

[ CASE REPORT ]

## Giant Hepatomegaly with Spleno-testicular Enlargement in a Patient with Apolipoprotein A-I Amyloidosis: An Uncommon Type of Amyloidosis in Japan

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### Abstract:

Hereditary systemic amyloidosis aside from transthyretin-related familial amyloid polyneuropathy is quite uncommon in Japan. We herein report a sporadic case of hereditary apolipoprotein A-I (apoAI) amyloidosis. The patient was a 43-year-old Japanese man who exhibited marked hepatomegaly with spleno-testicular enlargement. While he was initially thought to have primary AL amyloidosis, a proteomics analysis revealed that the amyloid was composed of variant apoAI with an E34K variant. To date, only one patient with apoAI amyloidosis has been reported in Japan. However, our study suggests that more patients may be present in Japan, and the majority may have been diagnosed with other types of amyloidosis due to its clinical similarity.

**Key words:** hereditary systemic amyloidosis, ApoAI amyloidosis, hepatic amyloidosis, testicular amyloidosis, proteomic analysis

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### Introduction

Over 30 distinctive precursors of amyloid fibrils have been identified as causes of different types of amyloidosis (1). Apolipoprotein A-I (apoAI) is a 28-kD nonglycosylated protein mainly produced by the liver and intestine (2) that constitutes the major apolipoprotein of high-density lipoprotein (HDL) and regulates its metabolism. In a mutated form, apoAI represents an amyloidogenic precursor in some cases of hereditary systemic amyloidosis (2), and over 20 amyloidogenic *APOAI* mutations have been reported (3-17).

Hereditary apoAI amyloidosis (AApoAI amyloidosis)

mainly involves the kidneys (5-12, 17), heart (13-15), and liver (16). Clinically, it can particularly resemble systemic immunoglobulin light-chain (AL) amyloidosis, which predominantly involves the kidneys, heart, and liver (18). Thus far, most patients with AApoAI amyloidosis have been reported in Western countries (3, 5-16), and it continues to be recognized as a very rare disorder in Asian countries.

We experienced a case of systemic amyloidosis with marked hepatic enlargement in addition to a swelling of the spleen and testis. While this patient was initially thought to have primary AL amyloidosis, a proteomics study showed that the amyloid was composed of a variant form of apoAI.

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## Case Report

A Japanese man with a history of atopic dermatitis and bronchial asthma developed mild liver dysfunction at 30 years old. By 38 years old, he had developed proteinuria with mild renal dysfunction and male infertility. Dyslipidemia and hyperuricemia were also found [serum low-density lipoprotein (LDL)-cholesterol, 221 mg/dL and uric acid, 8.8 mg/dL], and simvastatin (10 mg/day) and febuxostat (20 mg/day) were orally given. In addition, he began to take esomeprazole (10 mg/day) for gastroesophageal reflux disease. As his liver dysfunction and hepatomegaly gradually progressed [serum alkaline phosphatase (ALP) 797 IU/L and  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GTP) 297 IU/L], he underwent a liver biopsy at Hamamatsu University Hospital at 39 years old, which revealed a massive amyloid deposition, especially in the portal area (Fig. 1A-C). Monoclonal proteins were not detected in serum or urine specimens, and a bone marrow examination demonstrated no proliferation of plasma cells. While the biopsied liver was immunohistochemically stained using antisera against amyloid A protein (AA), transthyretin (TTR), and kappa and lambda immunoglobulin light chains (AL), no samples showed positive results.

From 41 years old, ursodeoxycholic acid (UDCA; 600 mg/day) was added because serum levels of ALP and  $\gamma$ -GTP were raised to 985 IU/L and 384 IU/L. Oral intake of telmisartan (20 mg/day) was also started for renal protection. In addition, atorvastatin calcium hydrate (10 mg/day) was substituted for simvastatin due to an insufficient effect.

At 42 years old, he was referred to our hospital for a further examination and treatment, with a tentative diagnosis of systemic AL amyloidosis due to dominant hepatic involvement. He had no family history of amyloidosis, hepatic failure, or renal failure; however, his father had had an enlarged abdomen of unknown etiology and died due to bronchial asthma at 44 years old.

