18F-fluorodeoxyglucose positron emission tomography might be useful for diagnosis of hepatic amyloidosis

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Abstract: We report on a woman with hepatic involvement of primary systemic (immunoglobulin light chain, AL) amyloidosis. Her diagnosis was confirmed by liver biopsy. Clinical symptoms of hepatic amyloidosis are generally mild at its first stage, with most frequent findings being hepatomegaly and alkaline phosphatase elevation. Recent advances in the understanding of the pathophysiology of systemic amyloidosis have made several treatments available. However, its prognosis is occasionally poor. Because liver biopsy is not always safe, other modalities for the diagnosis are needed. Of interest was that fluorodeoxyglucose (FDG) uptake into the liver was observed, compared with that into the spleen, in this patient, indicating that FDG positron emission tomography and computed tomography might be useful for the diagnosis of hepatic amyloidosis with mild liver dysfunction.

Keywords: amyloidosis, diagnosis, hepatic involvement, FDG PET

Introduction

Systemic amyloidosis has been recognized as one of the most serious incurable diseases. It is a relatively rare disease consisting of several subtypes according to amyloid origin, and it causes multiple organ dysfunctions by the deposition of insoluble amyloid protein in intercellular spaces of these organs.¹ Hepatic involvement is one of its phenotypes, and it is reported to complicate 56%–70% cases of systemic amyloidosis.^{2,3} However, it is too difficult to diagnose in its earlier stages because its symptoms and laboratory abnormalities are usually milder – irrespective of the amounts of amyloid deposition. Understanding of the pathophysiology and treatment of the disease has been improving, but its prognosis is still poor in some patients. Other diagnostic modalities are urgently required.

We report a case of hepatic involvement of primary systemic (immunoglobulin light chain, AL) amyloidosis, with severe amyloid deposition in the liver. Of note in this patient, fluorodeoxyglucose (FDG) uptake into the liver was observed, compared with that into the spleen, indicating that FDG positron emission tomography (PET) might prove to be helpful for the diagnosis of hepatic amyloidosis with mild liver dysfunction. FDG PET is one of the safe and useful diagnostic methods for determining her hepatic involvement of primary systemic AL amyloidosis, compared to liver biopsy.

Patient

A 76-year-old Japanese woman was referred to our hospital due to malaise, itching, anorexia, and liver dysfunction for 6 months. At her first visit to our clinic, her alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (γ -GTP) were 678 IU/L and

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330 IU/L, respectively. Alanine aminotransferase, aspartate aminotransferase, and whole blood cell counts were almost within normal range, although prothrombin time was slightly prolonged. Serum hepatitis viral markers and autoantibodies were negative (Table 1). The immunofixation electrophoresis of serum and urine did not demonstrate the presence of a monoclonal light chain (data not shown).

She had pulmonary tuberculosis at the age of 26. She took oral contraceptives, and she underwent surgery and blood transfusion for endometriosis at age 47. She had surgery without transfusion for osteoarthritis of the right knee and removal of colonic polyps, at 68 and 75 years old, respectively. Hypertension, hypercholesterolemia, and hypertrophic cardiomyopathy were diagnosed at age 56, 56, and 66, respectively, but no treatments were given. She did not have a past history of rheumatoid arthritis and had never received hemodialysis. She never smoked or drank alcohol. She was not a drug abuser, and no tattoo was found. At the time of admittance to our hospital, she was not taking any medications. Her father had esophageal cancer and alcoholic liver dysfunction, and her sister had skin cancer.

Although several clinical tests were performed at the outpatient clinic during a 6-month period, as the cause of her liver dysfunction remained unknown, she was then admitted to our hospital. Contrast-enhanced computed tomography (CT) revealed hepatomegaly with narrow portal vein, hepatic vein, and mild splenomegaly (Figure 1A–C). Although the association of liver and cardiac involvement is frequent, as her electrocardiogram and echocardiography showed normal

cardiac movement (left ventricular ejection fraction, 75%) and no dilatation of the inferior vena cava, we did not consider the possibility of cardiac involvement. Renal function was within normal range as late as 2 months before her death. Fluorine-18 (18F) labeled FDG PET/CT was performed. The FDG uptake into the liver but not into the spleen was observed (Figure 1D), although the mean standard uptake value was not so high (2.0 in the left lobe of the liver; 1.8–2.0 in the right lobe; and 1.3–1.4 in the spleen). Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography revealed narrowed intrahepatic bile ducts with smooth walls (Figure 2).

