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Hepatic Amyloidosis
—Two Cases Report—

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Amyloidosis is classified according to the distribution pattern of amyloid deposition sites and associated diseases. Hepatic amyloidosis is not infrequent, although rarely causes clinical liver disease. We report two cases of amyloidosis diagnosed by liver biopsy. One presented with symptoms related almost to the liver disease, such as jaundice, hepatomegaly and indigestion. Echocardiogram revealed hypertrophic cardiomyopathy, suggesting cardiac involvement of the amyloidosis. The patient died of hepatic failure. The other case was found in a patient with an end stage renal disease. Features of congestive heart failure in this case may reflect cardiac involvement. The pattern of hepatic amyloid deposition in both of these cases was diffuse perisinusoidal. The predominant intralobular deposition suggests that these are amyloidosis of the secondary type.

Key Words: *amyloidosis, liver*

INTRODUCTION

Amyloidosis is defined as the deposition of amyloid, an abnormal proteinaceous material, usually in two or more organs, and occurs with a variety of hereditary, neoplastic and inflammatory disorders(Kyle and Bayrd, 1975). There are two main types of amyloidosis, primary and secondary. Primary amyloidosis is associated most frequently with plasma cell dyscrasias(Isobe and Osserman, 1974) and involves principally the tongue, heart, gastrointestinal tract, skeletal and smooth muscle, ligament, nerve and skin. Secondary amyloidosis is most often associated with chronic inflammatory diseases, and the liver, kidneys, spleen and adrenals are the principal organs of involvement.

Primary amyloidosis involving the liver consists of the deposition in the portal areas, sometimes restricted only to the vessel. In contrast, secondary amyloidosis consists of the deposition in the space of Disse with the hepatocytes shrunken and embedded in the thick amorphous material. However, only occasionally, patients present with jaundice, hepatomegaly or portal hypertension as the first manifestation of amyloidosis(Kapp, 1965). We have experienced two cases of hepatic amyloidosis, one of which had predominant hepatic symptoms and the other no such symptoms but mild hepatomegaly.

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CASE HISTORY

Case 1

This 57-year old male was admitted to the Department of Internal Medicine because of indigestion, jaundice and weight loss for 1 month. Past history was unremarkable. On physical examination the liver was palpable 5 finger breadths below the right costal margin and was hard, tender and nodular. Laboratory examination revealed that the hemoglobin 15.4 gm/dl, the white cell count 12,700/mm^3 with 64% granulocytes, 29% lymphocytes, and 6% monocytes, and the platelet count 351,000/mm^3. The urine gave two positive test for protein. The total protein was 6.0 gm/dl, the albumin 3.1 gm/dl, the alkaline phosphatase 713U, the total bilirubin 3.7 mg/dl, the SGOT 45U, the SGPT 38U, the r-GTP 278U/l and the alpha-fetoprotein less than 31U/ml. The 24 hour urine protein was 1.4 gm. The creatinine clearance was 90.0ml/min/m^2 BSA. Abdominal ultrasonography and CT scan revealed hepatomegaly due to a diffuse infiltrative disease.

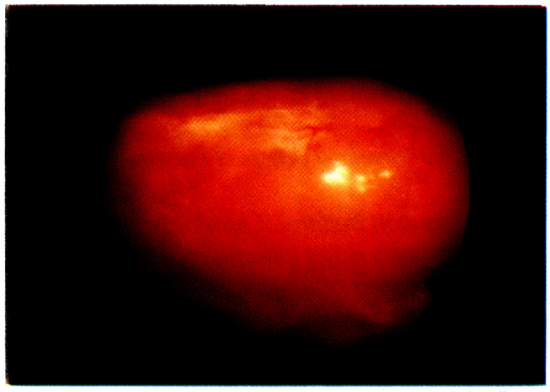

Fig. 1. Anteroinferior aspect of the right lobe of the liver shows an irregular surface with patchy whitish yellow areas and increased vascular markings (case 1).

