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【 CASE REPORT 】

Immunoglobulin Light Chain Amyloidosis with Severe Liver Dysfunction Accompanied by Factor X Deficiency

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Abstract:
Severe hepatic failure is rarely a cause of death in patients with immunoglobulin light chain (AL) amyloidosis. We herein report a case of AL amyloidosis involving a bleeding tendency due to factor X deficiency and marked hepatic involvement of amyloidosis. The patient died due to severe liver dysfunction two weeks after admission. The diagnosis was confirmed histologically by AL-λ amyloidosis, with the liver and spleen as the main lesions, on an autopsy. As treatment-related toxicity is strong in advanced cases, appropriate treatments are required to improve the prognosis of AL amyloidosis with severe liver dysfunction.

Key words: AL amyloidosis, hepatic amyloidosis, liver dysfunction, bleeding tendency, factor X

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Introduction

Immunoglobulin light chain (AL) amyloidosis is a multisystemic disorder caused by a malignant B cell clone that results in an insoluble fibrillary deposition. Hepatic deposition of AL amyloid is common; however, it is usually clinically silent, and the liver is rarely the dominant affected organ. The most frequent finding is increased levels of alkaline phosphatase and gamma-glutamyl transferase in patients with hepatic deposition of AL amyloid (1, 2). In addition, abnormal bleeding is frequently encountered in patients with AL amyloidosis. Deficiencies in coagulation factors in AL amyloidosis have been reported in factors II, V, VII, IX, and X (3-5). Acquired factor X (FX) deficiency due to AL amyloidosis is observed most frequently in clinical practice, accounting for about 6.3% to 14% of all cases of AL amyloidosis (6, 7). However, AL amyloidosis with severe liver dysfunction accompanied by a spontaneous bleeding tendency due to FX deficiency is very rare, and there has been only one histological case report of direct FX deposition onto amyloid (8).

We herein report a case of liver failure accompanied by retroperitoneal hematoma due to FX deficiency. The patient was diagnosed with AL amyloidosis on an autopsy, and the direct deposition of FX onto amyloid was histologically confirmed.

Case Report

A 72-year-old woman who presented with hematuria, subcutaneous bleeding, and intraoral bleeding was referred to our hospital.

Her laboratory data as an outpatient (day X-7 weeks) and after admission (day X+4) are shown in Table. Her total bilirubin and alkaline phosphatase levels were markedly increased at seven weeks. Her prothrombin time (PT) and activated partial thromboplastin time (APTT) had also doubled. The levels of coagulation factors, such as factor II, V, and von Willebrand factor, were within normal ranges except for the FX level, which was severely decreased (6%, normal > 70%), along with a slight decrease in factor IX (42%). The

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Table. Laboratory Data.

Parameter	Outpatient (Day X-7weeks)	Admission (Day X+4)	Normal range
Blood count			
White blood cells	4,500	6,300	3,300-8,600 /μL
Red blood cells	330×10^4	246×10^4	$386\text{-}492\times10^4$ /μL
Reticulocyte	24.8	48.6	7-25‰
Hemoglobin	9.9	7.4	11.6-14.8 g/dL
Hematocrit	30.2	21.9	35.1-44.4 %
Platelet	249×10^3	198×10^3	$158\text{-}348\times10^3$ /μL
Urine			
Protein	(+)	(±)	(-)
Occult blood	(3+)	(-)	(-)
Bence-Jones protein	(-)	ND	(-)
Blood chemistry			
Total bilirubin	0.9	12.3	0.4-1.5 mg/dL
Indirect bilirubin	ND	8	0.1-0.3 mg/dL
Aspartate aminotransferase	81	94	13-30 IU/L
Alanine aminotransferase	32	23	7-23 IU/L
Lactate dehydrogenase	201	266	124-222 IU/L
γ-glutamyl transpeptidase	213	191	9-32 IU/L
Alkaline phosphatase	1,576	2,926	106-322 IU/L
Total protein	7.3	6	6.6-8.1 g/dL
Albumin	3.6	2.6	4.1-5.1 g/dL
CHE	206	161	201-421 U/L
NH3	ND	103	12-66 μg/dL
Blood urea nitrogen	15.2	21.4	8-20 mg/dL
Creatinine	0.33	0.39	0.46-0.79 mg/dL
Sodium	140	135	138-145 mEq/L
Potassium	4	4.6	3.6-4.8 mEq/L
Chloride	100	101	101-108 mEq/L
Fe	48	30	40-188 μg/dL
Ferritin	343	152	12-60 ng/dL
C-reactive protein	0.57	0.16	<0.14 mg/dL
BNP	211.4	255.1	0-18.4 pg/mL
IgG	2,089	2,248	861-1,747 mg/dL
IgA	71	85	93-393 mg/dL
IgM	48	62	50-269 mg/dL
IgG-λ M-protein	(+)	NA	(-)
free light κ chain	7.9	NA	3.3-19.4 mg/L
free light λ chain	490	NA	5.7-26.3 mg/L
κ/λ ratio	0.02	NA	0.26-1.65
Coagulation test			
Activated partial thromboplastin time	44.8	89.4	24-39 sec
Prothrombin time	28.4	60.9	9-12.5 sec
Prothrombin time-international normalized ratio	2.51	5.43	0.9-1.2
Fibrinogen	284	62.4	160-360 mg/dL
Fibrinogen degradation product	6.8	5.1	0-10 μg/mL
Factor II activity	83	NA	75-135 %
Factor V activity	75	NA	70-135 %
Factor VII activity	63	NA	75-140 %
Factor VIII activity	>200	NA	60-150 %
Factor IX activity	42	NA	70-130 %
Factor X activity	6	5	70-130 %
von Willebrand factor activity	68	NA	60-170 %