On a physical examination, an abdominal bulge owing to a swollen liver was clearly seen, and a hard-enlarged liver edge was palpable for 8 fingerbreadths (about 12 cm) in the right hypochondriac region (Fig. 2A). There were no signs of purpura, jaundice, macroglossia, caput medusae, ascites, or leg edema, nor were there any signs of hepatic encephalopathy or polyneuropathy. The laboratory data are summarized in Table. He had an almost normal liver function, with the exception of elevated serum ALP 1,006 IU/L and  $\gamma$ -GTP 295 IU/L levels. However, renal dysfunction was observed with high serum levels of urea nitrogen (BUN; 33.2 mg/dL) and creatinine (Cr; 2.21 mg/dL). Serum uric acid was also increased (9.5 mg/dL). Urine protein was positive, and the total amount of urine protein was 2.7 g/day. His serum levels of apoAI and HDL-cholesterol were mildly decreased (93 and 32 mg/dL, respectively). Severe coagulopathy was not detected. Serum N-terminal prohormone of brain natriuretic peptide (NT-pro BNP) was slightly elevated at 194.0 pg/mL (normal <125.0).

There were no findings of amyloid cardiomyopathy on an electrocardiogram and echocardiogram. Upper gastrointestinal endoscopy demonstrated no gastroesophageal varices. Tissue biopsies taken from the duodenal mucosa were positive for amyloid deposition (data not shown). Abdominal computed tomography (CT) revealed a markedly enlarged liver, bilaterally atrophic kidneys with multiple cysts, and swelling of the spleen and bilateral testis (Fig. 2B-D). Chest CT showed no abnormal findings, including no thickening of the bronchial walls (data not shown).

Due to the presence of testicular enlargement and in order to examine his spermatogenic function, a testicular biopsy was also performed at 42 years old. Histopathology demonstrated marked amyloid deposition in degenerated seminiferous tubules and interstitium without spermatogenesis (Fig. 1E, F). The serum testosterone level was less than 5 ng/dL (normal: 131-871), and gonadotropins were elevated (luteinizing hormone: 52.8 mIU/mL, normal: 2.2-8.4 and follicle-stimulating hormone: 123.5 mIU/mL, normal 1.8-12).