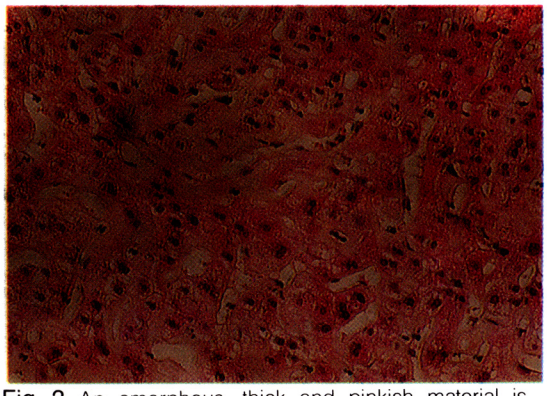

Fig. 2. An amorphous, thick and pinkish material is deposited in a large amount in the perisinusoidal space resulting in compression and atrophy of the hepatocytes (case 1) (hematoxylin-eosin, ×400).

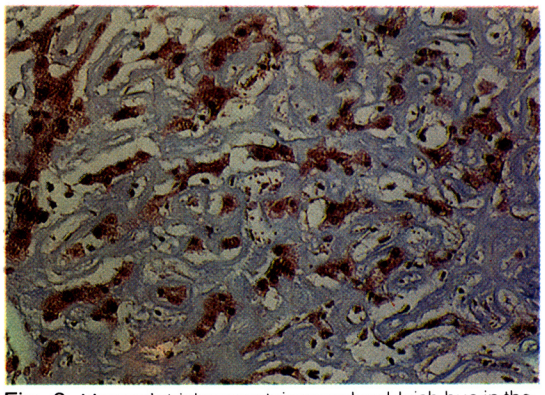

Fig. 3. Masson's trichrome stain reveals a bluish hue in the perisinusoidal deposit with complete obliteration of the sinusoids (case 1) (×400).

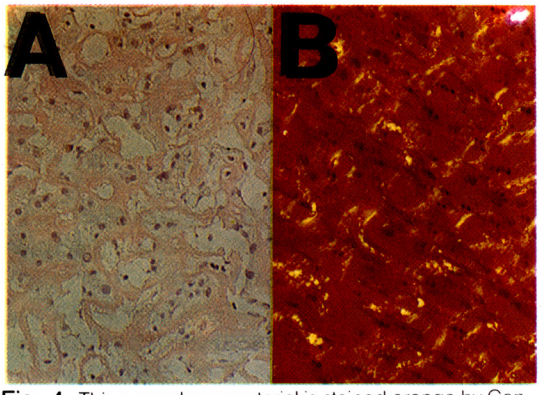

Fig. 4. This amorphous material is stained orange by Congo red stain (A, ×200) and shows green birefringence under the polarizing filter (B, ×200).

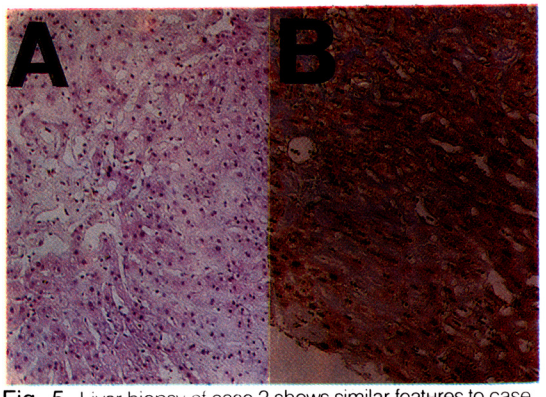

Fig. 5. Liver biopsy of case 2 shows similar features to case 1, but shows no vascular deposit (A: hematoxylin-eosin, ×200, B: Masson's trichrome, ×200).

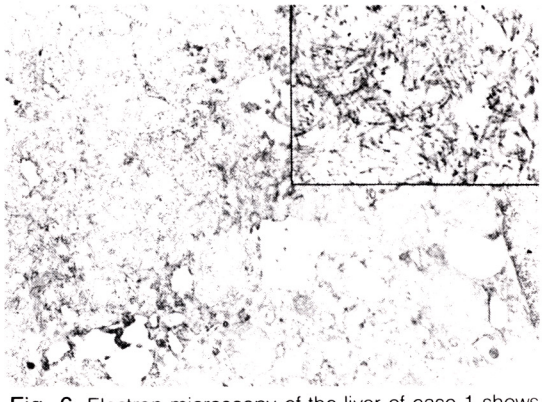

Fig. 6. Electron microscopy of the liver of case 1 shows many nonbranching fibrils of about 7 nm in diameter, encroaching upon and destroying the hepatocytes (uranyl acetate and lead citrate, ×8,000) (Inset: higher magnification, ×20,000).