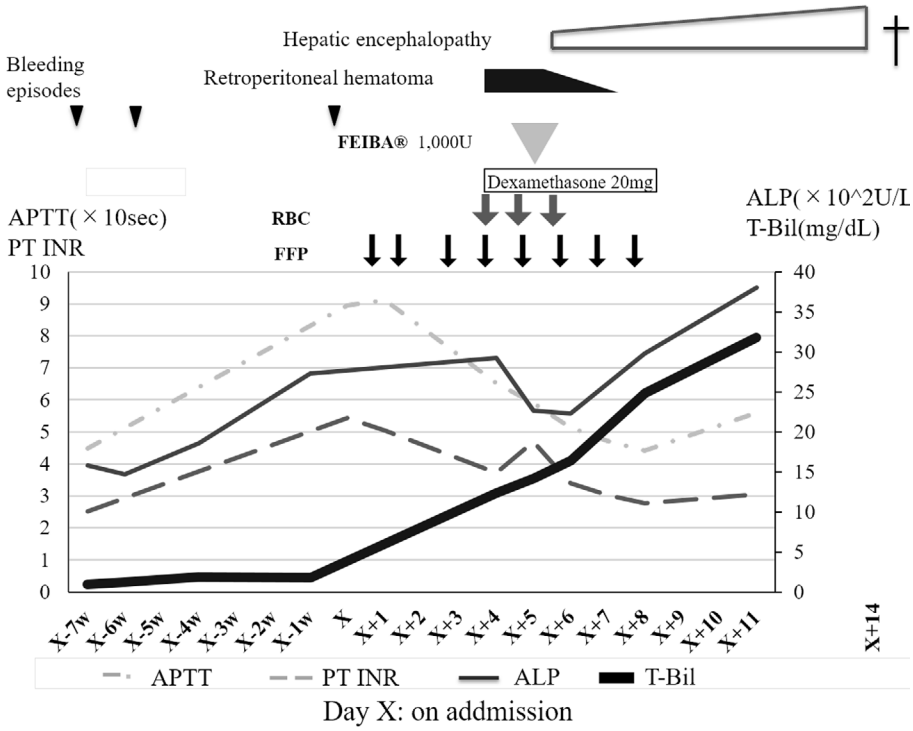

Figure 1. **The clinical course of the patient with AL amyloidosis accompanied by FX deficiency. Day X is the day of hospitalization. AL: immunoglobulin light chain, FX: factor X, FEIBA®: activated prothrombin complex concentrate**

PT and APTT mixing test showed a coagulation factor deficiency pattern. The serum immunoglobulin levels of IgG, IgA, IgM were 2,089, 71, 48 mg/dL, respectively, and serum immunoelectrophoresis demonstrated an IgG- λ monoclonal peak. A serum-free light chain assay demonstrated an increase in λ light chain (490 mg/L), with a κ/λ free light chain ratio of 0.02. Urine immunoelectrophoresis was negative for M protein. A bone marrow smear showed that 2.6% of plasma cells were positive for λ chain, cluster of differentiation (CD)138, and CD54 but negative for CD56. Amyloid deposition was not detected in bone marrow specimens.

Computed tomography revealed diffuse hepatomegaly, retroperitoneal hematoma, and mild pleural effusion and ascites. An obvious exacerbation of hepatomegaly was also confirmed at nine weeks. An echocardiogram showed an ejection fraction of 64.2% with diffuse left ventricular hypertrophy. Based on these findings and the lack of any personal or family history of bleeding, the patient was clinically diagnosed with hepatic amyloidosis with acquired FX deficiency.

