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Liver Biopsy–Proven Hepatic Involvement of Primary Amyloidosis：A Case Report

Shinya NISHIZAWA[1)2)], Yasuaki TAKEYAMA[1)], Daisuke MORIHARA[1)2)], Makoto YOSHIKANE[1)3)], Hirokatsu NISHIMURA[1)], Teruo MATSUMOTO[1)], Takashi TANAKA[1)], Shinjiro INOMATA[1)], Akira ANAN[1)2)], Makoto IRIE[1)], Kaoru IWATA[1)], Satoshi SHAKADO[1)2)], Tetsuro SOHDA[1)], Hiroshi WATANABE[1)3)] and Shotaro SAKISAKA[1)2)]

[1)] *Department of Gastroenterology and Medicine, Faculty of Medicine, Fukuoka University, Fukuoka, Japan*
[2)] *The Division of Advanced Clinical Research for Viral Hepatitis and Liver Cancer, Faculty of Medicine, Fukuoka University, Fukuoka, Japan*
[3)] *Fukuoka Red Cross Hospital, Fukuoka, Japan*

Abstract：Although amyloidosis commonly involves the liver, the clinical manifestations of liver involvement have not always been presented at the early stage of the disease. We report a case of a 72–year–old male with primary amyloidosis with cholestatic features. The patient had been administered atorvastatin (10 mg/d) for hyperlipidemia. Five months after this treatment, cholestatic liver injury (alkaline phosphatase (ALP), 994 IU/l ; gamma–Glutamyl transpeptidase (GGT), 770 IU/l) occurred. The atorvastatin treatment was stopped due to the suspicion of drug –induced cholestatic liver injury. However, even 3 months after the cessation of atorvastatin treatment, serum levels of ALP and GGT remained elevated. Abdominal ultrasound and computed tomography examinations demonstrated hepatomegaly without obstructive findings of the biliary system. The patient underwent liver biopsy, and histological analysis demonstrated amyloid light chain (AL)–type amyloidosis. Autopsy showed Amyloid deposit in multiple organs, including the spleen, cardiac muscles, kidneys, pancreas, diaphragm, tongue, esophagus, stomach, small intestine, and colon. Primary hepatic amyloidosis must be considered in patients who present with hepatomegaly with unexplained elevated levels of serum ALP and GGT.

Key words：**Hepatic amyloidosis, Cholestasis, Liver biopsy, AL type amyloidosis, Drug–induced liver injury**

Introduction

Primary systemic amyloidosis is an uncommon disease characterized by extracellular deposition of insoluble fibrils derived from immunoglobulin light chains. The liver is a common site of amyloid deposition in primary systemic amyloidosis. Hepatic involvement in primary amyloidosis is often clinically silent. A mild elevation of the serum alkaline phosphatase (ALP) level and hepatomegaly are the most common findings.[1)] Systemic amyloidosis is present 0.1–0.7% of the time in autopsy studies. Hepatic involvement is found in approximately 50% of these cases.[2)] Light－chain deposition disease of the liver may also be associated with amyloid light chain (AL)－type amyloidosis and produce severe cholestasis.[3)–6)] Moreover, severe hepatic involvement in primary amyloidosis patients induces hepatic failure.[7)8)] We report a case of primary hepatic amyloidosis confirmed by liver biopsy with suspicion of drug–induced cholestatic liver injury and without symptoms suggestive of gastrointestinal and renal dysfunction.

Correspondence to：Yasuaki TAKEYAMA, M.D., Ph.D.
Department of Gastroenterology and Medicine, Faculty of Medicine, Fukuoka University, Fukuoka, Japan, 7–45–1 Nanakuma, Jonan, Fukuoka 814–0180, Japan
Tel：81–92–801–1011, Fax：81–92–874–2663 E–mail：yaz@fukuoka–u.ac.jp

Case Report

A 72-year-old male was diagnosed with hyperlipidemia (total cholesterol level, 233 mg/dl ; triglyceride level, 181 mg/dl) at a regularly scheduled medical examination in May 2000. After that, the patient was administered atorvastatin 10 mg/day (Lipitor®, Pfizer Inc., New York, USA). The patient was almost healthy, and was not diagnosed with any diseases in annual medical examinations from 1987 to 2000. After atorvastatin administration, serum cholesterol (TC) level was improved to 165 in one month. In October 2000, routine laboratory tests revealed an aspartate aminotransferase (AST)level of 45 IU/l, an alanine aminotransferase (ALT) level of 13 IU/l, an alkaline phosphatase (ALP)level of 994 IU/l, a gamma-glutamyl transferase (GGT) level of 770 IU/l, and TC level of 177. The patient was asymptomatic and without viral and alcohol etiologies. An abdominal ultrasound examination demonstrated slight hepatomegaly with no findings of liver diseases or cholestatic disorders. Treatment with atorvastatin was discontinued due to the suspicion of drug-induced cholestatic liver injury, and the patient was then administered ursodeoxycholate (UDCA) (600 mg/day) for the improvement of cholestatic liver disorders. In January 2001, the patient was admitted to our university hospital for further examination of prolonged elevated serum ALP and GGT levels 3 months after the discontinuation of atorvastatin. Physical examination showed hepatomegaly, the liver to be elastic hard, with dull abdominal pain and liver is elastic hard. Neurological findings were normal. Table 1 illustrates the characteristics of the patient's laboratory data on admission. Type 2 and 3 ALP were expressed, indicating cholestatic liver disease. A lymphocyte-stimulation test that is frequently used for identifying the causative drug in drug-induced liver disease was negative for atorvastatin.

