Systemic AL amyloidosis presenting as progressive hepatic failure with coagulopathy: An autopsy case report

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ABSTRACT

Introduction: Systemic AL amyloidosis is defined as extracellular deposition of insoluble immunoglobulin light chains, amyloid fibril protein AL, in at least one vital organ. Here we report a case of systemic AL amyloidosis presenting as progressive hepatic failure with coagulopathy. Case Report: The patient was a 62-year-old African American female first admitted to our hospital due to jaundice, easy bruising, fatigue, and weight loss for three months. There were mild abnormal liver function tests with coagulopathy, polyclonal gammopathy, and mild hepatomegaly by imaging. She was discharged after correction of coagulopathy. She presented with altered mental status one month later. Lab results showed similar abnormal liver function tests and hepatomegaly but with severe coagulopathy. The patient was found to have oozing blood, severe hypoxia, and expired the next day. A complete autopsy revealed systemic amyloidosis microscopically, and confirmed by Congo red stain. The liver demonstrated the most extensive deposition of amyloid. Liquid chromatography tandem mass spectrometry revealed AL (kappa)-type amyloid deposition. Bone marrow showed kappa light chain predominance. Conclusion: Systemic amyloidosis presenting as progressive hepatic failure is very rare. Amyloidosis with liver involvement is one of the important differential diagnoses even when patients present with mild liver dysfunction (especially elevated alkaline phosphatase and gamma-glutamyl transerase) and coagulopathy.

Keywords: Coagulopathy, Hepatic failure, Systemic AL amyloidosis

INTRODUCTION

Systemic AL amyloidosis is defined as extracellular deposition of insoluble immunoglobulin light chains, amyloid fibril protein AL, in at least one vital organ [1]. Systemic AL amyloidosis with liver involvement often has subtle hepatic dysfunction. Here we report a very rare case of systemic AL amyloidosis presenting as progressive hepatic failure with coagulopathy.

CASE REPORT

The patient was a 62-year-old African American female with past medical history of asthma and hypertension. She presented at the emergency room with complaints of jaundice, easy bruising, fatigue, and weight loss of three months. She was alert, and her vital signs were within normal limits on admission. Lab results showed leukocytosis, normocytic anemia, thrombocytopenia, hypoalbuminemia, and mild coagulopathy with prolonged prothrombin time/international normalized ratio (PT/INR), D-dimer >20 ug/mL, fibrinogen equivalent units (FEU), mildly elevated gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and total/direct bilirubin (Table 1). Hepatitis B and C viral serology analysis and liver autoantibody testing were negative. Abdominal ultrasound and computed tomography (CT) revealed mild hepatomegaly (Figure 1) and with no
A focal lesion. Serum protein electrophoresis (SPEP) was polyclonal gammopathy. Renal function was normal with normal creatinine and urine protein was negative (Table 1). She was discharged after the correction of coagulopathy with vitamin K and transfusion. One month later, she presented at the emergency room again with altered mental status and significant abdominal distension after an episode of syncope at home. Her serum ammonia was elevated at 91 umol/L (reference range: 11–32 umol/L). CT imaging showed similar mild hepatomegaly. Renal function was abnormal with slightly increased creatinine and urine protein was not checked (Table 1). She had profound anemia, hypoalbuminemia and severe coagulopathy with PT > 100 sec, partial thromboplastin time (PTT) > 150 sec, and platelet of 47 K/uL (Table 1). She was found to have oozing blood from her intravenous therapy sites, worsening hypoxia and developed cardiac arrest. Advance cardiac resuscitation was initiated. However, she continued to deteriorate and expired the next day after admission.

A complete autopsy was performed. Main gross findings included a large amount of ascetic bloody fluid (3000 mL), hepatomegaly (2450 g, normal: 1400–1600 g), splenomegaly (220.1 g, normal: 125–195 g). The ascending colon showed focal mucosal hemorrhage and the mesentery had multiple large hematomas. Microscopically, there were multiple organs with extracellular amorphous and eosinophilic material deposition. Amyloid deposition was confirmed by positive Congo red special stain by showing apple-green birefringence under polarized light. The organs with amyloid deposition included: liver, kidneys, spleen,