Her treatment was initiated with fresh-frozen plasma (FFP) infusion and vitamin K2 administration, and the prothrombin time-international normalized ratio (PT-INR)/APTT improved to 3.73/65.2 seconds on Day X+4. However, retroperitoneal hematoma appeared, and hemoglobin levels decreased from 12.0 g/dL to 6.1 g/dL. After accounting for the off-label activated prothrombin complex concentrate (FEIBA®) prescription and school expenses, she received continued FFP infusion and a single dose of FEIBA® (1,000 U). Although the FX activity was not examined after FEIBA® administration, the active bleeding stopped, hemoglobin improved to 11.8 g/dL, and the PT-INR/APTT improved to 2.76/44.1 seconds on Day X+8. Unfortunately, her clinical condition continued to worsen with bilirubin elevation and hepatic encephalopathy. Her condition ultimately deteriorated with pulmonary edema and atelectasis, and she died two weeks after her admission. The clinical course after the onset is shown in Fig. 1.

On an autopsy, amyloid depositions were detected in the systemic organs, including the liver, spleen, heart, lungs, kidneys, adrenal glands, and gastrointestinal mucosa as well as around the blood vessels, with Congo red or direct fast scarlet (DFS) staining. Among the organs, hepato-splenic amyloid deposition was particularly marked (Fig. 2A-E, G-H). Likewise, FX deposition was also observed in the liver and spleen, where amyloid was co-stained with anti-FX antibody (Fig. 2F and I). The autopsy-based diagnosis in this case was AL-λ amyloidosis.

Discussion

AL amyloidosis is the most common form of systemic amyloidosis and results in the extracellular deposition of monoclonal light chain. AL amyloidosis can occur alone or in association with multiple myeloma (10-15%) (9) or, much less often, Waldenstrom macroglobulinemia or non-Hodgkin's lymphoma. As the rate of liver involvement in AL amyloidosis has been reported to be 9.6% (10),