Upper gastrointestinal endoscopy showed no abnormal gross findings, but a biopsy specimen from the duodenal bulb mucosa exhibited amyloid deposition in the interspace of smooth muscles (not shown); macroglossia was observed. Eosinophilic amorphous depositions positive for Dylon staining⁴ that were resistant to potassium permanganate treatment⁵ and positive for amyloid P component were found.⁶ These results strongly suggested AL amyloidosis.

A liver biopsy was performed. The specimen was occupied by a diffuse eosinophilic amorphous structure, and any cellular component could not be found, suggesting hepatic amyloidosis (Figure 3). The biopsy specimen had the appearance of inappropriate material, but we later confirmed the hepatic involvement of primary systemic AL amyloidosis. Her general condition was too poor to allow aggressive treatment. She died 4 months after first admission to our hospital. Necropsy showed cardiac, renal, and hepatic involvement of amyloidosis.

Table 1 Laboratory data on first visit to Chiba University Hospital

Component	Result	Normal values	Component	Result	Normal values	Component	Result	Normal values
WBC, $\times 10^3/\mu\text{L}$	5.8	4.0–9.0	TP, g/dL	6.9	6.5–8.2	HBsAg	(–)	(–)
Hemoglobin, g/dL	15.0	12.0–16.0	Alb, g/dL	4.4	3.9–5.1	Anti-HBs*	(–)	(–)
Platelets, $\times 10^3/\mu\text{L}$	221	150–350	AST, IU/L	34	13–33	Anti-HBc*	(–)	(–)
PT–INR*	1.22	0.86–1.06	ALT, IU/L	22	8–42	Anti-HCV	(–)	(–)
PT%*	74	81–121	LDH, IU/L	217	119–229	ANA	$\times 40$	$< \times 160$
NH_3 , $\mu\text{g/dL}$ *	48	12–66	ALP, IU/L	678	115–359	AMA*	(–)	(–)
T chol, mg/dL	188	125–219	γ -GTP, IU/L	330	10–47	AMA-M2*	(–)	< 7.0
BUN, mg/dL	14	8–20	T bil, mg/dL	0.8	0.2–1.2	ASMA*	(–)	(–)
Cre, mg/dL	0.86	0.47–0.79	D bil, mg/dL	0.2	0.0–0.2			
CRP, mg/dL	0.0	≤ 0.2	IgM, mg/dL	58	35–220			
AFP, ng/mL*	5.5	≤ 8	IgG, mg/dL	1,013	870–1,700			

Note: *These data were obtained later.

Abbreviations: WBC, white blood cells; PT/INR, prothrombin time international normalized ratio; NH_3 , ammonia; T chol, total cholesterol; BUN, blood urea nitrogen; Cre, creatinine; CRP, C-reactive protein; AFP, alpha-fetoprotein; TP, total protein; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ -GTP, gamma-glutamyl transpeptidase; T bil, total bilirubin; D bil, direct bilirubin; IgM, immunoglobulin M; IgG, immunoglobulin G; HBsAg, hepatitis B (HB) surface antigen; anti-HBs, HB surface antibody; anti-HBc, HB core antibody; anti-HCV, hepatitis C virus antibody; ANA, antinuclear antibody; AMA, antimitochondrial antibody; M2, pyruvate dehydrogenase complex-E2 (PDC-E2); ASMA, antismooth muscle antibody; (–), negative.

Figure 1 Contrast-enhanced CT revealed hepatomegaly and heterogeneity of contrast staining.

Notes: (A) Plain phase. (B) Early phase. Narrow intrahepatic portal vessels are shown (white arrow). (C) Late phase. Hepatic vessels are unclear. (D) FDG-PET/CT revealed heterogeneous uptake of FDG into the liver. SUV maximum range was: 3.2–3.7; 2.8–3.2; and 1.6–2.5 in the left, right lobes of the liver, and the spleen, respectively.

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; SUV, standard uptake value.