| Test name       | Reference range | First admission | Second admission |
|-----------------|-----------------|-----------------|------------------|
| Hematologic value |                 |                 |                  |
| WBC             | 4.5–11.0 K/uL   | 17.1            | 21.3             |
| RBC             | 4.2–5.4 M/uL    | 3.41            | 1.90             |
| Hemoglobin      | 12.0–16.0 g/dL  | 10.6            | 6.0              |
| Platelet        | 150–400 K/uL    | 126             | 47               |
| Coagulation     |                 |                 |                  |
| PT              | 11.8–15.0 sec   | 19.6            | >100             |
| INR             | 1.7             |                 | PT not clotted, unable to calculate INR |
| PTT             | 23.6–36.4 sec   | 30.1            | >150             |
| D-dimer         | ug/mL, FEU      | >20             | N/A              |
| Fibrinogen      | 200–500 mg/dL   | 108             | <15              |
| Electrophoresis |                 |                 |                  |
| Protein         | g/L             | 7.3 (increased polyclonal gamma globulins) |                  |
| Liver function  |                 |                 |                  |
| ALT             | 12–78 u/L       | 19              | 14               |
| AST             | 15–37 u/L       | 44              | 48               |
| ALP             | 45–117 u/L      | 231             | 184              |
| GGT             | 15–85 u/L       | 336             | 313              |
| Total bilirubin | 0.2–1.0 mg/dL   | 4.1             | 5.3              |
| Direct bilirubin| 0.0–0.2 mg/dL   | 2.8             | 3.4              |
| Albumin         | 3.4–5.0 g/dL    | 3.0             | 2.3              |
| Renal function  |                 |                 |                  |
| BUN             | 7–18 mg/dL      | 11              | 10               |
| Creatinine      | 0.6–1.3 mg/dL   | 0.8             | 1.6              |
| GFR             | >60 mL/min/1.73 m² | >60           | 33               |
| eGFR            | >60 mL/min/1.73 m² | >60           | 50               |
| Urine protein   | Negative        | Negative        | N/A              |

WBC: white blood cells; FEU: fibrinogen equivalent units; RBC: red blood cells; PT: prothrombin time; INR: international normalized ratio; PPT: partial thromboplastin time; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; BUN: blood urea nitrogen; GFR: glomerular filtration rate; eGFR: estimated glomerular filtration rate.
thyroid, bone marrow, adrenal glands, mesentery, and pancreas. There was no amyloid deposition in heart or brain. Among the organs with amyloidosis, the liver demonstrated the most extensive involvement. The normal liver architecture was distorted with markedly compressed hepatic plates by sinusoidal amyloid deposition (Figure 2). The pattern of sinusoidal deposition was resulting cholestasis and portal hypertension, which caused jaundice and ascites, respectively. Liver tissue block was sent to Mayo Clinic for liquid chromatography tandem mass spectrometry (LC-MS/MS) for amyloid typing. AL (kappa)-type amyloid deposition was detected. The bone marrow had approximately 5% of plasma cells highlighted by CD138 immunostain. Kappa and lambda in situ hybridization (ISH) was performed and showed predominant kappa expression in bone marrow. In summary, this patient had systemic AL amyloidosis causing severe progressive hepatic failure with coagulopathy due to underlying plasma cell dyscrasia in bone marrow, which was diagnosed by postmortem examination.

**DISCUSSION**

Systemic AL amyloidosis is uncommon and results in extracellular deposition of insoluble immunoglobulin light chains, amyloid fibril protein AL, in many different organs [1]. It is caused by misfolded immunoglobulin light chains produced by a clonal population of abnormal plasma cells in diseases such as multiple myeloma and other immunocyte dyscrasias [2]. The incidence has decreased in proportion with each decade from 77% to 69% to 50% [3]. The incidence increased with age with the median age at the diagnosis of 63 years [4]. The disease usually can affect any organ systems and heart involvement is the leading cause of morbidity and mortality [5]. The liver is the third most frequently affected organ after the heart and kidneys in systemic AL amyloidosis [6]. Liver involvement may also be seen in amyloid-associated (AA) amyloidosis, and very rarely familial transthyretin (ATTR) amyloidosis [7]. Hepatic dysfunction is usually clinically silent with normal or mildly abnormal liver function tests [8]. A few cases of acute or subacute hepatic failure have previously been reported in AL amyloidosis with multiple myeloma [8–17].

