Systemic Amyloidosis Manifesting as a Rare Cause of Hepatic Failure

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In 1854, the term "amyloid" was first used in the description of a liver specimen at autopsy by Virchow. The kidneys and heart are the most commonly involved organs in amyloidosis; liver and gastrointestinal tract involvement is less common, and the symptoms are usually mild. Here, we report the case of a 57-year-old male patient who presented with oral hemorrhagic bullae, thrombocytopenia and jaundice. Disseminated intravascular coagulation profile was positive. Abdominal sonography showed ascites, and abdominal computed tomography disclosed heterogeneous enhancement of the liver, with focal low attenuation regions and splenomegaly with poor contrast enhancement. Liver decompensation was highly suspected. Diagnostic laparoscopy with liver biopsy and colonoscopic biopsy from the rectum were subsequently performed. Typical apple-green birefringence was demonstrated on polarized light microscopy by Congo red staining. Systemic amyloidosis was diagnosed and colchicine prescribed. However, liver function deteriorated and intermittent gastrointestinal bleeding was found during the patient's hospitalization. The patient died due to uncorrectable coagulopathy and massive gastrointestinal bleeding. The final diagnosis was idiopathic amyloidosis with hepatic failure. Although amyloidosis rarely presents with hepatic failure, it should be considered in patients with signs of liver decompensation. Clinicians should be aware of this rare but potentially lethal presentation and arrange appropriate treatment promptly. [*J Chin Med Assoc* 2010;73(3):161–165]

Key Words: amyloidosis, hepatic failure, jaundice, thrombocytopenia

Introduction

In 1854, the term "amyloid", meaning starch or cellulose, was first used in the description of a liver specimen at autopsy by Virchow.[1] Amyloid deposits can be identified on the basis of their apple-green birefringence under a polarized light microscope after staining with Congo red, as well as the presence of rigid, nonbranching fibrils, 7.5–10 nm in diameter, on electron microscopy.[2] The kidneys and heart are the most commonly involved organs in amyloidosis.[3] Liver and gastrointestinal tract involvement is less common, and the symptoms are usually mild.[3,4] In this article, we present a case of systemic amyloidosis presenting as a rare cause of hepatic failure.

Case Report

A 57-year-old male patient presented at another hospital with a history of duodenal ulcer involving bleeding and oral hemorrhagic bullae in April 2008. Thrombocytopenia and hyperbilirubinemia were diagnosed and persisted for 2 months. He was then admitted to our

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hospital for persistent thrombocytopenia and jaundice in June 2008. Physical examination revealed icteric sclera and hepatosplenomegaly. No hepatic encephalopathy was found. Blood counts were as follows: white blood cell count, 11,600/mm^3 (normal, 4,800–10,800/mm^3); hemoglobin, 11.6 g/dL (normal, 12–16 g/dL); and platelet count, 97,000/mm^3 (normal, 130,000–400,000/mm^3). Serum biochemistry test results were: alanine aminotransferase, 23 IU/L (normal, 0–40 IU/L); alkaline phosphatase, 310 U/L (normal, 10–100 U/L); γ-glutamyltransferase, 139 U/L (normal, 8–61 U/L); albumin, 3.1 g/dL (normal, 3.7–5.3 g/dL); total bilirubin, 3.2 mg/dL (normal, 0.2–1.6 g/dL); and direct bilirubin, 2.0 (normal, 0–0.3 mg/dL). Urine routine results were: protein trace; 0–2 red blood cells/high-powered field; and 0–2 white blood cells/high-powered field. Disseminated intravascular coagulation profile was positive (Table 1). Autoimmune profiles, including antinuclear antibody, antimitochondrial antibody, antismooth muscle antibody and rheumatoid factor, were negative. Hepatitis B and C markers were both negative.