Discussion

We present a case of hepatic amyloidosis with severe amyloid deposition in the liver. Deposit diseases, including amyloidosis, metabolic diseases, and nonalcoholic fatty liver disease, which are increasing in our country⁷ as well as the diffuse infiltration of various malignant diseases, such as malignant lymphoma, should be considered as differential diagnoses for hepatomegaly. It is reported that 56%–95% of autopsy cases of amyloidosis were complicated by hepatic amyloidosis.^{2,8} The prognosis of hepatic amyloidosis is very poor, with a reported mean survival time of about 12–17 months.^{9,10} Clinical symptoms of hepatic amyloidosis are generally mild at the early stage, and the most frequent findings are hepatomegaly and ALP elevation. In addition, 57%–83% of hepatic amyloidosis cases are reported to exhibit hepatomegaly,^{2,8} but the severity does not correspond

to the amount of amyloid deposition. Jaundice is rare, only being observed in about 5% of the hepatic amyloidosis cases, but once jaundice appears, the remaining life duration will be very limited.^{11–13}

Contrast-enhanced CT findings, such as hepatomegaly with ill-balanced inappropriate narrow intrahepatic vessels, and/or heterogeneous stain pattern, are reported, but besides these, the disease is thought to lack definitive findings. Recently, the extraskelatal uptake of ^{99m}Tc-pyrophosphate in the liver was reported, and it was concluded to be specific for hepatic amyloidosis.^{14,15} Of interest, the sites of the liver with comparatively remaining hepatocytes become hypertrophic, compared with the sites with hepatocytes compressed by severe deposition of amyloid.¹⁶

An interesting, perhaps vital, observation was the uptake of FDG into the liver, compared with the spleen of

Figure 2 MRCP (A) and ERCP (B and C) revealed narrowed whole intrahepatic bile ducts with smooth walls (white arrows).

Abbreviations: MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography.

this patient (Figure 1D), indicating the possible usefulness of FDG PET/CT for the diagnosis of hepatic amyloidosis with mild liver dysfunction. Son et al reported that FDG uptake was observed in hepatic amyloidosis or primary amyloidosis associated with multiple myeloma.¹⁷ The fixation of FDG was observed in certain localizations of amyloidosis,¹⁸ but the fixation of a satellite lymphoma cannot be excluded. No hepatic uptake was described in these two studies, which supported our observation. It is difficult to provide a pathophysiological mechanism to explain FDG uptake in extracellular sites. It is possible

that the target cells might be macrophages that retain the amyloid deposits.

Pathologically, hepatic amyloidosis is divided into subtypes, according to the pattern of amyloid deposition.¹⁹ Of the three subtypes, the intralobular type features amyloid deposition in the space of Disse in the liver and is most common in AL amyloidosis. The portal type is defined with amyloid deposition in the vessel walls of the portal areas. The mixed type is defined with amyloid deposition in both hepatic lobules and portal areas. The present case was assumed to be the intralobular type, which can present massive amyloid

Figure 3 Liver biopsy showing deposition of amyloid protein.

Notes: Hematoxylin and eosin stain, original magnification 20× (A) and 100× (B); Congo red stain, 20× (C) and 100× (D).

deposition and hepatocyte atrophy (Figure 3).²⁰ Among the five major subtypes of systemic amyloidosis, the amyloid A protein (AA) amyloidosis was negative in the liver because the amyloid resisted the potassium permanganate treatment by direct fast scarlet staining; it was also negative by immunostaining, although amyloid P component was positive in biopsy specimens from the duodenum. Familial or senile transthyretin-related amyloidosis was also thought to be negative because there was no family history of amyloidosis, and the amyloid was negative by immunostaining. The beta 2-microglobulin-related amyloidosis was also negative since this patient had not undergone dialysis. The CD138-positive plasma cells were observed to proliferate in the bone marrow (data not shown). These accumulating plasma cells were accompanied by atypia, such as the disparity of nucleus, irregularity of karyotype, and some with two or three nuclei. The bone marrow analysis from autopsy samples showed that immunoglobulin (lambda) light chain-positive plasma cells were dominant (22% of total nucleated cell counts) over immunoglobulin (kappa) light chain-positive plasma cells, suggesting monoclonal proliferation of plasma cells. These results strongly suggested primary AL amyloidosis, A (lambda) type, associated with plasma cell dyscrasia. Multiple myeloma was negative because the proliferation

of the plasma cells was confined to bone marrow, and there was no evidence of extramedullary plasmacytoma, obvious lymph node enlargement, or plasma cell infiltration other than in bone marrow. The amyloid itself was negative for both anti-immunoglobulin (lambda) light chain antibody and anti-immunoglobulin (kappa) light chain antibody immunostaining. Such results are apparently often observed in AL amyloidosis because of the three-dimensional structural change and the regional diversity of the immunoglobulin light chain.²¹