The patient had no blood eosinophilia and a normal serum immunoglobulin G(IgG) level. Thyroid function tests and renal function tests including proteinuria were normal. Abdominal computed tomography and ultrasound examinations demonstrated slight hepatomegaly (liver span of 20 cm at the right costal margin). A liver biopsy revealed abundant amorphous eosinophilic deposits within the hepatic sinusoids. The deposits were localized within the space of Disse and were stained positively pink-red with Congo red (Fig. 1). Immunohistochemistry was positive for immunoglobulin A

Table 1. Charcteristics of the laboratory data on admission

〔Urinalysis〕		T－Bil	1.2mg/dl	IgG	751mg/dl
protein	negative	D－Bil	0.4mg/dl	IgA	316mg/dl
sugar	negative	AST	53IU/l	IgM	25mg/dl
sediment	n.p	ALT	12IU/l	IgE	20mg/dl
Ccr	86ml/min	LDH	366IU/l	RF	negative
〔CBC〕		ALP	844IU/l	LE test	negative
WBC	10,000μ/l	ALP1	0%	Hyaluronic acid	642.8ng/ml
Stab	0.0%	ALP2	90%	Bile acid	8μmol/l
Seg	59.8%	ALP3	10%	ICG (15 min)	33.6%
Eos	1.2%	ALP4	0%	Serum amyloid A	＜2.5μg/ml
Lym	30.2%	ALP5	0%	〔Urine biochemistry〕	
RBC	475×10⁴μ/l	ALP6	0%	Bence Jones Protein	negative
Hb	15.9g/dl	γGTP	469IU/l	〔Serological exam.〕	
Ht	46.9%	ChE	273IU/l	HBs antigen	negative
Plt	35.1×10⁴μ/l	BUN	20mg/dl	HBc antibody	negative
〔Coagulation〕		Cr	0.9mg/dl	HCV antibody	negative
PT	80%	TC	218mg/dl	ANA	20dil.
APTT	34.5sec	TG	184mg/dl	AMA	negative
〔Biochemistry〕		HDL－C	19mg/dl	〔Endocrine〕	
TP	7.2g/dl	CRP	1.0mg/dl	TSH	4.08μIU/ml
Alb	62.8%	Fe	156μg/dl	free T3	2.40pg/ml
α1	4.2%	UIBC	77μg/dl	free T4	1.32ng/dl
α2	10.3%	Ferritin	251ng/ml	〔Lymphocyte stimulation test〕	
β	9.5%	NH3	57μg/dl		negative
γ	13.2%	BTR	3.3		

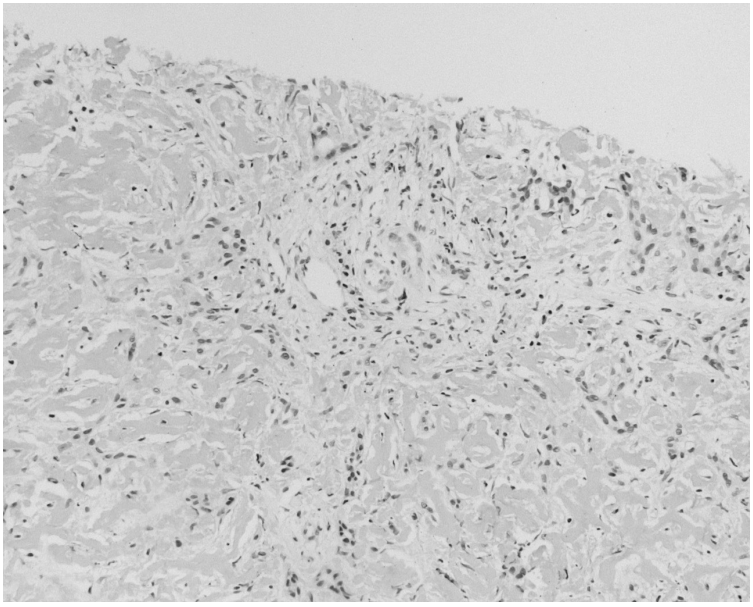

Fig. 1. Positive pink-red staining of the deposit with Congo red in liver biopsy. (Original magnification×200)

