

Severe Intrahepatic Cholestasis in an Elderly Patient with Primary Amyloidosis and Colon Adenocarcinoma

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Hepatic involvement in primary amyloidosis (AL type) is not rare but is often clinically silent. However, presentation with jaundice in AL-type amyloidosis is rare, with an incidence of less than 5% reported in the literature. It is considered to be a preterminal sign. We herein report on a case of primary hepatic amyloidosis presenting with severe intrahepatic cholestasis. Viral, drug, alcohol, and autoimmune etiologies were all excluded. A liver biopsy was performed because of unexplained cholestatic jaundice for 3 months. The pathology showed hepatic amyloidosis with extensive amyloid deposition in the expanded portal tracts and sinusoidal space. The patient received supportive treatment only, because of persistent jaundice, coexistent colon cancer with para-aortic lymph node metastasis, and possibly peritoneal carcinomatosis. Unfortunately, the patient died of sepsis 10 months after the onset of jaundice. We suggest that hepatic amyloidosis must be considered in the differential diagnosis of unexplained cholestatic jaundice. (*Chang Gung Med J* 2004;27:74-9)

Key words: intrahepatic cholestasis, hepatic amyloidosis.

Amyloidosis is a spectrum of disorders with extracellular deposition of insoluble amyloid fibrils. The original classifications of systemic amyloidosis were based on the presence or absence of underlying disease and organ involvements of the amyloid deposits. Early reports described patients who had an underlying disease and 'typical' involvements of the liver, spleen, kidney, and adrenal gland as having secondary (or reactive) amyloidosis, whereas patients with primary amyloidosis who had no underlying disease except complicating myeloma had an 'atypical' distribution in the heart, gut, muscles, nerves, lymph nodes, and skin.⁽¹⁾ As the basic biochemical and molecular properties of amyloid deposits have become better understood, the modern classification of amyloidosis is based on the nature of the fibrillar protein component. The names, AL and AA type of amyloidosis, originate from the letter

A which designates amyloid fibril protein and which is modified by the second letter to indicate the specific fibril protein. The amino terminal fragment of the immunoglobulin light chain found in the majority of amyloid deposits in both primary amyloidosis and amyloidosis associated with myeloma is designated 'AL', while the amyloid A protein component found in secondary amyloidosis is designated 'AA'. In a word, primary amyloidosis (AL type) is a syndrome with no apparent preceding or coexisting disease, and is caused by deposition of a monoclonal immunoglobulin light chain λ or κ , which can be detected in serum or urine. Secondary amyloidosis (the AA type) is a syndrome associated with a variety of chronic inflammatory diseases, and is caused by deposition of fibrils of AA protein derived from serum amyloid A protein.⁽²⁾ Up to 80% of patients with the primary AL type of amyloidosis have a sub-

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tle monoclonal gammopathy, but 14% of cases cannot demonstrate this underlying gammopathy. Multiple myeloma is found in 15% of cases of AL amyloidosis. The most common clinical manifestations in systemic AL amyloidosis are nephrotic syndrome, cardiomyopathy, carpal tunnel syndrome, and peripheral sensory neuropathy.^(2,3) The most common causes of secondary AA type amyloidosis are idiopathic inflammatory rheumatic disorders; while chronic microbial infections and malignant neoplasms account for the other underlying etiologies. The most common clinical presentations in systemic AA amyloidosis are proteinuria, nephrotic syndrome, or renal insufficiency.^(1,2) Hepatic involvement is common in both primary and secondary systemic amyloidosis, whereas clinical manifestations are often mild or absent with hepatic amyloidosis.^(2,3) Presentation with jaundice in primary amyloidosis occurred in fewer than 5% of cases in previous reports and was considered a preterminal sign.⁽⁴⁾ In addition, presentation with severe cholestasis is rare and has never been reported in Taiwan. We herein report a case of primary hepatic amyloidosis presenting with severe intrahepatic cholestasis.