This patient presented negative serum and urine immunofixations, although Lachmann et al reported that a monoclonal excess of circulating free immunoglobulin light chain was identified at diagnosis in 98% of patients with primary AL amyloidosis.²²

Variant forms of soluble proteins, such as fibrinogen, gelsolin, lysozyme, and apolipoprotein (apo) A-I have been associated with familial amyloidosis. As apo A-I is the main protein in high-density lipoprotein (HDL), most apo A-I variants are associated with decreased plasma HDL (hypoalphalipoproteinemia), hyperglyceridemia, and/or defective lecithin cholesterol acyltransferase activation.²³ Because the HDL was within normal limits, apo A-I-related amyloidosis could also be excluded in our case.

Liver biopsy has been thought to be contraindicated for hepatic amyloidosis because of the risks of hepatic bleeding and rupture. There are two reports concerning this issue.^{24,25} One reported that among the 98 hepatic amyloidosis patients undergoing liver biopsy, four were complicated by bleeding, with two of them needing blood transfusion. They recovered, and there was no hepatic rupture or biopsy-related death. The other reported that in 80 hepatic amyloidosis patients having liver biopsy, two were complicated by bleeding but recovered with conservative treatment.²⁴ Liver biopsy is an effective procedure for patients suspected of hepatic amyloidosis. Still, contrary opinions exist concerning liver biopsy for patients with hepatic amyloidosis.²⁵ Szturcz et al²⁶ reported a case of AL amyloidosis presenting with spontaneous liver hemorrhage and hemoperitoneum. Because liver stiffness is greater in patients with hepatic involvement of amyloidosis, liver stiffness measurement may also be a simple method with diagnostic value in such patients.²⁷ Testing of the abdominal fat aspirates might also help to eliminate the risky invasive procedure of liver biopsy.²⁸ Thus, in terms of risk/benefit, a combination of these noninvasive modalities, together with FDG PET/CT, should be considered before a liver biopsy, as FDG PET/CT is not histologically specific, and – of course – hepatic/systemic amyloidosis cannot be diagnosed with FDG PET/CT alone. However, we noticed splenic hypoperfusion using FDG PET/CT, and the radiological finding of splenic hypoperfusion has been well-described as a marker of systemic amyloidosis.^{29,30} Splenic hypoperfusion might be a useful clue when clinical findings fail to lead to an accurate diagnosis. If one PET image is insufficient, it might be necessary to use a maximum intensity projection image. Overall, there have been very few case reports on the possible usefulness of FDG/PET in the diagnosis of hepatic amyloidosis.³¹ Recent advances in the understanding of the pathophysiology of the disease have made several treatments possible, such as dexamethasone,¹¹ melphalan with prednisolone,³¹ melphalan with dexamethasone,³² thalidomide with dexamethasone,³³ lenalidomide with dexamethasone,³⁴ bortezomib with dexamethasone,³⁵ and autologous hematopoietic stem cell transplantation.³⁶ Survival benefits have been reported. But once the disease stage has progressed beyond a certain extent, these treatments can no longer be performed due to the serious symptoms and complications. Stem cell transplant is a preferred therapeutic modality, but only a minority of patients are eligible, due to either advanced disease stage at presentation or advanced age.

In conclusion, the clinical diagnosis of systemic amyloidosis at an earlier stage is a major challenge. We

presented a case of hepatic involvement of systemic amyloidosis in which we observed FDG uptake into the liver, compared with that into the spleen. Our case suggests that FDG PET/CT might be of potential interest in the search for a diagnosis. Further studies will be needed.

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Disclosure

The authors report no conflicts of interest in this work.

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