Primary Amyloidosis Presenting with Cholestasis and Hyperkinetic Portal Hypertension

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Abstract

Amyloidosis is not a single disease, but a series of diseases in which there is extracellular deposition of a protein in an abnormal fibrillar form. We report a 48-year old woman with subicteric coloration of scleras and hepatomegaly. Functional liver tests evidenced a high level of alkaline phosphatase and serum gamma-glutamyl transpeptidase with mild increase of bilirubin level. Color Doppler ultrasonography, showed a hyperkinetic portal hypertension. The liver biopsy found amyloid in sinusoids subendothelially. Immunohistochemical staining for anti λ light chain immunoglobulin was positive. Bone marrow morphology and immunohistochemistry confirmed lymphoplasmocytic lymphoma with amyloidosis.

Key words

Amyloidosis - liver - cholestasis - portal hypertension

Introduction

Amyloidosis is the extracellular deposition of a protein in an abnormal fibrillar form. Electron microscopic examination shows a fibrillar ultrastructure. Classification of amyloids is based on the protein involved. All types of amyloid appear the same with both Congo red staining and electron microscopic examination (1).

The fibrils in primary amyloidosis (AL) consist of the variable portion of a monoclonal immunoglobulin light chain (κ or λ) or, very rarely, heavy chains (2). Fibrils in secondary amyloidosis (AA) consist of protein- nonimmunoglobulin, derived from the circulating acute phase reactant serum amyloid A (SAA) by proteolytic cleavage. SAA is an apolipoprotein synthesized by hepatocytes, trans-criptionally regulated by cytokines. Juvenile and adult rheumatoid arthritis is the commonest underlying inflammatory conditions, although chronic sepsis, tuberculosis, Crohn´s disease and malignant neoplasms may be responsible (2, 3).

Familial amyloidotic polyneuropathy (FAP) is caused by the deposition of mutant transthyretin (prealbumin) or, rarely, fibrinogen, lysozyme, or apolipoprotein. FAP is characterized by progressive peripheral and autonomic neuropathy; amyloid may also affect the spleen, heart, eyes, thyroid and adrenals. However, fibrils of senile systemic amyloidosis consist of normal transthyretin. Amyloid associated with long-term dialysis consists of β_2-microglobulin (2).

More than 80% of patients with amyloidosis seen at the Mayo Clinic have amyloidosis of AL type. This can be divided into two categories: AL and AL with multiple myeloma, on the basis of the appearance and number of plasma cells in the bone marrow, amount of monoclonal (M) protein in the serum and urine, and the presence or absence of skeletal lesions (4).

Our report presents the unusual case of a patient with liver amyloidosis of AL type associated with cholestasis and portal hypertension.

Case report

A 48-year old woman was admitted because of weight loss of about 7kg for three months and postprandial nausea.

Physical examination revealed subicteric coloration of scleras and hepatomegaly.

Laboratory data showed hemoglobin concentration 148 g/L, RBC 5.12 x 10^{12} /L, Hct. 42.7 %, WBC 9.6 × 10^9/L, PLT 398 x 10^9/L, ESR 38 mm/h; fibrinogen 7.4 g/L; and C-reactive protein 45 mg/dl.

Functional liver tests indicated a severe cholestasis with a high level of alkaline phosphatase (941 IU/L) and serum γ-glutamyl transpeptidase (897 IU/L) with mild increase of bilirubin level (total 59.0 mmol/l; conjugated 37.5 mmol/l). Aminotransferases were increased (AST 78 IU/L, ALT 92 IU/L). The serum albumin and prothrombin time were normal.

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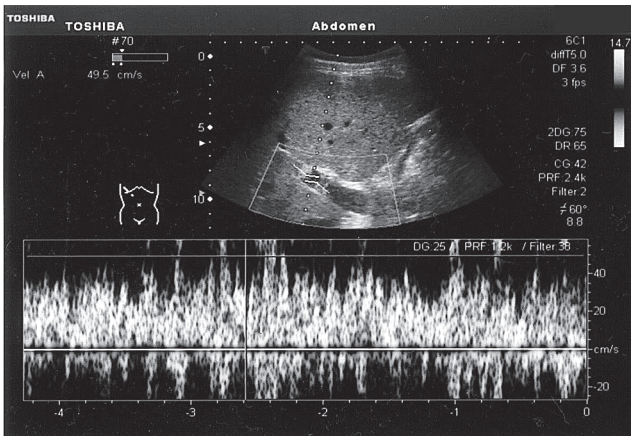

Fig.1 Doppler US of the portal vein, mean velocity rate 49.5 cm/sec.

