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Case report

Primary Amyloidosis Presenting with Nephrotic Syndrome and Atypical Intrahepatic Cholestasis: Report of 2 Cases

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Abstract

Liver is one of the most commonly involved organs in both primary and secondary systemic amyloidoses, but hepatic amyloidosis, manifested as mild to moderate enlargement, is usually not symptomatic nor it is clinically problematic. Rarely, massive hepatomegaly, severe cholestatic hepatitis or liver failure may be encountered in patients with systemic amyloidosis. Two cases with lambda light-chain amyloidosis presenting with nephrotic syndrome and atypical intrahepatic cholestasis are discussed with clinical features, laboratory and kidney, liver and bone marrow biopsy findings in view of the relevant literature.

Keywords: intrahepatic cholestasis, nephrotic syndrome, primary amyloidosis

Introduction

Among the various secondary causes of nephrotic syndrome in adults, systemic amyloidosis comprises an etiologically and clinically heterogenous group of patients (diseases) composed of cases with either primary or secondary amyloidosis, excluding the very rarely seen familial visceral forms. Both primary and secondary systemic amyloidoses may be complicated depending on the organs involved. Liver is one of the most commonly involved organs in both forms, but hepatic amyloidosis, manifested as mild to moderate enlargement, is usually not symptomatic nor it is clinically problematic. Rarely, massive hepatomegaly, severe cholestatic hepatitis or liver failure may be encountered in patients with systemic amyloidosis and light chain deposition disease with less than 50 reported cases [1]. Herein, we report two cases of primary amyloidosis presenting with nephrotic syndrome and atypical intrahepatic cholestasis.

Case 1

A 55-year-old female was admitted to our Nephrology Clinic with pretibial pitting edema for 2 months. History revealed no symptoms of heart, liver or thyroid disease and no drug use. She had no known previous disease but tingling in hands with normal electroneuromyography for 2 years. On admission she was good in general appearance, fully cooperative and oriented. Her tympanic temperature, heart and respiratory rate were normal and blood pressure was 90/60 mmHg. She had 3+ pretibial edema, decreased breath sounds over right lower zone, 6 cm hepatomegaly under subcostal margin on midclavicular line.

Table 1. Laboratory Features of Cases on Admission

Parameter	Case 1	Case 2
BUN (mg/dL)	17	15
Creatinine (mg/dL)	0.87	1
Albumin (g/dL)	1	1.2
24 hour urinary protein (mg/24 hour)	9810	7125
AST (U/L)	45	50
ALT (U/L)	31	28
GGT (U/L)	1733	543
ALP (U/L)	1351	513
Total/direct bilirubin (mg/dL)	0.6/0.2	0.7/0.2
Serum free kappa/lambda (mg/L)	26/384	12/124
Urinary free kappa/lambda (mg/L)	311/634	61/76
IgG/IgA/IgM (g/L)	5.4/2.6/1	2.1/1.6/1.1
Beta-2-microglobulin (mg/L)	3	3.1

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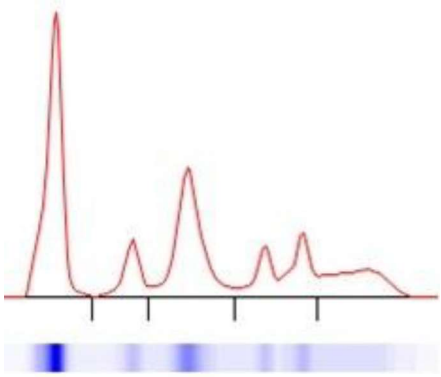

Fig. 1a.