CASE REPORT

A 75-year-old male farmer was rather well before, except for a history of diabetes mellitus controlled using regular oral hypoglycemic agents for 10 years. Unfortunately, he was diagnosed as having sigmoid cancer and underwent high anterior resection with colon-rectal anastomosis in November 1999. Pathology revealed stage Dukes B2. He was regularly followed up at a proctologic outpatient clinic without evidence of recurrence for 1 year. However, he suffered from generalized yellowish skin discoloration, tea-colored urine, and severe skin itching for 1 month starting in December 2000. He was referred to our outpatient clinic for further evaluation and treatment. Physical examination showed generalized yellowish skin discoloration, mild anemic conjunctiva, and icteric sclera. The liver was palpable with a span of 16 cm on the right middle clavicle line and 5 cm below the right costal margin with a blunt margin and elastic consistency. The spleen tip was also palpable. There was no ascites, leg edema, spider angioma, or palma erythema. Laboratory studies disclosed hemoglobin of 9.2 g/dl,

leukocytes of 10,600/mm³; platelets of 352,000/mm³, aspartate transaminase (AST) of 94 (normal, < 34) U/l, alanine transaminase (ALT) of 54 (normal, < 36) U/l, direct/total bilirubin of 102.6/184.7 (normal, < 6.8/22.2) μ mol/l, alkaline phosphatase (ALP) of 1605 (normal, 28-94) U/l, γ -glutamyl transferase (γ GT) of 747 (normal, < 26) U/L, prothrombin time of 11.8 (control, 11.5) s, albumin of 32 (35-55) g/l, and globulin of 21.5 (normal, 22-40) g/l. Hepatitis B surface antigen analyzed by radioimmunoassay (Ausria II, Abbott Laboratories, Chicago, IL, USA) and antibody to hepatitis C virus determined by a third-generation enzyme immunoassay kit (AxSYM[®] HCV, vers. 3.0 Abbott Laboratories) were both negative. Antinuclear antibody, antimitochondria antibody, and antismooth muscle antibody were all negative. Abdominal ultrasonography (US) revealed hepatosplenomegaly, gallbladder sandy stones, and a normal biliary tree. The clinical diagnosis was cholestatic hepatitis. Ursodeoxycholic acid at 200 mg thrice daily was prescribed. Follow-up liver biochemistry tests 1 month later showed AST of 86 U/l, ALT of 36 U/l, ALP of 1481 U/l, γ GT of 504 U/l, and total bilirubin of 283.9 μ mol/l. The clinical symptoms had not improved, and a liver biopsy was subsequently performed. Pathology revealed extensive deposition of a pinkish hyaline substance in the expanded portal tract and along all the sinusoidal spaces; this substance was positive for Congo red stain, mild chronic inflammatory cell infiltration, ductular proliferation in the portal area, and focal intracellular and intracanalicular cholestasis (Fig. 1). A further laboratory survey of hepatic amyloidosis showed blood urea nitrogen of 27 mg/dL, creatinine of 68.7 μ mol/l, cholesterol of 9.25 mmol/l, serum immunoglobulin (Ig) G of 5540 (normal, 6800-15,300) g/l, IgM of 485 (normal, 402-1675) g/l, IgA of 803 (normal, 747-3737) g/l, IgD of < 52.4 (normal, < 141) g/L, and IgE of 159 (normal, < 127) g/l. The serum protein electrophoresis showed an γ -globulin of 0.6g/dL, and immunoelectrophoresis disclosed no abnormal protein. Bone marrow aspiration revealed 6.3% plasma cell infiltration, and the pathology showed no amyloid deposition. However, urine immunofixation electrophoresis was positive for the paraprotein κ light chain. Twenty-four-hour urine protein was 605.6 mg/l in amount. The chest radiogram revealed a normal heart size, bilateral exaggerated lung marking, and blunting of the right

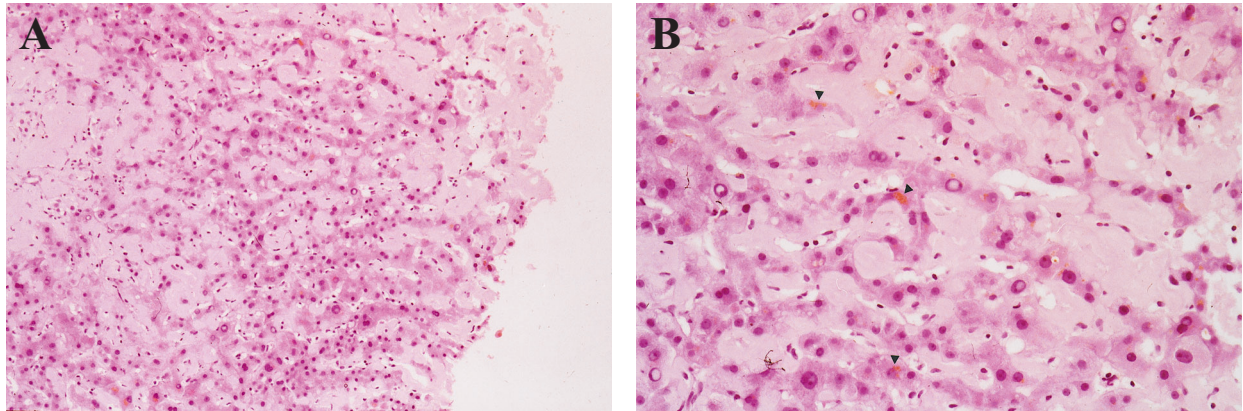


Fig. 1 A. Photomicrograph showing extensive deposition of a pinkish hyaline substance in the expanded portal tracts and along all of the sinusoidal spaces. (H&E, $\times 100$) B. Hepatocytes showing focal intracellular and intracanalicular cholestasis (arrow) (H&E, $\times 400$).

