Advanced Research in Gastroenterology & Hepatology
ISSN: 2472-6400

Case Report
Volume 20 Issue 4 - May 2024
DOI: 10.19080/ARGH.2024.20.556042

Adv Res Gastroentero Hepatol

Primary Hepatic Amyloidosis Related Liver Failure Rescued with Living Donor Liver Transplant: A Case Report

Shekhar Singh Jadaun[1], Shekhar Poudel[1], Naman Suroya[1], Priyank Dhiman[1], Sushant Bhatia[2], Mukesh Kumar[2], Anjali Kakati Gupta[3], Shweta Singh[4], Shaleen Agarwal[2], Subhash Gupta[2] and Sanjiv Saigal[1]*

[1]*Department of Hepatology, Centre for Liver and Biliary Sciences, Max Super Specialty Hospital, Saket, New Delhi, India*

[2]*Liver Transplant and GI Surgery, Centre for Liver and Biliary Sciences CLBS Max Super Specialty Hospital, Saket, New Delhi, India*

[3]*Department of Histopathology, Max Super Specialty Hospital, Saket, New Delhi, India*

[4]*Anesthesia & Critical Care, Centre for Liver and Biliary Sciences, Max Super Specialty Hospital, Saket, New Delhi, India*

Submission: May 16, 2024; **Published:** May 27, 2024

***Corresponding author:** Sanjiv Saigal, Principal Director and Head, Hepatology and Liver Transplant, Centre for Liver and Biliary Sciences CLBS Max Super Specialty Hospital, Saket , New Delhi, India

Keywords: Hepatic Amyloidosis; Liver Transplant; Amyloid Fibrils; Macroglobulin; Glycoprotein Serum; glycosaminoglycans

Abbreviations: LDLT: Living Donor Liver Transplantation; SAA: Serum Amyloid A; IHC: Immunohistochemistry; PET: Proton Emission Tomography

Introduction

Amyloidosis is a systemic infiltrative disorder characterized by deposition of amyloid fibrils in extracellular spaces. Amyloid fibrils consist of nonfibrillar glycoprotein serum amyloid P, glycosaminoglycans and various serum protein precursors. Amyloidosis can be divided into localized and systemic types. Systemic amyloidosis can be further divided into primary AL amyloidosis, secondary amyloid A (AA) amyloidosis, B2 macroglobulin-related amyloidosis and familial amyloidosis [1-3]. Liver involvement can be seen in both primary and secondly amyloidosis which can be subclinical or symptomatic. However, primary hepatic amyloidosis is a very rare variant in which deposition of amyloid protein primarily occurs in liver only [4, 5]. We are presenting an interesting case of sub-acute liver failure due to primary hepatic amyloidosis who underwent living donor liver transplantation (LDLT).

Case report

A 62-year-old female presented with history of slowly progressive painless jaundice and pedal edema for 4 months and abdominal distention for 2 weeks. She also had anorexia and mild pruritis. There was no past history of any liver disease or other chronic systemic illness. She was a non-smoker and had not consumed alcohol in the past. Physical examination showed deep icterus, hepatomegaly and ascites. Her baseline laboratory test values are given in Table 1. Ultrasound imaging showed hepatosplenomegaly. Her viral serological markers were negative. Autoimmune markers including anti-nuclear antibodies, anti-liver kidney molecule-1 antibodies and anti-smooth muscle antibodies were negative. MRI abdomen was done which showed hepatosplenomegaly with lobulated outline and widened inter-lobar fissure of liver. There were features of portal hypertension with prominent splenoportal axis, periportal collaterals along with moderate ascites. On gastroduodenoscopy she had esophageal varices. On history, physical examination and initial laboratory evaluation, etiology of liver disease could not be found out.

As cause of liver failure was not apparent, she underwent trans-juglar liver biopsy which showed effacement of acinar architecture with sinusoidal and portal deposits of hyaline, eosinophilic, extracellular, amorphous acellular material. The deposits were congophilic and demonstrated apple green birefringence on polarizing microscopy. Hepatocytes showed compression atrophy with glycogenated nuclei. These hepatocytes showed focal cholestasis. No significant fibrosis was seen. Immunohistochemistry (IHC) for serum amyloid A (SAA) protein

was negative. Bone marrow biopsy and rectal biopsy were also done to rule out multiple myeloma and systemic amyloidosis and were negative for both. Immunoelectrophoretic did not showed any abnormal monoclonal bands. Serum kappa/lambda ratio and serum beta2 microglobulin levels were normal. Urine examination did not show any significant proteinuria and was negative for kappa or lambda chain excretion. In cardiac evaluation 2D echo cardiography was normal. No abnormal FDG uptake was seen in whole body proton emission tomography (PET) scan. She was initially given steroids, cyclophosphamide and bortezomib. However, she did not respond to this treatment. She then received daratumumab and lenalidomide.