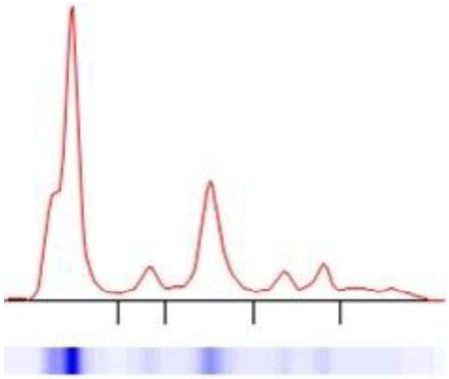

Fig. 1b.
Figure 1. Serum protein electrophoreses of Case 1a and Case 2b

Laboratory examination (Table 1) revealed deep hypoalbuminemia, nephrotic proteinuria, hyperlipidemia and decreased glomerular filtration rate (creatinine clearance = 71 mL/min). Complete blood count and prothrombin time were normal. No laboratory sign of glomerulonephritis was present. Serum protein electrophoresis (SPE) revealed hypoalbuminemia with an irregular gamma and a high alpha-2 band (Figure 1a). Serum and urinary levels of free light chains and immunoglobulins are shown in Table 1. Urinary immune fixation electrophoresis was positive for lambda light chain. Serum autoimmune and metabolic tests of liver injury and markers of viral hepatitis were all negative and no history of hepatotoxic drug use was present. Ultrasonographically kidneys were normal, liver was 161 mm with normal parenchymal appearance, intra- and extrahepatic bile ducts, portal and hepatic veins were normal. A coronal CT scan at the level of portal hilus showing hepatomegaly with normal portal vasculature and no finding of extrahepatic cholestasis is presented in Figure 3. Myocardial hypertrophy with granular echogenicity suggestive of cardiac amyloidosis, thickening of mitral valve leaflets and pleuropericardial effusion were detected echocardiographically. Duodenal and rectal biopsies were negative for amyloidosis. Percutaneous kidney, liver and bone marrow biopsies were performed. Kidney biopsy revealed prominent deposition of amorph eosinophilic extracellular material, showing positive staining with Congo Red and immunohistochemistry identified lambda light chain with positive P component, proving the diagnosis of lambda light chain amyloidosis (Figure 2a). Liver biopsy was also compatible with lambda light chain amyloidosis with the same immunohistochemical features. Importantly, amyloid deposition was more prominent in the perisinusoidal (Disse) space than in the periportal space (Figure 2a). Ten percents of lambda monotypic interstitial plasma cell infiltration was found in the bone marrow (Figure 2b). After the first cycle of melphalan and prednisolone chemotherapy on the 15th day of admission she had acute kidney injury requiring hemodialysis and hyperbilirubinemia developed without further increase in cholestatic enzymes (Table 2). Despite prophylactic anticoagulation she had a possible ischemic stroke with cardiovascular collapse and died. No autopsy was performed.

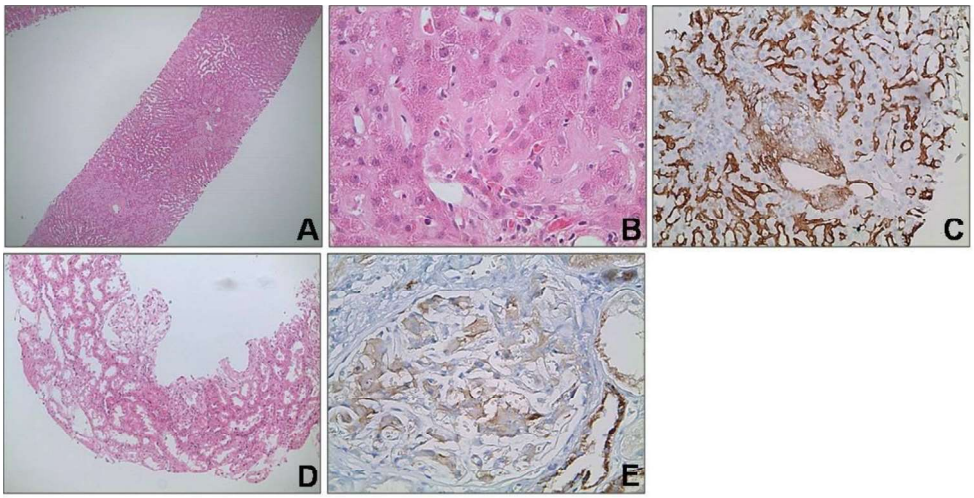

Fig. 2a.

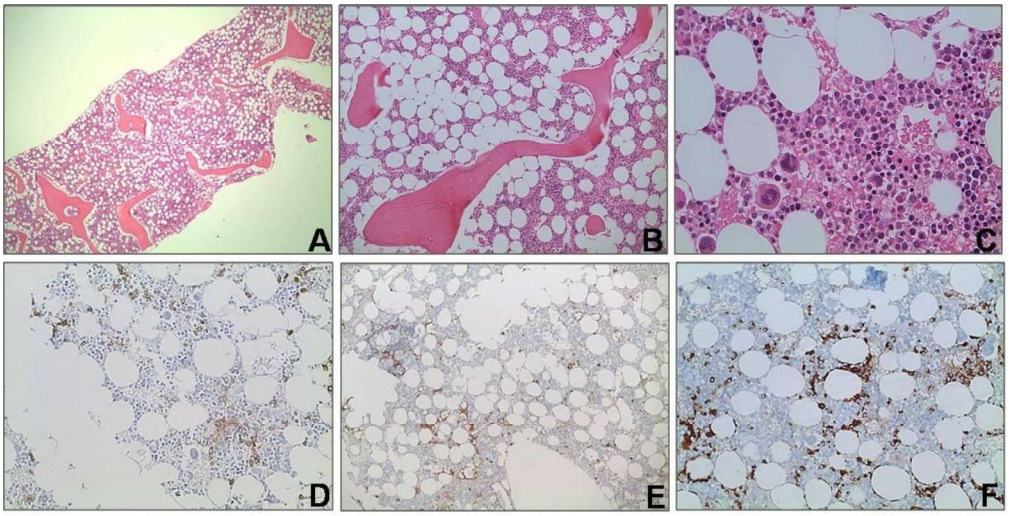

Fig. 2b.

