CASE REPORT | LIVER

Primary Hepatic Amyloidosis Presenting as Acute-on-Chronic Liver Failure

Madhumita Premkumar, MD, DM[1], Devaraja Rangegowda, MD, DM[1], Tanmay Vyas, MD, DM[1], Anand Kulkarni, MD[1], Shrruti Grover, MD[2], Rakhi Mahiwall, MD, DM[1], and Shiv Kumar Sarin, MD, DM[1]

[1]Department of Hepatology, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi, India
[2]Department of Pathology, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi, India

ABSTRACT

Systemic amyloidosis of amyloid light chain associated protein (AL), also called primary amyloidosis, frequently involves the liver, but rarely causes clinically apparent liver disease. The more common presentation is with acute renal failure. Hepatomegaly and mild elevation of alkaline phosphatase are the most common clinical and biochemical findings, respectively. We report a case of systemic amyloidosis of AL that clinically presented as acute-on-chronic liver failure and resulted in a fatal clinical course in a 56-year-old man.

INTRODUCTION

Hepatic involvement in systemic amyloidosis is common and occurs in myeloma-related (AL) amyloidosis (primary) and amyloid-associated (AA) amyloidosis (secondary or reactive). Significant clinical evidence of hepatic dysfunction is usually subclinical and may include hepatomegaly, mild jaundice, and, rarely, severe cholestasis.[1] Portal hypertension may complicate hepatic amyloidosis, and subcapsular hematoma and spontaneous rupture of liver have been reported.[2] Acute and fulminant liver failures have only been described for AL amyloidosis in the setting of myeloma.[3] A diagnosis of AL amyloidosis (primary hepatic amyloidosis) with progressive liver failure is rarely seen in the absence of myeloma, with few prior cases of primary amyloidosis presenting as acute liver failure in the reviewed literature.[4-10] The diagnostic challenge in this case now serves as a differential in the etiological work-up for progressive liver failure.

CASE REPORT

A previously healthy 56-year-old man presented with progressive jaundice for 6 weeks and abdominal distension with swelling of feet for 4 weeks. He also had symptoms of fatigue and mild generalized itching. His past medical history was unremarkable, with no prior history of liver disease. On physical examination, he was deeply icteric, had bilateral pitting lower-limb edema, a left-sided pleural effusion, a short apical systolic murmur, and a flapping tremor. His abdominal examination revealed massive hepatosplenomegaly with moderate ascites. His clinical presentation was akin to acute-on-chronic liver failure (ACLF) with the appearance of ascites and encephalopathy within 2 weeks of presentation with jaundice. His primary physician referred the case to our center after he developed signs of liver decompensation. Hence his initial diagnostic work-up focused on identifying the underlying etiology. Complete blood count and serum electrolytes were within normal limits. Laboratory studies showed blood urea 45 mg/dL, creatinine 0.9 mg/dL, total bilirubin 22 mg/dL, serum albumin 24 g/L, international normalized ratio 3.2, alkaline phosphatase 1,496 IU/L, γ-glutamyltransferase 136 IU/L, alanine aminotransferase 128 IU/L, and aspartate aminotransferase 170 IU/L. C-reactive protein was elevated, and immunoglobulin (Ig) levels were normal with
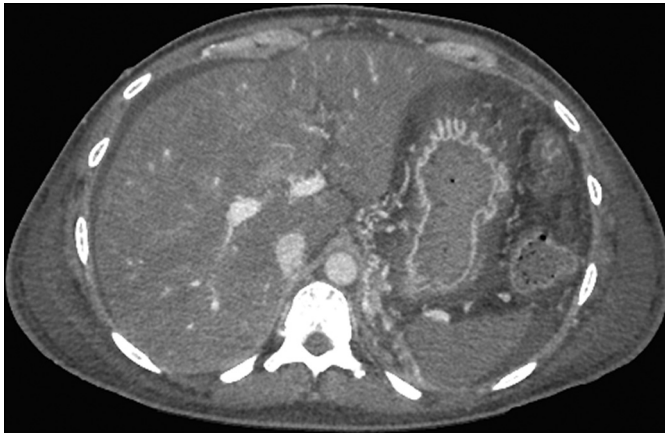
Figure 1. Abdominal CT showing an enlarged liver with patent hepatic and portal veins.

IgG 12 g/L, IgA 3.15 g/L, and IgM 0.52 g/L. Serum protein electrophoresis and β2 microglobulin were within normal limits, and urinalysis was negative for Bence-Jones proteinuria. Alpha-fetoprotein was within the normal range. Serologies for hepatitis were all unremarkable. Autoimmune work-up, including antinuclear, anti-smooth muscle, and anti-DNA antibodies, were negative. The 24-hour urinary protein excretion was 0.068 g/L.