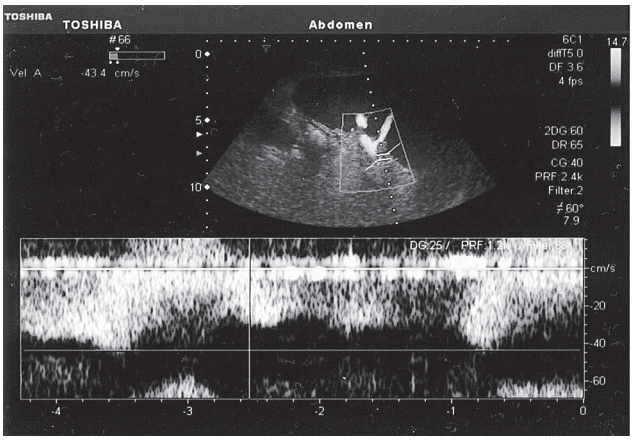

Fig.3 Doppler US of the splenic vein, mean velocity rate 43 cm/sec.

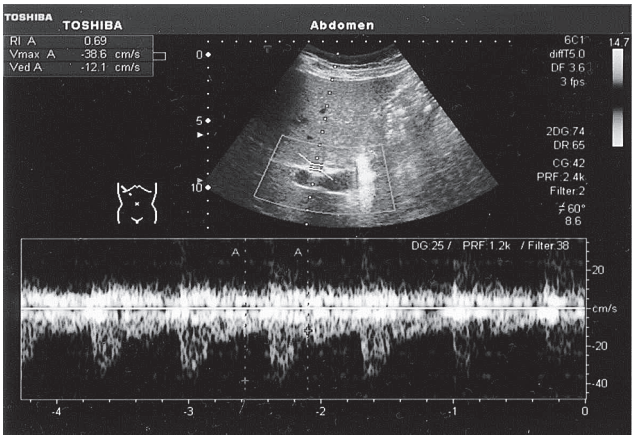

Fig.2 Doppler US of the hepatic artery, velocity rate 38.6/12 cm/sec.

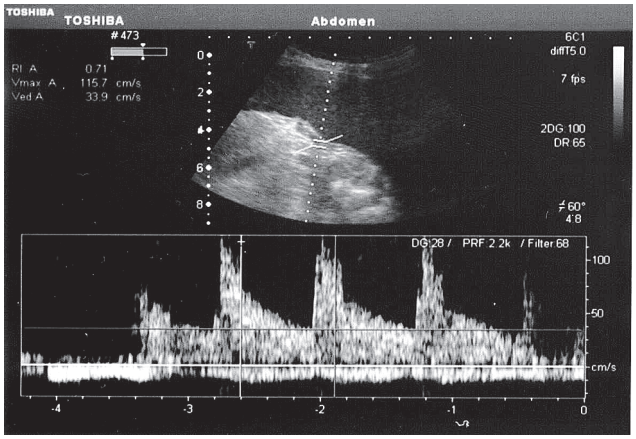

Fig.4 Doppler US of the splenic artery, mean velocity rate 115/34 cm/sec.

The serum antimitochondrial antibody, antinuclear antibody, smooth muscle antibody, and perinuclear antineutrophil cytoplasmic antibodies were absent.

Chest X-ray was normal. Upper fiberpanendoscopy showed reflux oesophagitis grade A.