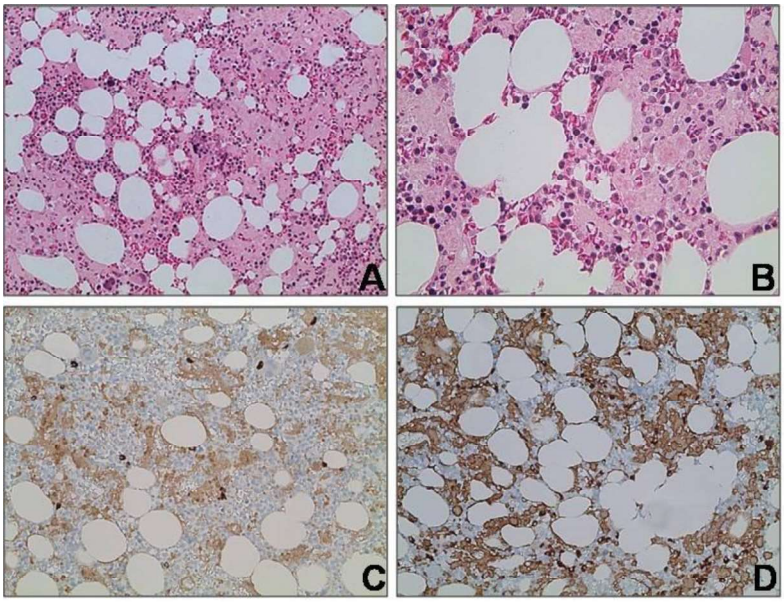

Fig. 2c.

Fig. 2. Liver and kidney biopsy findings of Case 1 (**a**); **A-C**. Amoprh hyaline appearance in Disse space (H&E x25, x400) and immunohistochemical lambda expression (x200). **D-E**. Amorph hyaline appearance due to glomerular amyloid deposition (H&E x100) and immunohistochemical lambda expression (x200). Bone marrow biopsy findings of Case 1 (**b**); **A-C.** Scattered interstitial plasma cells in hypercellular bone marrow biopsy (H&E x25, x100, x400). **D-F**. Immunohistochemical expressions of CD38, kappa, and lambda (x200, x100, x200). Bone marrow biopsy findings of Case 2 (**c**); **A-B**. Extracellular amorph hyaline appearance due to amyloid deposition in bone marrow biopsy (H&E x200, x400). **C-D**. İmmunohistochemical kappa and lambda expression (x200).

Table 2. Chronologic Laboratory Features of Case 1

Parameter	Day 0	Day 15	Day 27	Day 31	Day 33
Creatinine (mg/dL)	0.87	1.98	3.8	2.7	4.9
AST (U/L)	45	35	41	47	47
ALT (U/L)	31	51	57	60	61
GGT (U/L)	1733	2592	2026	1918	1902
ALP (U/L)	1351	2315	1056	1249	1415
Total/direct bilirubin (mg/dL)	0.6/0.2	1.5/0.7	11.9/6.7	6.5/4.6	5.7/3.5
Prothrombin time (second)	10.9	12.2	12	12	12.1

Due to nephrotic loss and replacement, serum albumin is not presented chronologically; Undulations of serum creatinine is due to hemodialysis

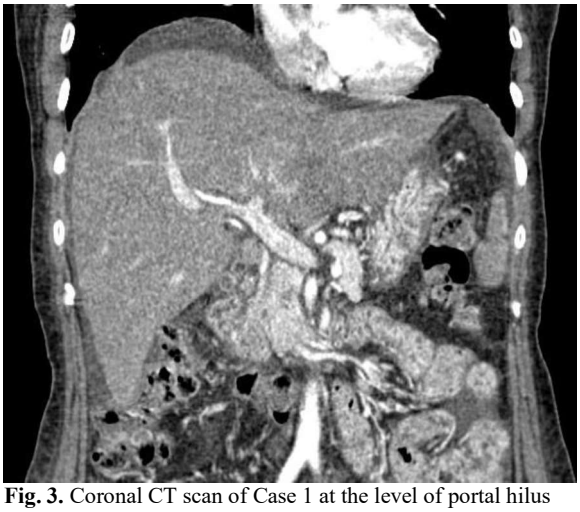

Fig. 3. Coronal CT scan of Case 1 at the level of portal hilus showing hepatomegaly, normal portal vein and no finding of extrahepatic cholestasis