Abdominal sonography showed a moderate amount of ascites and multifocal hypoechoic regions in the enlarged spleen (Figure 1). Heterogeneous enhancement of the liver with focal low attenuation regions and splenomegaly with poor contrast enhancement (Figure 2) were shown on abdominal computed tomography (CT). Magnetic resonance imaging (MRI) revealed relatively high signal intensity on T1-weighted imaging (T1WI), with heterogeneous enhancement of the liver parenchyma and high signal intensity on T1WI, low signal intensity on T2-weighted imaging (T2WI), and poor contrast enhancement of the spleen (Figure 3).

As no definite diagnosis was made, diagnostic laparoscopy with liver biopsy was subsequently performed. The gross appearance of the liver was normal. Microscopically, diffuse amyloid deposition was noted in the sinusoidal spaces (Figure 4A). Typical apple-green birefringence was demonstrated on polarized light microscopy by Congo red staining (Figure 4B). Kappa and Lambda stains were both positive. Portal areas were free of amyloid deposition. There was neither cirrhosis nor malignancy in the liver specimen. In addition, serum electrophoresis and immunoelectrophoresis showed a moderate increase of γ-globulin and mild increase of β-globulin and α2 without monoclonal spike. Colonoscopic biopsy from the rectum also disclosed amyloidosis. Hence, systemic amyloidosis was diagnosed and colchicine prescribed. However, liver function deteriorated and intermittent gastrointestinal bleeding was found during the patient's course of hospitalization. The patient died due to uncorrectable coagulopathy and massive gastrointestinal bleeding in August 2008. The final diagnosis was idiopathic amyloidosis with hepatic failure.

Table 1. Autoimmune profiles and viral hepatitis markers

DIC profile	Data	Normal range
D-dimer (μg/mL)	12.13	< 2.09
FDP (μg/mL)	27.9	< 5.0
INR	1.78	0.85–1.15
APTT (s)	55	23.9–35.5
Fibrinogen (mg/dL)	194	

DIC = disseminated intravascular coagulation; FDP = fibrinogen degradation products; INR = international normalized ratio; APTT = activated partial thromboplastin time.

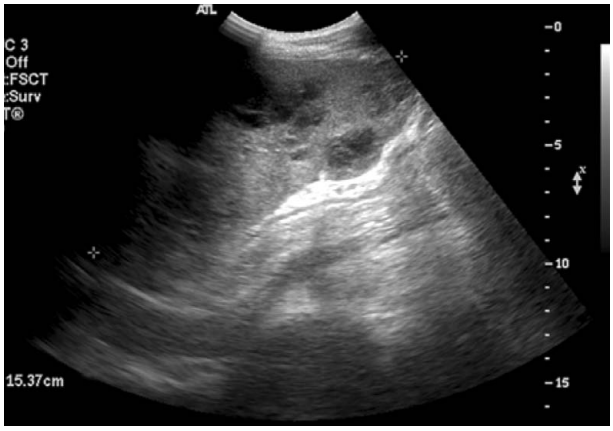

Figure 1. Abdominal sonography shows splenomegaly with multifocal hypoechoic regions.

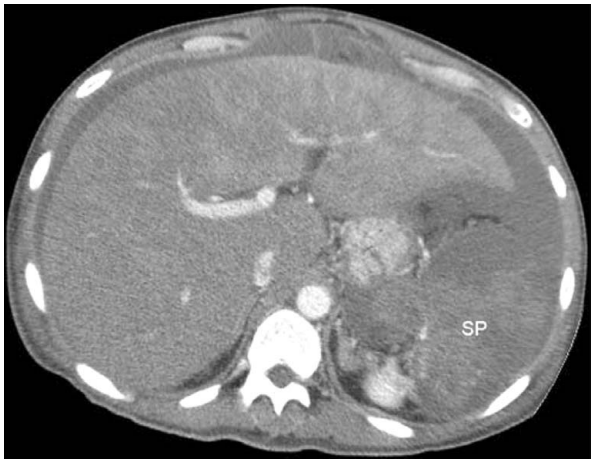

Figure 2. Abdominal computed tomography reveals heterogeneous enhancement with focal low attenuation regions in the liver parenchyma and splenomegaly with poor contrast enhancement. SP = spleen.