Systemic AL amyloidosis with an undetectable plasma cell dyscrasia is extremely rare [18]. Our patient’s clinical manifestation is similar to a reported case of AL amyloidosis with fulminant hepatic failure without detectable underlying plasma cell dyscrasias [19]. The clinical features shared are: both patients presenting with jaundice and large amount of ascites with no prior history of liver disease, rapid deterioration of liver function with elevated ALP and GGT (marked increased in the reported patient, but mildly elevated in our patient), imaging showing hepatomegaly with the liver measured 16.6 cm in craniocaudal span by computed tomography (CT) (our patient with the measurement of 16.4 cm), and SPEP negative for monoclonal gammapathy. Additional findings of lab tests of these two patients are: the reported patient with markedly elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT), our patient with mildly elevated AST, normal ALT, and significantly elevated PT/PPT. Liver biopsy in the reported patient has demonstrated amyloidosis with extensive liver involvement/sinusoidal amyloid deposition which is similar to the liver findings of our patient on autopsy. The clinical features of both cases can be used for early recognition of hepatic amyloidosis and tissue biopsy for confirmation is necessary especially in patients without known underlying disease.

Coagulopathy is a known manifestation in patients with AL amyloidosis with hepatic involvement. Vitamin K administration has effectively corrected our patient’s mild coagulopathy with prolonged PT (at first hospital admission) although no vitamin K level checked. The vitamin K deficiency may be caused by absorption defects due to the patient’s hepatic cholestasis. Studies
have showed that AL amyloidosis associated factor X deficiency found in patients with liver dysfunction due to marked hepatic involvement of amyloidosis [20, 21]. Rarely, coagulopathy has been reported in patients with AL amyloidosis without hepatic involvement [22]. These patients have acquired loss of functional von Willebrand factor (VWF), and develop acquired von Willebrand syndrome (AVWS) with adult-onset bleeding diathesis, clinically similar to congenital von Willebrand disease (VWD) [22]. Tests for the levels of factor X and VWF have not been performed in our patient, and are important to consider for testing in patients with progressive hepatic disease with coagulopathy.

Work-up for progressive hepatic failure with coagulopathy of unknown etiology can be challenging in clinical practice. Multidisciplinary approaches including serology tests, imaging, and histology examination may be applied together for reaching an early diagnosis, which is essential for patient’s treatment and prognosis. It has been noticed that the most frequent finding in patients with liver involved systemic AL amyloidosis is increased levels of ALP and GGT [23]. Systemic AL amyloidosis with liver involvement should be excluded when patients present with etiology-unknown liver decompensation especially with elevated ALP and GGT, and hepatomegaly with no focal lesion. Liquid chromatography and tandem mass spectrometry can help typing the AL amyloid on biopsy specimen, which is the gold standard for diagnosis. Protein electrophoresis (SPEP) alone is not sufficient for the measurement of monoclonal gammopathy in systemic AL amyloidosis. Plasma cell dyscrasia in AL amyloidosis is usually subtle. Serum/urine immunofixation electrophoresis (IFE) and serum free light chain (sFLC) should be performed as a combination of tests [18, 24]. In our patient, the underlying plasma cell dyscrasia is identified by postmortem bone marrow examination. In systemic AL amyloidosis the plasma cell burden may be still within normal range or slightly increased (5–10%) [24], and light chain predominance can be demonstrated by kappa and lambda ISH as that seen in our case. Early diagnosis of systemic AL amyloidosis by appropriate testing is vital for patient’s prognosis.

Systemic AL amyloidosis can be treated effectively at early stage with significant improvement of median survival [25]. The aim of therapy is rapid elimination of the amyloid precursors by suppression of the synthesis of the extracellular deposits. Treatment strategies including new types of drugs, such as proteasome inhibitors and immunomodulators, along with chemotherapy and stem cell transplantation can effectively suppress the production of amyloid light chain [26]. It has been reported patients with kappa AL amyloidosis with more liver involvement (lambda 7% vs kappa 18%), and patients with lambda AL amyloidosis with more kidney (lambda 66% vs kappa 57%) and neurological involvement (lambda 16% vs kappa 9%) [27]. The study shows that the light chain type also predicts the survival in patients having stem cell transplant: patients with kappa light chain amyloidosis with better progression-free and overall survival, while the two groups of patients with the same complete response rate (43%) and similar overall response rates (lambda 85% vs kappa 91%) [27]. Liver transplant combined with chemotherapy has been investigated as a successful strategy for certain AL amyloidosis patients with liver failure [28]. The current challenge is to diagnose of amyloidosis in the early stage and provide the rapid and effective treatment to the patients with severe organ damages.

CONCLUSION

Systemic AL amyloidosis with progressive hepatic failure with coagulopathy is very rare. The early presentation may be subtle. The importance of awareness and early recognition of AL amyloidosis with liver involvement should be emphasized. Adequate combination of testing and tissue biopsy with Congo red stain and typing of the precursor proteins by LC-MS/MS can be helpful in making the correct diagnosis.

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