### Amyloid typing and the APOAI gene analysis

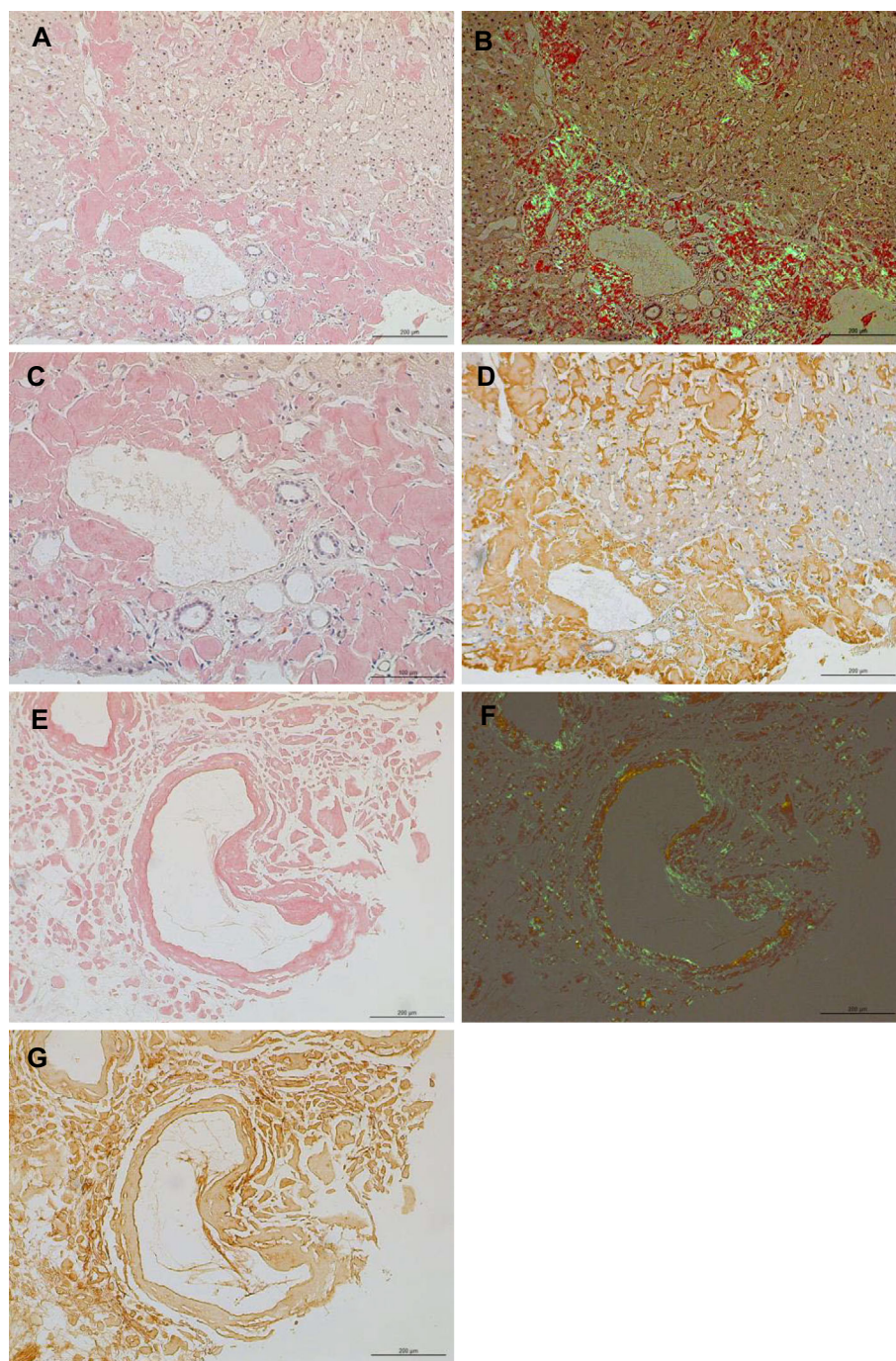
As the type of amyloidosis remained unknown, a proteomics analysis of liver amyloid using laser-microdissection (LMD) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) was carried out according to previously reported methods (19). In addition to several trypsin-digested peptides derived from the wild-type apoAI, the following two peptides were detected: DSGRDYVSQFK, DYVSQFK (Fig. 3A, B). These peptides corresponded to wild-type apoAI fragments at positions 24-34 and 28-34, except for K34 (wild-type, E34) (Fig. 3B). While apoE was also identified prominently in this study, it is known that apoE abundantly co-exists in all types of amyloid fibrils with serum amyloid P-component (SAP) (20). A further investigation including a genetic study of apoE was therefore not performed.

A direct DNA sequence analysis of the APOAI gene showed that the patient was heterozygous for c.t172G>A mutation, inducing a substitution of Lys for Glu at position 34 (E34K) (Fig. 3C). To confirm this finding, tissue specimens from the patient's liver, testis, and gastrointestinal mucosa were immunohistochemically stained using goat anti-human apoAI antiserum (ab7613; Abcam, Cambridge, UK), and all specimens showed clearly positive reactions (Fig. 1D, G). A definite diagnosis of AApoAI amyloidosis was thus made at 42 years old.

This study was performed following the tenants of the Declaration of Helsinki. The DNA analysis was conducted after obtaining approval from the IRB of Shinshu University, and written informed consent was obtained from the patient.

### Clinical follow-up after a diagnosis of AApoAI amyloidosis

To reduce the rate of hepatorenal disease progression and improve his general condition as much as possible, conven-



**Figure 1.** Histopathological findings of biopsied liver (A-D) and testis (E-G) specimens. Congo red staining of the liver biopsy specimen (A, B: polarized view, C) showed massive amyloid deposition, especially in the portal area. In addition, nodular and pericellular amyloid deposits were seen in the lobules. The amyloid deposits immunohistochemically had a positive reaction with anti-human apoAI antibody (D). Testis biopsy specimens showed massive amyloid deposition in the seminiferous tubules and interstitium, and sperm formation was not seen (E, F: polarized view). The amyloid deposits were also positive for anti-human apoAI antibody (G). Bars=200  $\mu$ m (A, B, D, E-G), 100  $\mu$ m (C). apoAI: apolipoprotein A-I

tional symptomatic treatments with angiotensin receptor blocker, anemia treatment with iron supplement and erythropoietin formulation, and electrolyte level management therapies were performed at outpatient clinics of the nephrology and hepatology divisions at Hamamatsu University Hospital. In addition, a regular checkup and evaluation of his systemic

amyloid involvement was performed at Shinshu University. The oral intake of UDCA was stopped at 43 years old because it was thought to have no obvious therapeutic effect on his liver dysfunction (ALP 1,215 IU/L;  $\gamma$ -GTP 339 IU/L).