Abdominal ultrasonography revealed hepatosplenomegaly with no focal liver lesions and normal intra- and extrahepatic bile ducts. Computed tomography of the abdomen showed the liver measured 16.6-cm in craniocaudal span, with a subtle lobulated outline and widened interlobar fissures. The main portal vein was mildly dilated with thin collaterals, suggestive of portal hypertension. There was no evidence of retroperitoneal or mesenteric lymphadenopathy (Figure 1). Transthoracic echocardiography showed normal chambers with diastolic dysfunction, normal systolic function with ejection fraction of >60%, and no pericardial effusion. Ascitic fluid analysis showed 500 cells, 90% lymphocytes, high serum albumin ascitic gradient (2.1), low protein (2.4 g/L), and low adenosine deaminase (5.7 IU/L). Polymerase chain reaction was negative for tuberculosis and there were no malignant cells on cytology. These findings were consistent with portal hypertension.

Transjugular liver biopsy was performed. Hepatic venous pressure gradient was 14 mm Hg, confirming the clinical diagnosis of portal hypertension. Liver biopsy showed near complete effacement of acinar architecture by sinusoidal and portal deposits of extracellular, pale eosinophilic, hyaline, amorphous, acellular material. Hepatocytes showed pressure atrophy and focal presence of canalicular bile. Portal tracts showed no significant inflammation with F1 fibrosis (Figure 2). The material stained positive with Congo red and displayed green birefringence when viewed under polarized light, confirming amyloid deposition. Stains for iron and copper
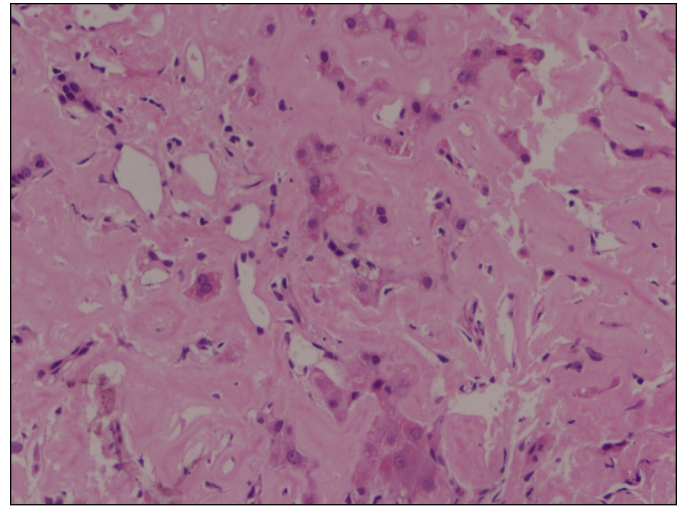

Figure 2. Liver biopsy showing near complete effacement of acinar architecture by sinusoidal and portal deposits of congophilic, extracellular, pale eosinophilic, hyaline, amorphous, acellular material. Hepatocytes showed pressure atrophy and focal presence of canalicular bile was noted. Portal tracts showed no significant inflammation. There was no significant fibrosis. Hematoxylin and eosin stain.

deposition were not remarkable. Immunohistochemistry revealed that the amyloid deposits consisted largely of light chains, with λ being stronger than κ (Figure 3). Bone marrow aspiration showed erythroid hyperplasia with normoblastic to mild megaloblastic erythropoiesis. Plasma cells were 9%. No evidence of myeloma was seen. Serum free light chains were negative. Skeletal survey did not reveal any lytic lesions. Rectal biopsy showed maintained crypt architecture. There were focal deposits of acellular eosinophilic amorphous material in the wall of blood vessels in submucosa. These deposits also showed apple green birefringence on staining with Congo red under polarization. This confirmed extrahepatic deposition of amyloid (Figure 4).

The patient's clinical condition rapidly deteriorated over the next few days, and he developed fulminant liver failure and sepsis. He could not be offered chemotherapy due to liver failure, and was deemed unfit for liver transplantation. He died within 12 days of presentation at our center.
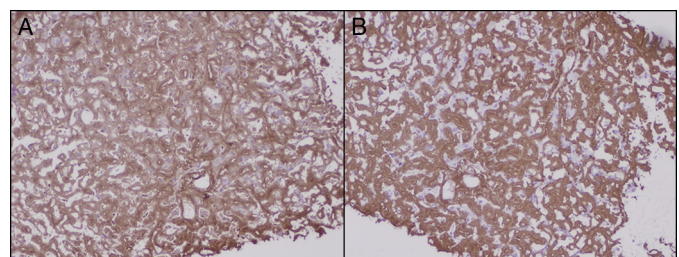

