PRIMARY SYSTEMIC AMYLOIDOSIS PRESENTING WITH SEVERE HYPERLIPIDEMIA : A CASE REPORT

REIKO MIZUNO, SHINICHI FUJIMOTO*, TOSHIO HASHIMOTO, TOSHIHIKO NISHINO
HIDEO SHIIKI, HIROSHI NAKANO* and KAZUHIRO DOHI
*First Department of Internal Medicine, *Department of Clinical and Laboratory Medicine, Nara Medical University*
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Abstract: Primary systemic amyloidosis with severe hyperlipidemia, suspected to be secondary to hepatic involvement, is described. A 48-year-old man was admitted with pretibial edema and abdominal fullness. Laboratory data showed severe hyperlipidemia with lipoprotein X and nephrotic syndrome. Based on biopsy findings of the kidney and liver, he was diagnosed with primary systemic amyloidosis. Hyperlipidemia in this patient was too severe to result only from nephrotic syndrome. Moreover, with lipoprotein X present, we suggest that hepatic amyloidosis can be a cause of severe hyperlipidemia in primary systemic amyloidosis. (奈医誌. J. Nara Med. Ass. **50**, 159～163, 1999)

Key words : hepatic amyloidosis, hyperlipidemia, primary systemic amyloidosis

INTRODUCTION

Primary systemic amyloidosis is a rare disorder characterized by excessive production and accumulation of aberrant monoclonal light chains. This insoluble light chain deposits in tissues as a fibrillar protein called amyloid, resulting in organ dysfunction and ultimately death. Amyloidosis has been described as a cause of secondary hyperlipidemia in patients with renal involvement and nephrotic syndrome. While the liver is recognized as a major site of amyloid deposition[1] and has an important role in lipid catabolism, hepatic amyloidosis has not been routinely described as a cause of secondary hyperlipidemia[2-5]. In this paper, we report a patient with primary systemic amyloidosis who presented with severe hyperlipidemia, suspected to result from hepatic involvement of amyloidosis.

CASE REPORT

A 48-year-old man was referred to our hospital because of primary systemic amyloidosis in April, 1998. The patient had been well until 4 months before admission, when pretibial edema and abdominal fullness developed. Two months before admission, he was admitted to another hospital where he was diagnosed with nephrotic syndrome and severe hyperlipidemia. There was no past history or family history of illness, except for his paternal uncle who had died of lung cancer. Renal and liver biopsies revealed massive deposits of amyloid fibrilar protein identified as AL type in both kidney and liver (Fig. 1, 2), primary systemic amyloidosis was diagnosed. The patient was transferred to our hospital.

On admission, he complained of abdominal fullness and anorexia. Physical examination showed hepatomegaly 4 fingerbreadths below the right costal margin and pretibial edema. Yellowish brown pigmentation was noted on the abdomen. Splenomegaly, lipemia retinalis, and

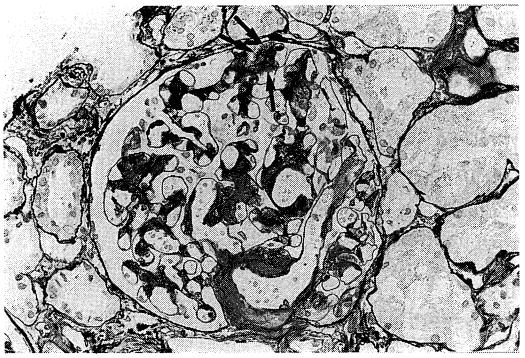

Fig. 1. Microscopic findings of renal biopsy specimens showed diffuse glomerular amyloid deposits in the mesangium and along the capillary walls. Amyloid spicules were observed in the subepithelial position (arrow). (Periodic acid-methenamine silver stain × 400).

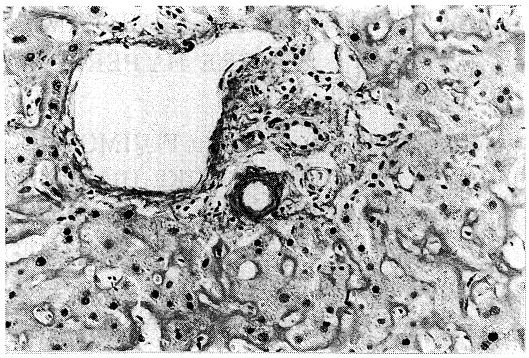

Fig. 2. Microscopic findings of liver biopsy specimens showed severe atrophy of hepatocytes secondary to massive Intralobular deposition of amyloid, partly accompamied with necrosis. The accumulation of amyloid was observed along the vessel wall. (Congo red stain ×200).