(IgA)-kappa type, amyloid A (AA) staining was negative, and AL staining was positive in the liver. Esophagogastroduodenoscopy, colonoscopy, and gastrointestinal biopsy were performed. Esophagogastric varices were absent. Amyloid protein deposition was observed in the stomach, duodenum, colon, and rectum. Electrocardiogram analysis showed normal sinus rhythm without any findings of abnormal conduction such as low voltage. Echocardiography did not reveal wall hypertrophy. Renal functions were normal without any evidence of albumin and Bence-Jones protein in the urine. The serum was negative for monoclonal (M) protein, antinuclear antibody (ANA), and rheumatoid factor (RF). Bone marrow biopsy revealed normocellular marrow without plasma cell infiltration. Multiple myeloma and rheumatoid arthritis were excluded. The patient was diagnosed with primary hepatic amyloidosis(AL type). After obtaining informed consent, a patient non-treatment decision was made. Within 3 months after diagnosis(in May 2001), the patient complained of symptoms suggestive of gastrointestinal dysfunction such as nausea, vomiting, epigastralgia, constipation, and diarrhea. Electrocardiogram analysis showed low voltage indicating abnormal cardiac conduction. Ultrasound showed severe hepatomegaly (liver span of 28 cm at the right costal margin)and ascites. Hepatomegaly progress, laboratory data showed exacerbationan, AST level was 168 IU/l, ALT level was 37 IU/l, ALP level was 1,552 IU/l, GGT level was 392 IU/l, and TC level was 309 IU/l. In June 2001, the patient died from multiple organ failure. Autopsy revealed a liver volume of 3,625 g. Histopathologic analysis revealed that most of the hepatocytes had collapsed due to the deposition of the amyloid protein in the entire hepatic parenchyma. The amyloid protein had accumulated in multiple organs, including the spleen, cardiac muscles, kidneys, pancreas, diaphragm, tongue, esophagus, stomach, small intestine, and colon.

Discussion

Initially, the patient was suspected to be suffering from drug-induced cholestatic liver injury because of a history of atorvastatin administration that is a known factor for chronic cholestasis. However, even 3 months after the cessation of atorvastatin treatment, serum ALP and GGT were elevated in this patient. Diagnostic imaging revealed slight hepatomegaly without mechanical biliary obstruction. These findings were not compatible with drug-induced liver injury ; therefore, liver biopsy was performed for the diagnosis of liver injury. Drug-induced liver injury is sometimes associated with hepatomegaly.[9] Gavilan *et*

al. reported a case of primary amyloidosis in a previously asymptomatic 65–year–old woman who was admitted to a hospital because of icterus and ascites mimicking drug–induced acute hepatic failure.[10] Interestingly, Couture *et al.* reported hyperlipidemia as the first biochemical manifestation of primary hepatic amyloidosis.[11] Our patient was treated with atorvastatin for hyperlipidemia that might have been induced by hepatic amyloidosis. The mechanism regarding the elevation of the serum cholesterol level due to Amyloid deposition remains unclear, but a biliary excretion disorder at the small bileduct is hypothesized to exist.

The most common causes of death from amyloidosis are renal failure and cardiac disease. Hepatic failure can occur but is quite rare. AA amyloidosis is treated by controlling the underlying disease. The treatment of AL–type amyloidosis is difficult because melphalan and prednisone provide only a 30% response rate with a mean survival period of 18 months[12]; however, the response to a higher dose of melphalan is greater (60%). Breems *et al.* reported the case of a patient who responded to high－dose melphalan chemotherapy and autologous stem cell reinfusion.[13] Liver transplantation is the definitive treatment for familial amyloidotic polyneuropathy (FAP) with a 75% 5－year survival rate. Kumar *et al.* reported a patient with primary amyloidosis with progressive liver failure who underwent sequential liver and stem cell transplantation leading to the resolution of the disease; this was only the second case of a patient who had undergone successful liver transplantation for this disorder.[14] However, these approaches should be considered only in cases without extrahepatic involvement.

We report a case of liver biopsy－proven hepatic involvement in amyloidosis. A rare complication of liver biopsy is rupture with bleeding. Fine–needle aspiration cytology may be useful in the diagnosis of hepatic amyloidosis.[15] The diagnostic evaluation of any patient with acute liver disease of unknown origin should comprise a careful history to exclude alcohol abuse, recent episodes of hypotension, and epidemiological risk factors of infectious hepatitis. Specific serology and molecular biology studies for common viruses involved in viral hepatitis, as well as screening for autoimmune liver diseases should also be performed. All patients should also undergo an abdominal US examination to exclude mechanical biliary obstruction. Clinicians should consider the diagnosis of primary hepatic amyloidosis in patients who present with hepatomegaly with unexplained elevated levels of serum ALP and GGT.

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