Figure 3. (A and B) λ and κ staining revealed that the amyloid deposits consisted largely of light chains, λ being stronger than κ (magnification 40x).
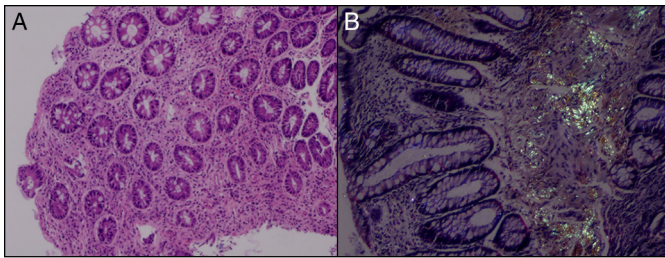
Figure 4. (A) Hematoxylin and eosin staining of rectal biopsy showing focal deposit of acellular eosinophilic amorphous material in the wall of blood vessels in submucosa. (B) Congo red staining under polarized light showing apple green birefringence on rectal biopsy, confirming extrahepatic amyloid deposits.

DISCUSSION

Hepatic failure can present as acute liver failure, ACLF, or a chronic decompensation of an end-stage liver disease. ACLF has been defined by the Asian Pacific Association for the Study of the Liver (APASL) as an acute hepatic insult manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.[10] Among the infectious etiologies, reactivation of hepatitis B virus infection, either spontaneously or due to intensive chemotherapy or immunosuppressive therapy, as well as acute hepatitis E virus infection and hepatitis C virus infection have been reported.[11] Alcoholic hepatitis commonly causes decompensation of stable liver disease in various studies.[11]

Amyloidosis is a medical condition of abnormal protein metabolism, characterized by extracellular deposition of misfolded, normally soluble proteins and polypeptides in fibrillary form. Amyloidosis is classified on the basis of the chemical composition of the amyloid fibrils and their precursor protein to morphologically identical but chemically different types. There are two principal types of amyloidosis. The first is AL amyloidosis, which is associated with plasma cell dyscrasias and malignant B-cell-type lymphoproliferative malignancies and is characterized by the deposition of the variable region of the immunoglobulin κ or λ light chains. The second is AA amyloidosis, which is associated with chronic infectious and noninfectious inflammatory conditions, Hodgkin lymphoma, and non-lymphoid malignancies and is characterized by the deposition of amyloid A fibrils, which are derived from the serum AA precursor protein. Both types can be localized or systemic.[1]

Multiple myeloma is the second most common hematologic malignancy (13%) and constitutes 1% of all cancers. AL amyloidosis arises from diseases with disordered immune cell function, such as multiple myeloma and other immunocyte dyscrasias, and it is the most common form of systemic amyloidosis. Liver involvement is less common in myeloma (32%) when compared with chronic leukemia (80–100%), myeloproliferative diseases, acute leukemia (60–70%), and non-Hodgkin lymphoma (50–60%).[12]

Although the liver may demonstrate amyloid deposits, AL amyloidosis is not associated with significant liver dysfunction.[13] A recent study determined that only 0.44% of cases with liver failure were attributable to an infiltrating malignancy.[3] Cases of acute liver failure have previously been reported in AL amyloidosis.[4-10] These cases usually presented due to myeloma, which was absent in our patient. He did not have any chronic inflammatory condition, malignancy, or family history of amyloidosis. The clinical presentation of progressive liver failure with rapid deterioration and subsequent death in our case is therefore remarkable and is now being recognized as a distinct presentation of primary amyloidosis.material. Hepatocytes showed pressure[5,10]

In contrast, if we examine cases of systemic AA amyloidosis, there is an associated amyloid deposition in other organs, which carries a poor prognosis. Lovat et al presented a series in which 138 patients had AA amyloidosis, 180 had AL amyloidosis, 99 had hereditary amyloid syndromes, and 67 had dialysis related (β2 microglobulin) amyloid.[13] In that study, there was a significant drop in the 5-year survival from 72% in patients without liver involvement to 43% in patients with liver involvement.[14] The diagnosis requires a liver biopsy and a bone marrow examination. We recommend the use of a transjugular technique to prevent a major bleed. Different histological patterns described in hepatic amyloidosis include a vascular pattern, in which primarily the hepatic arteries and arterioles are involved, and a sinusoidal/linear pattern, in which the amyloid deposits in the space of Disse along the hepatic sinusoids.[15] These patterns of hepatic amyloid deposition occur singly or in conjunction and cannot be used to distinguish between the various forms of systemic amyloidosis.