Patient responded to treatment initially however her bilirubin again started rising. She also developed hepatic encephalopathy in progressive course. Due to progressively rising bilirubin associated with decompensation in the form of ascites and hepatic encephalopathy, she was considered for liver transplant after thorough evaluation. In the absence of suitable cadaveric donor, she was taken for living donor liver transplant (LDLT) after due clearance, donor being her son. She received a modified right liver lobe graft weighted 710 grams and GRWR of 1.1 with a single biliary anastomosis. Donor had an uneventful recovery and was discharged on day 7 after surgery. Explant liver biopsy showed completely distorted liver architecture by thick deposits of amyloid in all the sinusoidal linings, trapping the hepatocytes resulting in atrophy and necrosis. Hepatic sinusoids were clogged with amyloid. Zone 3 cholestasis was present in the perivenular areas. Depositions of amyloid were also present around the portal vessels and also in the portal extracellular matrix. Amyloid deposits showed Apple green birefringence with polarized light in Congo red staining. On immunohistochemistry amyloid consisted of light chain (AL) proteins and SAA was negative. (Figure 1A-E). Her post-operative course was smooth and uneventful. Serum bilirubin and other liver biochemistry parameters gradually improved. Patient was discharged on 18th postoperative day. During follow up patient is doing well except a brief hospitalization for viral pneumonia. Her liver function tests continue to be normal 4 months after transplant.

Discussion

This is a rare case of primary hepatic amyloidosis presented as sub-acute liver failure who successfully underwent LDLT. Amyloidosis is a disorder characterized by extracellular depositions of misfolded abnormal proteins in fibrillar form. Two main types of amyloidosis are primary and secondary types. Primary type (AL) characterized by deposition of monoclonal light chains in extracellular matrix. Primary amyloidosis can represent a form of plasma cell dyscrasias or monoclonal B cells lymphoproliferative disorder. Secondary amyloidosis (AA) seen in presence of chronic inflammatory diseases and characterized by extracellular deposition of amyloid A protein (SAA) [6]. Primary systemic amyloidosis can be associated with multiple myeloma in about 20% cases. Symptomatic or subclinical involvement of liver is common in multiple myeloma but liver failure is rarely seen [7-9]. However, in our case no evidence of extrahepatic amyloid deposition or multiple myeloma was found so ruling out the systemic amyloidosis and multiple myeloma. Our case did not have any past history of chronic illness [10].

Common clinical presentation of primary hepatic amyloidosis includes hepatomegaly and raised serum alkaline phosphatase. Amyloid deposits can be vascular or sinusoidal. Initially amyloid deposits usually start in periportal region in space of Disse and progressively lead to hepatocyte atrophy due to compression [1]. Amyloid deposits in sinusoids leads to portal hypertension and related complications. Presence of cholestatic jaundice and portal hypertension portends a very poor prognosis. Lovat et al showed significantly decreased survival in amyloidosis after symptomatic involvement of liver [11]. Treatment of primary AL amyloidosis include myeloma type chemotherapy and haemopoietic stem cell transplantation. While in secondary form control of underlying chronic liver disease is important to halt the disease progression. Primary hepatic amyloidosis is extremely rare variant with very poor prognosis. Median survival of less than nine months has been reported in patients with presence of jaundice and portal hypertension. Currently evidences for appropriate treatment modalities are lacking [12,13].

Role of liver transplant is well established in familial amyloidotic polyneuropathy. In primary systemic amyloidosis with liver involvement, liver transplant along with autologous bone marrow stem cells transplant has been reported previously in 2 cases. However, LDLT has not been reported in literature for primary hepatic amyloidosis previously [6,14]. Premkumar et al reported a case similar clinical presentation as ours however, liver transplantation could not be done in that patients [5]. There are many unanswered questions about primary hepatic amyloidosis due to very limited literature and scarce evidences. Long term course and management of these patients after liver transplant is not clear. There is serious concern regarding recurrence of amyloidosis. Liver transplant will not affect the production of amyloid AL protein and recurrence is likely even after transplant. Monitoring to detect early recurrence and treatment in case of recurrence is not defined presently. This case also highlights importance of keeping low threshold for rare causes of liver failure during diagnostic evaluation.

Conclusion

In conclusion, this case report describes a very rare case of primary hepatic amyloidosis presenting as liver failure who underwent successful liver transplantation. One important learning point in this case is necessity of keeping hepatic amyloidosis in deferential diagnosis especially when initial diagnostic evaluation has failed to clinch the diagnosis. Trans-juglar liver biopsy appears safe in these patients. In cases with

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advance liver failure, chemotherapy may not be effective and without liver transplantation prognosis is very poor. Early prediction and diagnosis as well as availability of effective therapies is the current unmet need. More studies are needed to understand post liver transplant disease course and management of these patients as current evidences are scarce.

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