costophrenic angle. Cardiac US showed mild mitral regurgitation, tricuspid regurgitation, and left ventricular hypertrophy.

He was diagnosed as having AL-type hepatic amyloidosis and received supportive treatment. Unfortunately, bloody stool passage and progressive abdominal fullness bothered him 4 months later. A sigmoidoscopic examination showed an annular mass at a 20-cm distance from the anus. Pathology proved it to be an adenocarcinoma. Abdominal computed tomography (CT) showed inhomogeneous infiltration of the liver, the presence of massive ascites, a dirty appearance of the omental and mesentery fat, and multiple para-aortic lymph node enlargement. The serum-ascites albumin gradient was 2 g/dl. Ascites cytology was negative for malignancy. Because of persistent jaundice, para-aortic lymph node metastasis, and suspicion of peritoneal carcinomatosis, he was judged to be unsuitable for chemotherapy. He died of sepsis 2 months after the diagnosis of recurrent sigmoid cancer.

DISCUSSION

The most common amyloid syndromes involve infiltration of the kidneys, heart, and peripheral nervous system.⁽¹⁾ Liver involvement is usually seen in patients with the systemic primary AL type and secondary AA type of amyloidosis. Using quantitative radiolabelled serum amyloid P protein scintigraphy, liver involvement was shown in 54% of patients with the AL type of amyloidosis and 18% of those with

the AA type.⁽²⁾ In contrast to the frequent histological involvement of the liver, clinical amyloidosis rarely manifests as a liver disease. In 2 published series of AL-type amyloidosis, Kyle and Gertz reported the incidences of hepatomegaly to be 34% and 83%, respectively. The incidences of raised ALP levels of more than twice the upper limit of normal (ULN) were 16% and 45%, while those of elevated serum bilirubin levels were only 4% and 8%, respectively. Of these, the majority of bilirubin levels were less than $2 \times$ ULN.^(3,5) Severe intrahepatic cholestasis with jaundice as a primary clinical manifestation, as in the present case, is rare in AL amyloidosis. In contrast, no icteric case complicating AA amyloidosis has been reported in the past 50 years.⁽⁶⁾ A review of the literature revealed that there were 33 cases of AL amyloidosis associated with severe intrahepatic cholestasis.^(4,6-14) Of these 33 patients, 23 were men and 10 were women, and the median age was 61 (range, 29-85) years. Clinical features were hepatomegaly in 85%, ascites in 57.6%, pruritus in 40.7%, splenomegaly in 29%, and gastrointestinal bleeding in 18.5%. The median value of serum ALT was 50.6 (range, 34-192) U/l, of bilirubin was 265 (range, 99.2-752.4) $\mu\text{mol/l}$, and of ALP was 1132 (range, 243-1920) U/l. Cholestatic jaundice appears to be uncommon and was considered a preterminal sign. Gertz et al. reported that patients with serum total bilirubin of 25.7 $\mu\text{mol/l}$ only had 1.8 months of median survival.⁽⁵⁾ Of a total 33 patients in our review of cases,^(4,6-14) the major cause of death was renal failure (in 14 patients). Hepatorenal failure was

reported in 7 patients, cardiac failure in 4, liver failure in 2, and hepatocardiac failure in 1. One patient died of spontaneous intrahepatic hemorrhage, and 3 cases died of unspecified causes. One patient was well for 18 months after liver transplantation. Only 2 case reports in the literature describe the concurrence of primary amyloidosis with colon carcinoma as in the present case.^(15,16)

The pathogenesis of cholestasis in cholestatic hepatic amyloidosis may contribute to the compression of the intrahepatic bile ducts by amyloid deposits predominately in the portal area and sinusoidal space,⁽⁴⁾ as seen in the present case. Obstructive jaundice caused by amyloid deposits in the extrahepatic and large intrahepatic bile ducts has been reported,⁽¹⁷⁾ therefore cholestatic jaundice must be distinguished from obstructive jaundice in AL-type amyloidosis. In the present case, the intrahepatic and extrahepatic bile ducts were not dilated on repeated abdominal US and CT studies. The prevalence of ascites in hepatic amyloidosis is 14%-47%, and it is usually associated with nephrotic syndrome or cardiac failure, but portal hypertension may play an important role.⁽¹⁸⁾ In the present case, the ascites appeared with a value of the serum-ascites albumin gradient of over 1.1 mg/dl during the final hospitalization. The ascites was transudative, and it was probably a result of portal hypertension, heart failure, or renal involvement rather than peritoneal carcinomatosis.