On the 17th hospital day peritoneoscopic liver biopsy was done. The surface was generally smooth and yellowish red, inferior margin appeared blunt. But the anteroinferior aspect was irregular and somewhat nodular. The sections of the liver showed marked deposition of an amorphous, thick and pinkish material in the perisinusoidal areas with complete obliteration of the sinusoids. The hepatocytes appeared shrunken and embedded in the deposits. Portal tracts were mildly widened and the vessel wall deposit was present. This substance was stained blue by Masson's trichrome stain, and orange by Congo red stain with green birefringence under the polarizing filter. Electron microscopic examination showed fibrillar amyloid which encroached upon and destroyed the hepatocytes. Globular deposits were not found. Serum immunoelectrophoresis was within normal limit. Intravenous pyelography, radiologic study of the upper gastrointestinal tract and barium enema were unremarkable. Echocardiogram showed mild pleural effusion and hypertrophic cardiomyopathy, which was suggestive of cardiac involvement.

The patient was suffered from progressive jaundice, elevation of the SGOP, SGPT, prolongation of the prothrombin time, and ascites. The patient died of hepatic failure with hepatic encephalopathy on the 59th hospital day.

Case 2

This 50 year-old male was admitted to the Department of Internal Medicine due to watery diarrhea of a 5 days duration and a known end stage renal disease. He had been relatively well until 18 years ago, when generalized edema had developed and he had been admitted for 1 month under the impression of poststreptococcal glomerulonephritis.

After discharge the renal symptom was aggravated and hemodialysis had been undertaken three times per week since 5 years ago. Eight months before this admission he was suffered from right scrotal swelling which prompted him to admit to our hospital. Blood pressure was 180/130 mmHg. The urea nitrogen was 37.5 mg/dl, the creatinine was 14.2 mg/dl, the sodium 139 mEq/l, the potassium 4.5 mEq/l, the chloride 97 mEq/l, and the carbon dioxide 27 mM/l. Chest PA revealed features of congestive heart failure and pleural effusion. EKG demonstrated inferior wall myocardial ischemia. Bassini's hernioplasty was done.

Four months after the discharge he was admitted again via the emergency room because of abdominal pain and diarrhea. Physical examination revealed diffuse abdominal tenderness. The hemoglobin was 6.3 gm/dl, the hematocrit 20.1%, the sodium 125 mEq/l, the potassium 3.0 mEq/l, the total protein 3.9 gm/dl, the albumin 1.6 gm/dl, the urea nitrogen 64.5 mg/dl, the creatinine 10.4 mg/dl, the calcium 8.6 mg/dl, and the phosphorus 1.8 mg/dl. Rectal examination revealed fresh bleeding and the examination of stool for occult blood was positive. Chest PA revealed left pleural effusion. Sputum culture grew Pseudomonas aeruginosa and sputum AFB was positive once per three times. Flat and upright abdomen film showed multiple calcified densities in both renal areas and marked decrease in the renal size. Radiographic examination of the gastrointestinal tract showed duodenitis. Serum CEA was 16.5 ng/ml.

On this third admission the blood pressure was 120/90 mmHg. He was chronically ill looking and poorly nourished. The skin was warm and dry and there were petechiae on the face, neck, trunk, anterior chest and abdomen. Conjunctivae were severely pale. Tongue and lips were dried. Abdomen was soft and distended. Fluid wave and shifting dullness was present. The liver was palpable 3 FB below the right costal margin and it felt hard, nontender with sharp margin. Bowel sounds were increased. Mild pitting edema was noted. Rectal examination revealed external hemorrhoid. The hemoglobin was 3.9 gm/dl, the hematocrit 15.1%, the total protein 5.1 gm/dl, the albumin 2.5 gm/dl, the urea nitrogen 84.1 mg/dl, the creatinine 23.4 mg/dl, the SGOT 25U, and the SGPT 33U. HBs antigen was negative, but anti-HBs and anti-HBc antibody were positive. Blood and stool culture were negative. Sputum culture grew Klebsiella pneumoniae and Pseudomonas. Hemodialysis was done on the 5th hospital day. Abdominal CT scan showed diffuse enlargement of the liver without focal lesion, ascites, multiple lymphadenopathy in paraaortic areas and contracted kidneys with multiple cysts and calcification. On the 14th hospital day hemodialysis was done again. Under the impression of tuberculosis, peritoneoscopic liver biopsy was performed on the 26th hospital day. The edge of the liver was blunt and the color appeared slightly yellow. The liver had occasional dimplings on its surface with purple colored vascular staining. The section of the liver showed deposition of an amorphous, thick and light pink material in the perisinusoidal space. There were neither portal widening nor vascular deposit. This material was stained orange by Congo red stain and revealed green birefringence under the polarizing filter.

