors suggested that insufficient hepatic synthesis or urinary protein loss due to nephrotic syndrome was not the cause of the factor X deficiency.

Several clinical and pathological aspects appear to be unique to the present case compared with previously reported cases of acquired factor X deficiency due to AL-amyloidosis. First, our patient initially developed subcutaneous and gastrointestinal bleeding as a result of a significant decrease in factor X activity (<0.3%), but neither proteinuria nor diarrhea was observed as an initial manifestation of AL-amyloidosis. However, nine months later, nephrotic syndrome (with proteinuria up to 9 g/day) and severe diarrhea suddenly occurred and thereafter progressed rapidly. Although renal involvement is observed in two-thirds of all patients with AL-amyloidosis at the time of diagnosis, it seldom appears during the follow-up duration if renal manifestations are absent at the onset of AL-amyloidosis (9). Second, amyloidosis is diagnosed by tissue biopsy staining with Congo red, which produces pathognomonic apple green birefringence under polarized light. All types of amyloidosis, regardless of precursor proteins, self-assemble into characteristic β-pleated secondary structure that are deposited and appear on electron microscopy as 8- to 11-nm linear nonbranching fibrils (9). Although we identified several atypical pathological features that were characteristic of AL-amyloidosis, DFS-positive deposits failed to produce red-to-green dichroism under polarized light, and they were negative for β2-microglobulin and amyloid A. However, electron microscopy displayed the typical ultrastructural appearance.
of randomly arranged fibrils 11-17 nm in external diameter. Considering the electron microscopic findings of the bone marrow and intestine, it would be very hard to make any diagnosis other than that of amyloidosis. The clinical features together with the atypical histological findings suggested that our patient should be classified as an atypical case of AL-amyloidosis, although we could not reach this conclusion during the early clinical course. In addition to a significant reduction of factor X activity (<0.3%), our patient showed a moderately decreased factor IX activity (32%), factor XI activity (55%) and factor XII activity (46%). As multiple factors deficiencies, including factors II, VII, VIII, IX, X, XI and XII, have been previously reported (6, 7, 10), we assumed that the combined deficiencies of factor IX, X, XI, and XII observed in our case were most likely due to selective uptake by vascular amyloid deposits rather than due to insufficient hepatic synthesis, increased fibrinolysis, abnormal circulating coagulation factor inhibitors, or inherited coagulation factors deficiencies. Amyloid fibrils could also lead to a greatly reduced circulating half-life of factor X (5, 6, 11). While the patient had a severe factor X deficiency associated with spontaneous subcutaneous and gas-

**Figure 3.** Clinical course of the patient, including serial changes of serum albumin. Abbreviations: FFP: fresh frozen plasma, PCC: prothrombin complex concentrate (PCC, PPSB®), BMA: bone marrow aspiration, FPB: abdominal fat pad biopsy

**Figure 4.** Colon photomicrographs. A: Deposition of hyaline material in the colon (Hematoxylin and Eosin staining, ×200). B: The deposited hyaline material exhibited slight DFS-positivity (DFS stain, ×200). The findings are similar to those seen in the patient’s bone marrow.
trointestinal bleeding, bleeding complications are relatively infrequent in systemic AL-amyloidosis with acquired factor X deficiency, and the baseline factor X level is not predictive of bleeding risk (10). Systemic AL-amyloidosis patients might have other predispositions to bleeding that are not easily quantified, but our patient did not have thrombocytopenia, platelet dysfunction associated with renal insufficiency, hyperfibrinolysis, vitamin K deficiency due to malabsorption, or a defective hepatic synthetic function at onset. Amyloid deposition in the vessel wall may result in vascular friability that might also contribute to bleeding. Therefore, patients with factor X deficiency due to AL amyloidosis are not similar to congenital hemophilia patients, where the degree of factor deficiency is the major predictor of bleeding complications. The differences in bleeding tendency among congenital factor X deficiency patients and typical and atypical systemic AL-amyloidosis-associated patients with similar levels of factor X are not yet clear. It is also difficult to analyze them because AL-amyloidosis bleeding is multifactorial, and factor X may be normally synthesized in liver but have a reduced circulatory half-life. Consistent with a previous report, the present patient’s factor X levels did not normalize after the administration of FFP or PPSB. Therefore, our case reflects the wide variability of clotting factor deficiencies, and it is tempting to speculate that atypical AL-amyloidosis might be related to its unique clinical behavior, including combined deficiencies of clotting factors.

In summary, this single case of acquired factor X deficiency associated with atypical amyloidosis suggests that a larger study involving a larger series of patients is needed. The present case also emphasizes the need for clinical awareness when bleeding complications occur in patients, especially in those with atypical features of amyloidosis.

The authors state that they have no Conflict of Interest (COI).

References


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