In patients with progressive cholestatic jaundice of unknown cause and other clinical features such as macroglossia, hepatosplenomegaly, proteinuria, congestive heart failure, orthostatic hypotension, carpal tunnel syndrome, and peripheral neuropathy, systemic amyloidosis with hepatic involvement should be considered.⁽¹⁹⁾ A liver biopsy at the onset of suspicion of liver involvement can provide early diagnosis of hepatic amyloidosis. Electrophoresis alone is insufficient as a screening tool for patients with hepatic amyloidosis because a monoclonal spike is not common on serum protein electrophoresis, which always results from urinary loss of protein. A combination of serum and urine immunoelectrophoresis can increase the diagnostic information.⁽⁵⁾ As the clone is often subtle, as in the present case, the paraprotein was found only by a more-sensitive technique such as immunofixation electrophoresis. It can detect serum or urinary monoclonal or light chain

immunoglobulins in 90% of patients with AL-type amyloidosis.⁽¹⁹⁾ In patients with proteinuria, especially when associated with unexplained hepatomegaly, an unexplained raised ALP level, unexplained hepatomegaly associated with monoclonal protein detected in serum or urine, or a Howell-Jolly body found in the peripheral blood smear, hepatic amyloidosis should be considered.⁽⁵⁾ A histological diagnosis is required to confirm all suspicious involved organs, such as the kidney or liver. However, a liver biopsy was reported to have a 5% hemorrhagic rate in patients with amyloidosis.⁽²⁾

The overall survival in AL-type amyloidosis is poor with a median survival of less than 2 years.⁽¹⁹⁾ No significant difference was found between those with and without liver involvement.^(2,5) Congestive heart failure, the presence of urine light chains immunoglobulin hepatomegaly, and underlying multiple myelomas were the major factors adversely affecting survival during the first year after the diagnosis of AL-type systemic amyloidosis,⁽²⁰⁾ and the only laboratory parameter in relation to the prognosis is the raised bilirubin level.⁽²⁾ The presence of severe intrahepatic cholestasis in AL-type amyloidosis indicates a poorer prognosis, and 80% of reported patients died within 6 months after the onset of jaundice.^(9,14) The present case received only supportive treatment and was deemed unsuitable for chemotherapy. Unfortunately, he died of sepsis 10 months after the onset of jaundice. In spite of the poor prognosis of patients with AL-type hepatic amyloidosis, up to 43% of patients have clinical improvement and prolonged survival with intensive chemotherapy regimens.⁽²⁾

In summary, cholestatic jaundice as the first presentation of primary hepatic amyloidosis is rare. When clinical features such as proteinuria, macroglossia, hepatosplenomegaly, congestive heart failure, orthostatic hypotension, carpal tunnel syndrome, or peripheral neuropathy appear in a patient with unexplained intrahepatic cholestatic jaundice, hepatic amyloidosis should be considered as a probable etiology.

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以重度肝內膽汁鬱積為表現之肝臟類澱粉沉著症

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肝臟之原發性類澱粉沉著症並不少見，但臨床表現多無症狀。根據文獻的報告，臨床上出現黃疸的機率少於百分之五，且常是疾病末期的表現。以重度肝內膽汁鬱積為表現者更是罕見。我們報告一位75歲男性病患，因持續黃疸住院。在排除病毒性肝炎，藥物性肝炎，酒精性肝炎，自體免疫性肝炎及膽管阻塞後，經肝臟切片證實為類澱粉沉著症並且有廣泛類澱粉物質沉積在門脈區及竇狀區。由於該病患同時罹有大腸癌合併淋巴結及疑有腹膜轉移，僅接受支持性療法，病患不幸於黃疸出現後10個月死於敗血症。我們認為不明原因之黃疸應將肝臟類澱粉沉著症列入鑑別診斷。(長庚醫誌 2004;27:74-9)

關鍵字：膽汁鬱積，肝臟類澱粉沉著症。

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