DISCUSSION

Amyloidosis is defined by the presence of extracellular deposits of insoluble protein fibrils which have certain physicochemical properties (Skinner and Cohen, 1983). Based on the abnormal proteins deposited it may be divided into several forms such as AL, AA and AF forms, each having a distinct serum protein precursor. The AL form, in which the abnormal protein is derived from the light chain of the immunoglobulin, constitutes the primary and myeloma associated forms, and mainly affects the heart, gastrointestinal tract, tongue and muscle. In AA form, the amyloid is the amyloid protein A. It constitutes the secondary form and affects mainly the liver, spleen, kidneys, and the adrenals. The abnormal protein of the AF form which constitutes the heredofamilial amyloidosis is derived from the prealbumin.

The clinical manifestation of amyloidosis varies and depends on the involved organ or tissue. Hepatic involvement is common in not only secondary but also primary forms (Levine, 1962), but rarely causes symptoms related to the liver disease. Changes of liver function test are usually minimal (Kyle and Bayrd, 1975) and tend to occur late in the course of the disease. However, hepatomegaly is a rather common finding (Suh et al, 1983), although jaundice is usually mild and occurs in only 5-10% of patients (Levy et al, 1971). Hepatic coma developed in one patient reported by Levine (1962). The present cases were found to have hepatomegaly with features of diffuse infiltrative liver disease, and the case 1 showed an elevation of the GOT and GPT. Nevertheless the amyloidosis could not be suggested by physicians until the liver biopsy.

Renal involvement was suspected in case 1 because of proteinuria. In case 2, however, it is uncertain whether the azotemia reflected to the end stage renal disease alone or combination of both the glomerular disease and the renal amyloid deposit. The most important clinical manifestations of renal involvement are proteinuria and edema (Cohen, 1967; Ogg et al, 1981; Han et al, 1982). If azotemia develops due to amyloid deposition, the prognosis is grave (Ogg et al, 1981; Oh et al, 1983).

The cardiac mainfestation consists of congestive heart failure and cardiomegaly, either with or without murmurs (Buja et al, 1970; Park et al, 1984). The myocardium, the endocardium, the valves and the pericardium may be involved. Hypertrophic cardiomyopathy of the case 1 and congestive heart failure of the case 2 may be due to amyloid deposits, but not conclusive.

Gastrointestinal symptoms may result form direct involvement of the autonomic nervous system. Skin and neurologic manifestations are also common (Lee, 1966; Rubinow and Cohen, 1978; Park et al, 1979).

Amyloid appears eosinophilic, glassy, and amorphous on hematoxylin-eosin stained sections, and shows metachromasia with crystal violet or methyl violet stain, violaceus hue with periodic acid-Schiff stain and green birefringence under the polarizing microscope after Congo red stain. Thioflavine dyes or Sirius red stains may be used for diagnosis. The amyloid fibrils have a characteristic electron microscopic appearance, and are composed of fine, nonbranching rigid fibrils of 7 to 10nm in diameter (Cohen and Calkins, 1959). In both of the present cases, most of the amyloid accumulated in the space of Disse, completely obliterating the sinusoids. This predominantly perisinusoidal pattern is different from that of primary amyloidosis, in which deposition occurs in the portal areas, sometimes restricted to the portal vessel wall. In globular amyloidosis, a peculiar type, which is typically seen in 11% of the hepatic amyloidosis, the deposition occurs as round bodies within the space of Disse and shows a predilection toward the perivenular region and occasionally portal areas (Kanel et al, 1981). In the present cases such a pattern is not found.

The cause of death in amyloidosis is largely attributed to renal or cardiac failure. Case 1 died of hepatic failure and hepatic encephalopathy without significant renal impairment.

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