Case 2

A 56-year-old female, being followed in the Hepatology Inpatient Clinic because of hepatomegaly, hypoalbuminemia, ascites and pretibial edema with the initial diagnosis of liver failure, was referred to our Nephrology Clinic because of concomitant nephrotic proteinuria. She had known coronary heart disease but no symptom of cardiac failure was present and echocardiography was normal except for minimal pericardial effusion. She had a surgical release for carpal tunnel syndrome 5 months prior to admission and diagnosed as combined hyperlipidemia at that time. Vital signs and physical examination were normal except for 3+ pretibial edema and mild ascites with 2 cm hepatomegaly under subcostal margin on midclavicular line. Her complete blood count, prothrombin time, serum creatinine and electrolytes were normal. Deep hypoalbuminemia, hyperlipidemia, and nephrotic proteinuria were present. Detailed laboratory examination is shown in Table 1. Her liver was 20 cm with a normal parenchymal density, intra- and extrahepatic bile ducts, and portal and hepatic veins were normal on computed tomographic examination of the abdomen. Tests for viral, autoimmune and metabolic liver diseases were all normal. No laboratory sign of glomerulonephritis was present. SPE was similar to that of Case 1 with more prominent prealbumin and hypogammaglobinemia plus irregularity of the gamma band (Figure 1b). Serum and urinary levels of free light chains and immunoglobulins are shown in Table 1. Ultrasonography of the kidneys was normal. Bone marrow aspiration and biopsy revealed 6% of lambda monotypic interstitial plasma cell infiltration (Figure 2c), almost all of which showed atypia in flow cytometric examination and expressed deletion of both 13q and 17p. Lambda light chain amyloidosis was also evident in bone marrow biopsy with positive staining with Congo Red and immunohistochemical P component and lambda light chain positivity (Figure 2c). She was diagnosed with primary systemic lambda light chain amyloidosis. Due to poor prognostic clinical and genetic features, an autologous hematopoietic stem cell transplantation is planned after remission induction with bortezomib-based therapy and appropriate pre-transplant conditioning regimen.

Discussion

In patients with systemic amyloidosis of both primary or reactive types, the differential diagnosis of cholestasis may be challenging, especially in cases with multisystemic and complicated disease that may lead to cholestatic type of liver injury secondarily due to treatment related issues or systemic infections. Although hepatic involvement is common in patients with systemic amyloidosis of both types, it is usually asymptomatic. Rarely, amyloid infiltration of the liver causes massive hepatomegaly, severe cholestasis and liver failure and prognosis is usually poor in those with survival measured in months [1,2]. In patients with plasma cell dyscrasias cholestasis may be related to light-chain or rarely heavy chain deposition disease, amyloidosis or plasma cell infiltration of the liver. Although metabolic imaging techniques like 18-fluorodeoxyglucose positron emission tomography or serum amyloid P scintigraphy can differentiate between these, the most accurate diagnostic modality is liver biopsy. Interestingly in patients with hepatic amyloidosis serum ALP or GGT elevation may be the only laboratory sign and they can increase to 10 to 50 times the normal with mild or no increase in bilirubin. Later in the course of the disease hyperbilirubinemia ensues [3]. This may be related to the infiltration of the perisinusoidal space fist by the amyloid fibrils causing hepatocellular membrane injury releasing ALP and GGT, then granular deposits in interhepatocellular, pericanalicular and periductal spaces sequentially leading eventually to portal amyloidosis impairing bilirubin transport. After chemotherapy Case 1 had hyperbilirubinemia with a peak of 11.9 mg/dL of total bilirubin on the 27th day of admission, possibly due to superposed intrahepatic cholestatic effect of chemotherapy since hyperbilirubinemia was partially reversible and not accompanied by further increase in cholestatic enzymes (Table 2). Minimal increase in ALT, AST and lactate dehydrogenase and no prolongation of prothrombin time suggested no extensive hepatocellular damage. Some reported cases with light or heavy chain deposition disease without amyloidosis exhibit the same clinical and laboratory features of intrahepatic cholestasis [1]. Such disproportionate pattern of increase in cholestatic enzymes and bilirubin can also be seen in chronic partial obstructive diseases of biliary tree, early in the course of any extrahepatic cholestatic disease, and other infiltrative disease of the liver like lymphomas. In case of amyloidosis, how deposition of extracellular proteins in the granular or fibrillar (amyloid) form causes hepato-

cellular membrane injury in the early course of disease remains to be clarified. Primary biliary cirrhosis, which is rarely reported to be associated with secondary systemic amyloidosis and nodular amyloid deposition in the biliary tree causing extrahepatic type cholestasis should be kept in mind in the differential diagnosis in patients with systemic amyloidosis with cholestasis, making imaging and biopsy an imperative [2-4].

Conflict of interest statement. None declared.

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