Table 1. Laboratory data on admission

Urinalysis			Alb	2.7	mg/dl
sugar		(−)	Glu	89	mg/dl
protein	6.4	g/day	Na	139	mEq/l
blood		(+)	K	4.4	mEq/l
BJP		(+)	Cl	102	mEq/l
Hematology			Blood coagulation		
RBC	523×10^4	/μl	bleeding time	2	min
Hb	17.0	g/dl	PT	10.4	min
Ht	49.3	%	APTT	36.1	sec
WBC	8,800	/μl	TT	48	sec
Plt	24.7×10^4	/μl	HPT	122	%
Blood chemistry			Serology		
T-Bil	0.4	mg/dl	CRP	0.1	mg/dl
ALP	1,193	IU/l	IgA	185	mg/dl
GOP	81	IU/l	IgG	396	mg/dl
GTP	107	IU/l	IgM	49.6	mg/dl
γ-GTP	82	IU/l	M protein	(+)	IgA κ
LDH	348	IU/l	Lipoprotein fraction		
ChE	404	IU/l	α	9.1	%
AMY	170	IU/l	pre-β	19.6	%
Scr	0.8	mg/dl	β	71.4	%
BUN	15	mg/dl	CM	0.9	%
CK	66	IU/l	renal function		
TC	890	mg/dl	Ccr	64.8	ml/min
TG	810	mg/dl	liver function		
TP	5.0	mg/dl	ICG	19.4	%

eruptive xanthomas were absent. The urine was positive for protein (4.1 g per day) and blood. Initial laboratory findings are shown in Table 1. His lipid profile, which was within normal limits 2 years before, showed marked hypercholesterolemia (890 mg/dl) and hypertriglyceridemia (810 mg/dl). Plasma lipid concentrations in parents and siblings were normal. Alcohol intake was minimal. Plasma lipoprotein fractionation showed raised concentrations of very low density lipoprotein (VLDL) and low density lipoprotein (LDL). In addition, lipoprotein X was positive.

Serum levels of total bilirubin, alkaline phosphatase, AST, ALT, and ICG retention rate were elevated. Total protein was depressed with hypoalbuminemia. There was no increase in serum IgA, IgG, or IgM concentrations ; no monoclonal immunoglobulin was seen on electrophoresis. The bone marrow showed no amyloid infiltration or evidence of multiple myeloma. No lytic lesions were seen in skeletal radiographs. Abdominal ultrasonography and computed tomography showed marked hepatomegaly with ascites. Biopsy of the stomach and rectum also demonstrated amyloid infiltrarion. Cardiac involvement was ruled out by endomyocardial biopsy, as well as normal electrocardiography and echocardiography. The patient has now received several courses of chemotherapy.

DISCUSSION

1. Primary systemic amyloidosis as a cause of secondary hyperlipidemia

In the present case, the lipid profile showed severe hypercholesterolemia and hypertriglyceridemia with high concentrations of VLDL and LDL. We have seen a similar lipoprotein pattern in patients with nephrotic systemic, myxedema, familial hypercholesterolemia, familial apolipoprotein E 3 deficiency and so on. Of these causes, nephrotic syndrome due to primary systemic amyloidosis is most likely in this case. Certainly, nephrotic syndrome is generally recognized as a cause secondary hyperlipidemia. It Is reported that hyperlipidemia is present in 70 to 100 % of patients with nephrotic syndrome. However, in a survey of 360 patients with nephrotic syndrome, Olbricht reported mean total cholesterol (TC) and triglycerides (TG) of 390±40 mg /dl and 270±60 mg/dl, respectively[6]. Shinomiya reported that the TC value in nephrotic syndrome could be estimated by the following calculation ; 600−[serum albumin level (mg/dl)] ×100 (mg/dl)[7]. Therefore, it appears that this patient's hyperlipidemia was too severe to result only from nephrotic syndrome. It is possible that the hyperlipidemia was associated with amyloidosis of the liver, which has an important role in the catabolism of both VLDL and LDL. The presence of lipoprotein X in addition to other laboratory findings in our patient suggested the parenchymal and cholestatic liver dysfunction. Therefore, the severe hyperlipidemia may be due partly to overproduction and partly to impaired catabolism of lipoprotein, resulting from renal or hepatic involvement with primary systemic amyloidosis.