Real-time and color Doppler ultrasonography, using Toshiba Aplio machine with 3.75 MHz sector duplex probe, showed an enlarged bright liver, with the right lobe craniocaudal diameter of 164 mm and left lobe diameter of 104 mm without focal changes and nodulations of parenchyma. Portal vein was 8.7 mm in diameter, with hepatopetal blood flow, high mean velocity rate of 49.5 cm/sec (Fig.1). Resistivity index (RI) of hepatic artery was increased (0.69) with velocity rate of 38.6/12 cm/sec (Fig.2). The spleen was also enlarged, with diameters of 150 x 40 mm. Splenic vein was 7 mm in diameter with mean blood flow rate of 43 cm/sec (Fig.3). RI of splenic artery was increased (0.71) with high velocity rate of 115/34 cm/sec (Fig.4). Gall bladder was without gallstones, and bile ducts were not dilated. The pancreas structure was homogeneous. Both kidneys had normal macromorphological appearance.

Histopathological analysis of liver tissue verified the amyloid in sinusoids with subendothelial disposition with characteristic staining (Fig.5). Immunohistochemical staining for anti λ light chain immunoglobulin was positive (Fig.6), while staining for anti κ light chain was negative.

After histological confirmation of AL amyloidosis, additional diagnostic tests were performed, including sternal punction and iliac bone marrow biopsy, immunofixation of the serum proteins and skeletal x-ray. Sternal punction found 25% of small lymphocytes, with 1/2 LyPlc morphology. Bone marrow showed interstitial and paratrabecular fibrillar deposits with Congo-red and PAS positivity. Morphology and immunohistochemistry confirmed lymphoplasmocytic lymphoma with amyloidosis.

Skeletal X-rays were all normal. The immunofixation of the serum proteins revealed a monoclonal immunoglobulin light chain λ type. Bence-Jones proteins were not detected, while proteinuria was 1.28 g/L.

Discussion

Amyloidosis is not a single disease, but a series of diseases in which there is extracellular deposition of a protein which, although it may be derived from different and unrelated sources, folds into a β pleated sheet (5).

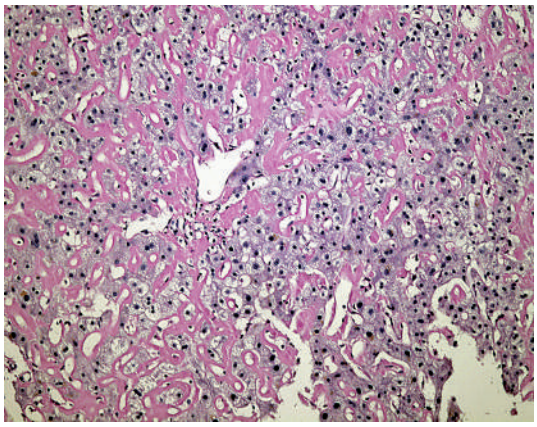

Fig.5 Amyloid in sinusoids subendothelially with characteristic staining (DPASx100).

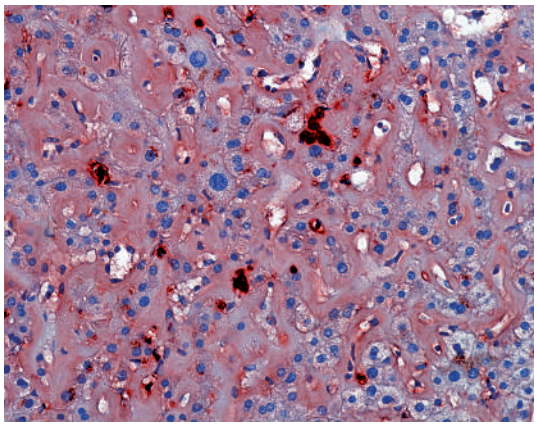

Fig.6 Positive immunohistochemical staining for anti light chain immunoglobulin (x400).

The liver is a common site of amyloid deposition in primary systemic amyloidosis (6). Symptoms of hepatic involvement may include early satiety, weight loss, chronic nausea, dyspepsia, and right upper quadrant fullness or discomfort. Nephrotic syndrome or renal insufficiency is the initial finding in more than one fourth of patients. Congestive heart failure is the main feature at diagnosis in one sixth of patients. Dyspnea and pedal edema are frequent in patients with congestive heart failure. Paresthesia and syncope are other prominent features in patients with peripheral neuropathy or autonomic neuropathy, and peripheral neuropathy is the main manifestation in one sixth of patients. Purpura, particularly in the periorbital and facial areas, is present in 15 % of patients (4,7).