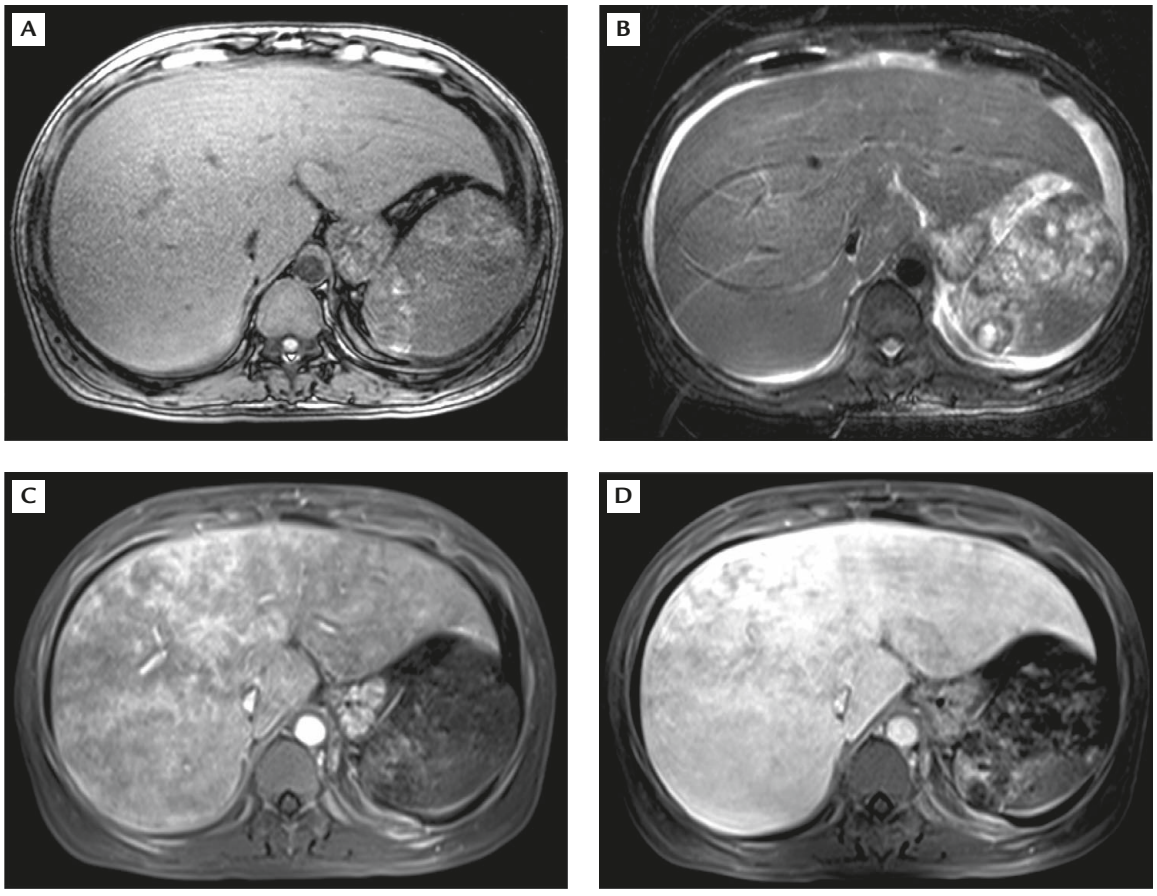

Figure 3. On abdominal magnetic resonance imaging, the liver parenchyma has: (A) relatively high signal intensity on T1-weighted imaging; and (B) low signal intensity on T2-weighted imaging; with (C) heterogeneous enhancement in the arterial phase. Heterogeneous signals of splenic parenchyma with: (A) high signal on T1-weighted imaging; (B) low signal on T2-weighted imaging; and (C, D) poor contrast enhancement were noted.