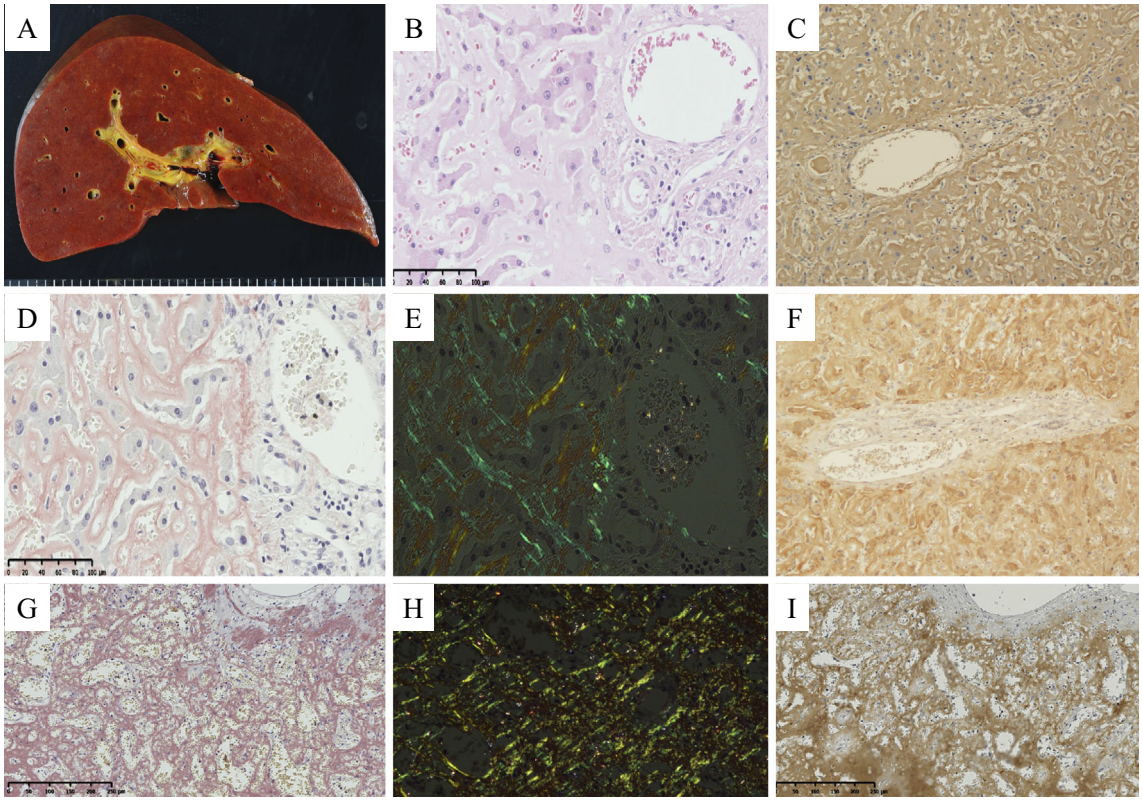

Figure 2. **Autopsy findings of the liver and spleen. A) The enlarged and icteric liver (1,635 g) with a firm and waxy cut surface. B) Sinusoidal deposition of amyloid with compression atrophy of liver cell plates (HE staining). C) Positive staining of amyloid λ corresponding to sinusoidal deposition of amyloid (anti-amyloid λ immunohistochemistry). D, G) Positive DFS staining of sinusoidal amyloid deposition in the liver (D) and spleen (G). E, H) An apple-green birefringence under polarized light examination of the DFS-stained section of the liver (E) and spleen (H). F, I) Positive staining of factor X, which indicates the coexistence of factor X with amyloid in the liver (F) and spleen (I) (anti-factor X immunohistochemistry). HE: Hematoxylin and Eosin, DFS: direct fast scarlet**

30% (2), 49% (7), or 70% (11), hepatic deposition seems quite common, with the next most frequently affected organs being the kidneys and heart. However, liver enzyme tests are usually normal or mildly elevated in patients with hepatic amyloidosis. An elevated concentration of alkaline phosphatase (86%) is the most frequent finding (1, 2, 12). Although jaundice is detected in 21% of patients with AL hepatic amyloidosis (12), most such patients present with nonspecific symptoms, such as involuntary weight loss, fatigue, abdominal pain, edema, and anorexia. The early diagnosis of AL hepatic amyloidosis is difficult.

Hemorrhaging is a frequent manifestation of amyloidosis. Abnormal bleeding is detected in 28% of cases, and abnormal coagulation is noted in 51% (7). FX deficiency causes the most frequent bleeding manifestations and is the most clinically significant. The mechanism underlying FX deficiency accompanied by AL amyloidosis is still not completely understood. Tashiro et al. reported that FX directly deposits on amyloid (8). Similarly, in this case, FX existed in union with amyloid in the liver and spleen. Although severe liver dysfunction may cause FX deficiency due to a synthetic defect, the direct binding/absorption of FX onto amyloid fibrils is considered to be a major mechanism of FX deficiency, a hypothesis supported by the pathological findings from the present case.

The prognosis of AL hepatic amyloidosis is generally very poor, and the median survival of patients with AL hepatic amyloidosis is 8.5 months. Furthermore, the median survival of patients with concentrations of bilirubin >34 μmol/L is only 1 month. Recently, the successful treatment of AL amyloidosis with high-dose melphalan, followed by autologous stem cell transplantation (HDM/SCT), bortezomib, or lenalidomide-based chemotherapy, has been reported (13, 14). A patient with hepatic involvement and FX deficiency was reported to have survived for more than three years after undergoing HDM/SCT (15). However, the eligibility criteria for hematopoietic stem cell transplantation (HSCT) for AL amyloidosis are generally stricter than those for such treatment for multiple myeloma because of organ dysfunction, especially of the heart and kidneys, and the high therapy-related mortality (TRM). At the Mayo Clinic, to be considered transplant-eligible, the following criteria must be met: "physiologic" age ≤70 years old; performance score ≤2; troponin T <0.06 ng/mL; creatinine clearance ≥30 mL/min; New York Heart Association class I/II; and no more than two major organs can be significantly involved

(liver, heart, kidneys, or autonomic nerves) (16). However, another study found that, in 69 patients with AL amyloidosis, hepatic involvement, and concentrations of bilirubin <34 μmol/L who had received HDM/SCT, hepatic involvement did not lead to an increase in the TRM, which was 13%, and the overall survival at 5 years was 61% (17). In our patient, the cardiac and renal functions were maintained, despite infiltration in the heart and kidneys. However, unfortunately, the progression of liver dysfunction could not be prevented with high-dose dexamethasone. Successful treatment by HDM/SCT after liver transplantation was reported in a 54-year-old patient whose bilirubin level (up to 710 μmol/L) had rapidly increased and hepatic failure and hepatic encephalopathy had progressed, as observed in our case. He was in stable remission three years after undergoing liver transplantation (18). These findings suggest that the early initiation of therapy is crucial for improving the prognosis, and HDM/HCT after liver transplantation may be the best life-saving option in cases of acute hepatic failure progression, as in the present case.

In summary, we encountered a case of AL hepatic amyloidosis accompanied by FX deficiency. Although FFP infusion and FEIBA® stopped the active bleeding, we were unable to control the severe liver dysfunction. As AL hepatic amyloidosis often undergoes rapid exacerbation, advanced-stage patients might lose the chance to receive HSCT because of worsening hepatic dysfunction. Supportive care against hepatic dysfunction, including liver transplantation, as well as intensive chemotherapy may improve the prognosis.

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

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