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

(Intern Med Advance Publication)
(DOI: 10.2169/internalmedicine.2864-19)

Introduction

Immunoglobulin light chain (AL) amyloidosis is a multisystemic disorder caused by a malignant B cell clone that results in an insoluble fibrillar 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%).
### Laboratory Data.

| Parameter                        | outpatient (Day X-7 weeks) | admission (Day X+4) | Normal range          |
|----------------------------------|----------------------------|---------------------|-----------------------|
| **Blood count**                  |                            |                     |                       |
| White blood cells                | 4,500                      | 6,300               | 3,300-8,600 /μL       |
| Red blood cells                  | 330x10⁴                    | 246x10⁴             | 386-492x10⁴ /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                         | 249x10³                    | 198x10³             | 158-348x10³ /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-κ 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                  | 70-130 %              |
| Factor V activity                | 75                         | NA                  | 70-130 %              |
| Factor VII activity              | 63                         | NA                  | 70-130 %              |
| Factor VIII activity             | >200                       | NA                  | 70-130 %              |
| Factor IX activity               | 42                         | NA                  | 70-130 %              |
| Factor X activity                | 6                          | 5                   | 70-130 %              |
| von Willebrand factor activity   | 68                         | NA                  | 0.00 %                |
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 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), 30% (2), 49% (7), or 70% (11), hepatic deposition seems
FX deficiency, a hypothesis supported by the pathological synthetic defect, the direct binding/absorption of FX onto vere liver dysfunction may cause FX deficiency due to a in union with amyloid in the liver and spleen. Although se deposits on amyloid (8). Similarly, in this case, FX existed deficiency accompanied by AL amyloidosis is still not com clinically significant. The mechanism underlying FX deficie the most frequent bleeding manifestations and is the most mal coagulation is noted in 51% (7). FX deficiency causes Abnormal bleeding is detected in 28% of cases, and abnorm 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).

Acknowledgement

We would like to thank Professor Hironobu Naiki (University of Fukui) for performing the anti-light chain constant lesion staining.

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