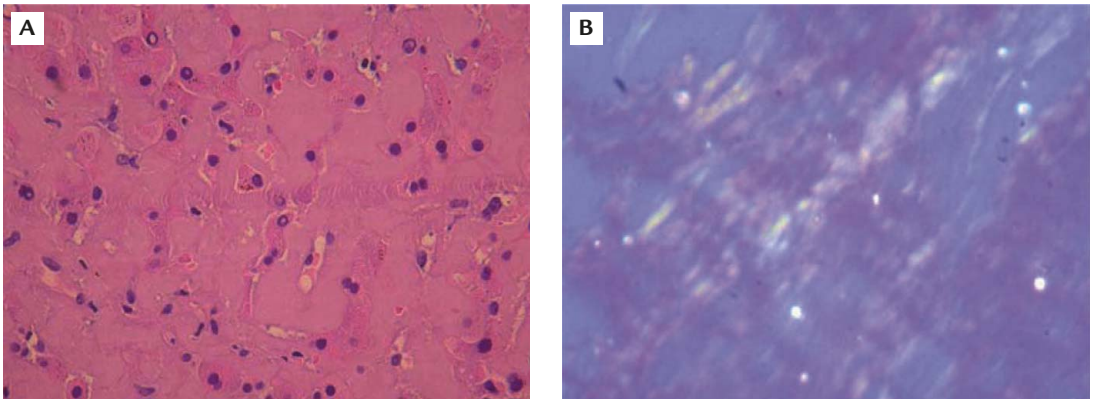

Figure 4. (A) Liver biopsy specimen stained with hematoxylin-eosin-safran shows diffuse amorphous substance deposited in the sinusoidal spaces (800×). (B) Typical apple-green birefringence of amyloid deposition is demonstrated on polarized light microscopy by Congo red staining.

Discussion

Amyloidosis is a disorder of extracellular deposition of insoluble proteinaceous material.[3] There are 2 major classification systems applied for amyloidosis. The first classifies the disease according to the structure of the amyloid fibrils. Among the numerous types of amyloid fibril, amyloid A protein (AA type), amyloid light chain

(AL type), and β_2-microglobulin (β_2-MG type) are the most prevalent.[5] AA type is usually found in chronic inflammatory disease such as tuberculosis, neoplasia, rheumatoid arthritis, osteomyelitis, primary biliary cirrhosis, and Crohn's disease.[5] AL type is associated with the generalized deposition of excess light chains, and 15% of patients with this type will also have multiple myeloma.[4] The β_2-MG type is related to long-term hemodialysis.[5]

Another widely applied system classifies amyloidosis into systemic type and localized type based on the clinical manifestations and the organ involved.[6] In the localized type, amyloid infiltration is restricted to an isolated organ, while the deposits can be found in multiple organ systems in the systemic type. In a previous study, only a quarter of patients had involvement of a single organ at presentation; the remaining patients had involvement of 2 organs (36%) or ≥ 3 organs (39%).[3]

Systemic amyloidosis was found in 0.7% of 11,912 autopsies between 1932 and 1960.[7] It usually presents after the 5th decade of life and is male-predominant.[6] The most common symptoms are fatigue, weight loss, edema and proteinuria renal dysfunction. The most commonly involved organs are the kidneys (46%) and the heart (30%).[3] The liver (9%) and gastrointestinal tract (7%) are less commonly involved, but the incidence is increased when systemic amyloidosis is confirmed.[3,4] Hepatic involvement was found in 56–95% of patients with systemic amyloidosis.[7,8] It was present in 60% of cases with AA amyloidosis, 62–90% with AL amyloidosis, and 22–43% with multiple myeloma-associated amyloidosis.[7,9]