2. Liver dysfunction and dyslipoproteinemia

The liver plays a crucial role in lipoprotein synthesis and clearance, so it is hardly surprising that hepatic disease, including hepatic amyloidosis, may be accompanied by qualitative and quantitative derangements of lipoprotein metabolism. Hepatic and biliary disease have separate influences on parenchymal damage and cholestasis. Cholestasis, regarded as a functional disorder of bile flow, causes qualitative and quantitative changes in lipoproteins because of

accumulation of abnormal LDL[8-10]. In cholestasis, three abnormal LDL particles can be separated by column chromatography, which are never seen in normal subjects. These particles are lipoprotein-Y, lipoprotein-X, and modified LDL particles depleted in cholesterol esters but enriched with triglycerides. The formation of these particles may result from reflux of biliary lecithin and free cholesterol into plasma coupled with a relative hepatic lipase and lecithin cholesterol acyl transferase (LCAT) deficiency.

In general, patients with parenchymal liver disease are likely to have normal or low total serum cholesterol and phospholipid levels, but additional cholestasis may cause circulating LP-X and marked hyperlipidemia[8,11]. In patients with reduced total cholesterol concentrations. the cholesterol ester fraction is prominently reduced. Patients with chronic parenchymal disease without cholestasis tend to have significantly reduced cholesterol production rates or activity of LCAT, which may contribute to low plasma cholesterol concentrations. Hepatic synthesis is likely to be reduced[12]. Moreover, impairment of releasing lipid into plasma due to reduced synthesis of apolipoprotein also may be associated[8]. However, in practice, individual patients frequently have varying combinations of hepatocellular and cholestatic disease. Thus, dyslipoproteinemia is seen with various patterns. In our patient, in addition to the presence of lipoprotein X, total bilirubin, alkaline phosphatase, AST, ALT, and ICG retention rate were elevated ; the liver histology revealed massive deposits of amyloid fibrillar protein identified as AL type. From laboratory and pathologic findings, it was suggested that liver function was impaired by both parenchymal damage and cholestasis due to hepatic involvement by amyloidosis. However, since laboratory findings suggesting liver dysfunction showed only relatively mild abnormalities, severe hyperlipidemia in this patient may result not only from liver dysfunction but also from other causes.

3. Hepatic amyloidosis

Amyloid diseases constitute a group of conditions with diverse causes characterized by an accumulation of ultrastructurally fibrillar material in various tissues and in quantities sufficient to compromise vital organ function. The associated disease states may be inflammatory, hereditary, neoplastic, or primary, and deposition can be local or systemic. Although amyloid deposition in the liver is common in amylodosis of all types, it is rarely of clinical importance[1,13,14]. It has been reported that intrahepatic cholestasis with marked elevations of bilirubin and alkaline phophatase occurs in only about 5 % of patients with hepatic amyloidosis[1]. Cutaneous stigmata of chronic liver disease (e.g. spider angiomas, palmar erythema) and portal hypertension are unusual. In a recent series of 474 patients with primary systemic amyloidosis, Kyle reported that only 25 % had hepatomegaly at diagnosis[15]. Serum alkaline phosphatase, glutamic-oxaloacetic transaminase, total bilirubin, and prothrombin time were elevated in 26, 34, 11, and 16 % of cases, respectively. Kyle also reported that serum cholesterol was elevated (>7.8 mmol/L) in 27 % of cases, and serum triglycerides were increased (>3.4 mmol/L) in 13 % of cases. Amyloidosis has been recognized as a cause of secondary hyperlipidemia in patients with nephrotic syndrome due to renal involvement, but hepatic amyloidosis itself has not. However, recent cases of primary hepatic amyloidosis have shown severe hyperlipidemia in the absence of nephrotic syndrome, In these cases, it was thought that severe hyperlipidemia might result from liver dysfunction due to hepatic amyloidosis[4,5]. It is also possible that lipoprotein catabolism was impaired by formation of

immune complexes, as seen in multiple myeloma or autoimmune hyperlipidemia with hyper-IgA globulinemia[16,17]. Thus, the mechanism of lipoprotein metabolism in primary systemic amyloidosis is complex and uncertain. However, hepatic involvement in primary systemic amyloidosis should be considered an important cause of hyperlipidemia, independent of complicated nephrotic syndrome. Further studies of hepatic lipoprotein metabolism in a large population of patients with primary systemic amyloidosis are needed to clarify the causes of hyperlipidemia in this disease.

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