Management of this condition remains unclear. Patients with myeloma and an indolent hepatic presentation are candidates for chemotherapy. The role of liver transplantation in the management of systemic amyloidosis is well established in the familial forms like familial amyloidotic polyneuropathy and transthyretin.[16] On the other hand, there is only limited success with transplantation for treating AL amyloidosis as the disease progression is unaltered in the presence of a plasma cell dyscrasia. Therefore, the use of a combined approach with autologous stem cell transplant and liver transplant have been recently described.[16,17]

In conclusion, this case describes a patient with systemic AL amyloidosis, who presented with fatal liver failure, an unusual clinical presentation of primary hepatic amyloidosis. The diagnostic challenge in this case can serve as a differential in the etiological work-up for progressive liver failure. We urge clinicians to exercise a high degree of clinical suspicion to detect

and refer such cases early. Aggressive chemotherapy and referral for transplant may improve outcomes in ACLF syndromes.

DISCLOSURES

Author contributions: M. Premkumar and D. Rangegowda wrote the manuscript. R. Mahiwal and SK Sarin edited the manuscript. S. Grover provided the pathology images. SK Sarin is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained from the deceased patient's next of kin for this case report.

REFERENCES

1. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. *N Engl J Med*. 2003;349(6):583–96.
2. Bujanda Beguiristain L, Alberdi AF, et al. Spontaneous rupture of the liver in amyloidosis. *Am J Gastroenterol*. 1997;92(8):1385–6.
3. Rowbotham D, Wendon J, Williams R. Acute liver failure secondary to hepatic infiltration: A single centre experience of 18 cases. *Gut*. 1998;42:576–80.
4. Ales NC, Daniels JT, Frizell ER, et al. Multiple myeloma-associated amyloidosis manifesting as fulminant hepatic failure. *South Med J*. 2001;94 (10):1036–8.
5. Takayasu V, Laborda LS, Bernardelli R, et al. Amyloidosis: An unusual cause of portal hypertension. *Autops Case Rep*. 2016;6(2):9–18.
6. Yamamoto Y, Maeda N, Kawasaki H. Hepatic failure in a case of multiple myeloma associated amyloidosis (kappa-AL). *J Gastroenterol*. 1995; 30:393–7.
7. Oe Y, Nakaya I, Yahata M, et al. κ I light chain AL amyloidosis presenting with rapidly progressive renal and hepatic failure with unusual renal amyloid distribution. *Clin Nephrol*. 2012;77(1):66–70.
8. Dohmen K, Nagano M, Iwakiri R, et al. A case of prominent hepatic cholestasis developing to hepatic failure in lambda-AL amyloidosis. *Gastroenterol Jpn*. 1991;26(3):376–81.
9. Norero B, Pérez-Ayuso RM, Duarte I, et al. Portal hypertension and acute liver failure as uncommon manifestations of primary amyloidosis. *Ann Hepatol*. 2013;13(1):142–9.
10. Misiakos EP, Bagias G, Tiniakos D, et al. Primary amyloidosis manifesting as cholestatic jaundice after laparoscopic cholecystectomy. *Case Rep Surg*. 2015;353818.
11. Sarin SK, Kumar A, Almeida JA, et al. Acute-on-chronic liver failure: Consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). *Hepatol Int*. 2009;3(1):269–82.
12. Ebert EC, Nagar M. Gastrointestinal manifestations of amyloidosis. *Am J Gastroenterol*. 2008;103(0):776–87.
13. Lovat LB, Persey M, Madhoo RS, et al. The liver in systemic amyloidosis: Insights from 123I serum amyloid P component scintigraphy in 484 patients. *Gut*. 1998;42(5):727–34.
14. Wu XN, Zhao XY, Jia JD. Nodular liver lesions involving multiple myeloma: A case report and literature review. *World J Gastroenterol*. 2009;15:1014–7.
15. Suhr OB, Ando Y, Holmgren G, et al. Liver transplantation in familial amyloidotic polyneuropathy (FAP): A comparative study of transplanted and non-transplanted patient's survival. *Transpl Int*. 1998;11(suppl 1):S160–3.
16. Binotto G, Cillo U, Trentin L, et al. Double autologous bone marrow transplantation and orthotopic liver transplantation in a patient with primary light chain (AL) amyloidosis. *Amyloid*. 2011;18(suppl 1):132–4.
17. Walz-Mattmuller R, Horny HP, Ruck P, Kaiserling E. Incidence and pattern of liver involvement in haematological malignancies. *Pathol Res Pract*. 1998;194:781–9.