The diagnosis of amyloidosis demands careful clinical evaluation and is established by tissue biopsy. Notably, the prognosis is worse for patients with the systemic type compared to those with the localized type.[9] Accordingly, it is crucial to differentiate between them by laboratory, radiological and even pathological examinations. The common organs to be biopsied in the clinical setting are the rectum, subcutaneous fat, kidney, bone marrow, small intestine and liver.[4] In our patient, systemic amyloidosis was diagnosed by tissue biopsy from both the liver and rectum. Although liver involvement is common and hepatomegaly is noted in 40–50% of patients with systemic amyloidosis, jaundice, elevated serum aminotransferase concentrations, and impaired liver functional reserve are relatively rare.[4,7,10] A previous study demonstrated that severe cholestatic presentations appear to be largely limited to patients with advanced systemic AL amyloidosis.[11] Coagulation problems in amyloidosis are historically associated with bleeding tendencies.[12] Increased clotting has been observed in isolated cases diagnosed with low-grade disseminated intravascular coagulation.[12]

Our 57-year-old male patient presented with hepatic decompensation as the initial symptom of systemic amyloidosis, with rapid deteriorating clinical manifestations. Consequently, clinicians should maintain a high index of suspicion so that they can promptly diagnose systemic amyloidosis with liver involvement and closely monitor clinical outcomes. The outcome for patients may be lethal if there is misdiagnosis, delayed diagnosis or if they are not prescribed appropriate management.

Our patient also manifested with splenic involvement. In a previous study, splenomegaly was often associated with hepatomegaly and was found in 15–31% of patients with systemic amyloidosis.[4] In addition, splenic dysfunction or hyposplenism, which is from amyloid infiltration, occurs in 24% of cases.[10] This has been reported to cause spontaneous splenic rupture and might increase the risk of serious infection.[4]

Radiologic findings of hepatic involvement are usually nonspecific.[5] Abdominal sonography may show heterogeneous echogenicity of liver parenchyma. CT findings include diffuse or focally decreased parenchyma attenuation and triangular-shaped hepatomegaly. MRI shows significantly increased signal intensity on T1WI without a significantly altered signal intensity on T2WI.[5] Regarding splenic amyloidosis, heterogeneous echogenecity of splenic parenchyma, splenomegaly with low signal intensity on T2WI, and poor contrast enhancement on MRI are the usual imaging findings. Retrospectively, in our patient, the hypoechoic areas of the spleen on ultrasonography and decreased parenchymal attenuation of the liver and spleen on CT and MRI hinted at liver amyloidosis and splenic involvement.

The treatment of amyloidosis is directed both toward the affected organs and to the specific type of the disease.[1] In AA-type amyloidosis, the treatment modalities are based on the underlying diseases and aim to reduce the amyloid precursor by intensive anti-inflammatory/immunosuppressive therapy.[11] If the etiology cannot be identified in AA-type amyloidosis, empirical anti-inflammatory treatment may be prescribed.[13] In AL-type amyloidosis, oral mephalan and prednisolone have confirmed efficacy over no therapy or therapy with colchicine only.[1] Treatment with high-dose intravenous melphalan with autologous blood stem-cell support results in complete remission of the plasma-cell dyscrasia and normalization of the number of plasma cells in bone marrow in 65% of patients.[1] In < 10% of patients with AL amyloidosis, progressive heart failure results in mortality. Cardiac transplantation, followed by intensive chemotherapy, may be an alternative treatment for these patients.[1] The prognosis

of amyloidosis is diverse, but is generally poor if the disease is untreated.[1] Factors associated with a poor prognosis include older age, reduced serum albumin concentration, end-stage renal failure at baseline, and the degree by which serum amyloid A protein concentration is elevated during follow-up.[13]

In conclusion, although amyloidosis rarely presents with hepatic failure, it should be considered in patients with signs of liver decompensation. Clinicians should be aware of this rare but potentially lethal presentation and arrange appropriate treatment promptly.

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