Malabsorption occurs in fewer then 5% (8). It is important to bear in mind that many gastrointestinal symptoms may be a function of autonomic neuropathy interfering with gastric motility. Involvement of the gastrointestinal tract can be focal or diffuse and symptoms usually are linked to the location and extent of AL amyloid deposit. Achalasia, haematemesis, gastroparesis and pseudo-obstruction are among the many possible manifestation of gastrointestinal amyloid.

Hepatomegaly in patients with amyloidosis suggests hepatic involvement although occasionally the liver may not be enlarged. Gertz and Kyle reported that the liver is palpable at diagnosis in one fourth of patients, whereas splenomegaly is present initially in only 5% (9). However, Park et al described hepatomegaly in 79 (81%) of 98 patients with primary hepatic amyloidosis (6).

Our patient manifested only few clinical signs (weight loss, hepatomegaly and subicterus).

In the study of Gertz and Kyle, 77 consecutively enrolled patients were evaluated, 19 (25%) had hepatic amyloidosis, and 58 (75%) had amyloidosis without liver involvement (9). However, using Iodine^{123} amyloid P-component scintigraphy, Lovat and associates in 1998 showed amyloid of the liver in 54% of 118 patients with AL (10).

Hepatocellular failure is as rare as the portal hypertension (sinusoidal type), with poor prognosis. The amyloid is deposited between the columns of liver cells and the sinusoidal wall in the space of Disse. The liver cells are not directly involved but are compressed to a variable extent. The mid-zone and portal areas are most heavily infiltrated. Occasionally in AL type the amyloid is found only in the portal tracts in the walls of hepatic arterioles, around the interlobular arteries and lying free in clumps (11).

Severe intrahepatic cholestasis may rarely complicate AL amyloidosis. It is presumably due to the intense amyloid deposition interfering with bile passage into canaliculi and small bile ducts (12). However, obstructive jaundice from the deposition of amyloid-like substances in the extrahepatic bile ducts has been reported (13). Spontaneous rupture of the liver is rare (14).

The serum alkaline phosphatase value is increased in one fourth of patients. The degree of hepatomegaly is disproportionate to the liver enzyme abnormalities. Hyperbilirubinemia is an infrequent finding, and indicates a poor prognosis. The prothrombin time is prolonged in approximately 15% of cases (15).

However, most patients have extrahepatic evidence of AL, and nephrotic syndrome is common (36%), followed by congestive heart failure in 20%.

Our patient evidenced intrahepatic cholestasis, with hyperbilirubinaemia and increased alkaline phosphatase, without extrahepatic manifestations. Diagnosis of liver AL amyloidosis was established by the percutaneous liver biopsy, histology and immunohistochemistry.

The most important screening test for amyloidosis is immunofixation of the serum and urine to detect a monoclonal immunoglobulin light chain (16).

Although biopsy of the affected tissue is likely to be diagnostic, percutaneous liver biopsy causes hemorrhage in 4-5% of patients with amyloid and is avoided (17).

Park et al diagnosed 98 patients with amyloidosis. None of their patients experienced hepatic rupture or death due to liver biopsy, and only 4 (4%) bled after biopsy (6). Before liver biopsy, clinicians considered amyloidosis in differential diagnosis in only 14/98 patients (26%).

When chronic liver disease is complicated by portal hypertension, the increased resistance is usually sinusoidal, as is reported in cases with hepatic amyloidosis. While

distinctions between pre, post and sinusoidal processes are conceptually appealing, functional resistance to portal flow in a given patient may occur at more than one level. Hyperkinetic portal hypertension is a rare form, and is usually described in massive splenomegaly, Morbus Gaucher and arterio-venous fistula (11,18).

Hyperkinetic portal hypertension in our case was due to increased blood flow in both portal and splenic vein. This hemodynamic form of portal hypertension is rarely reported in amyloidosis.

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