Despite those conventional treatments, however, his liver

**Table. Laboratory Data at 42 Years Old.**

White blood cell	8,880 (2,970-9,130)	/ $\mu$ L	Glucose	93 (75-110)	mg/dL
Red blood cell	4.41 (4.14-5.63)	$10^6$ / $\mu$ L	Hemoglobin A1c	5.7 (4.6-6.2)	%
Hemoglobin	11 (12.9-17.4)	g/dL	Ammonia	26 (<70)	$\mu$ g/dL
Hematocrit	33.4 (38.6-50.9)	%	Na	141 (136-145)	mEq/L
Platelet	14.7 (14.3-33.3)	$10^4$ / $\mu$ L	K	4.5 (3.4-4.5)	mEq/L
Total protein	8.3 (6.5-8.0)	g/dL	IgG	1819 (870-1,700)	mg/dL
Albumin	4.3 (4.0-5.0)	g/dL	IgA	282 (110-410)	mg/dL
Blood urea nitrogen	33.2 (8-21)	mg/dL	IgM	200 (35-220)	mg/dL
Creatinine	2.21 (0.63-1.05)	mg/dL	Ca	9.5 (8.7-10.3)	mg/dL
Uric acid	9.5 (3.7-7.0)	mg/dL	NTproBNP	194 (<125)	pg/dL
Total-bilirubin	0.41 (0.3-1.4)	mg/dL	TroponinT	0.008 (<0.09)	ng/mL
ALP	1,006 (115-330)	IU/L	PT%	71.1 (70-130)	%
$\gamma$ -GTP	295 (13-70)	IU/L	APTT	24.6 (23-38)	sec
AST	29 (11-28)	IU/L	Fibrinogen	463 (180-350)	mg/dL
ALT	29 (9-36)	IU/L	D-dimer	1.5 (<1.0)	$\mu$ g/mL
LDH	133 (120-220)	IU/L	24hrCCr	29.6 (62-108)	mL/min
CK	37 (43-272)	IU/L	Urine sugar	(-) (-)	
LDL-cholesterol	139 (<139)	mg/dL	Urine occult blood	(-) (-)	
HDL-cholesterol	32 (>40)	mg/dL	Urine protein	(+++)	(-)
Triglyceride	321 (30-149)	mg/dL	Total urine protein	2.7	g/day
ApoAI	93 (122-161)	mg/dL			
ApoAII	32.2 (25-35)	mg/dL			
ApoB	0.09 (<0.1)	mg/dL			
ApoCII	4.3 (1.6-4.2)	mg/dL			
ApoCIII	13.2 (5.5-9.5)	mg/dL			
ApoE	5.3 (2.7-4.5)	mg/dL			

Parentheses denote normal values.

ALP: alkaline phosphatase,  $\gamma$ -GTP:  $\gamma$ -glutamyl transpeptidase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CK: creatine kinase, LDL-cholesterol: low density lipoprotein-cholesterol, HDL-cholesterol: high density lipoprotein-cholesterol, ApoAI: apolipoprotein A-I, ApoAII: apolipoprotein A-II, ApoB: apolipoprotein B, ApoCII: apolipoprotein C-II, ApoCIII: apolipoprotein C-III, ApoE: apolipoprotein E, NTproBNP: N-terminal prohormone of brain natriuretic peptide, PT%: prothrombin time activity, APTT: activated partial thromboplastin time, 24hrCCr: 24-hour creatinine clearance

and renal function gradually deteriorated over two years. At 44 years old, serum ALP and  $\gamma$ -GTP were increased to 1,403 and 391 IU/L, respectively. Serum transaminases were mildly increased (aspartate aminotransferase, 53 IU/L; alanine aminotransferase, 44 IU/L). At 45 years old, the serum albumin level and prothrombin time activity (PT%) were decreased to 3.1 g/dL and 57.7%, respectively, and signs of portal hypertension, such as ascites and caput medusae, became apparent. Since the serum levels of BUN and Cr were increased to 101.3 and 5.51 mg/dL, respectively, hemodialysis was initiated. As he was thought to need liver transplantation or combined hepatorenal transplantation, he was referred to another university hospital to have his eligibility for transplantation evaluated.

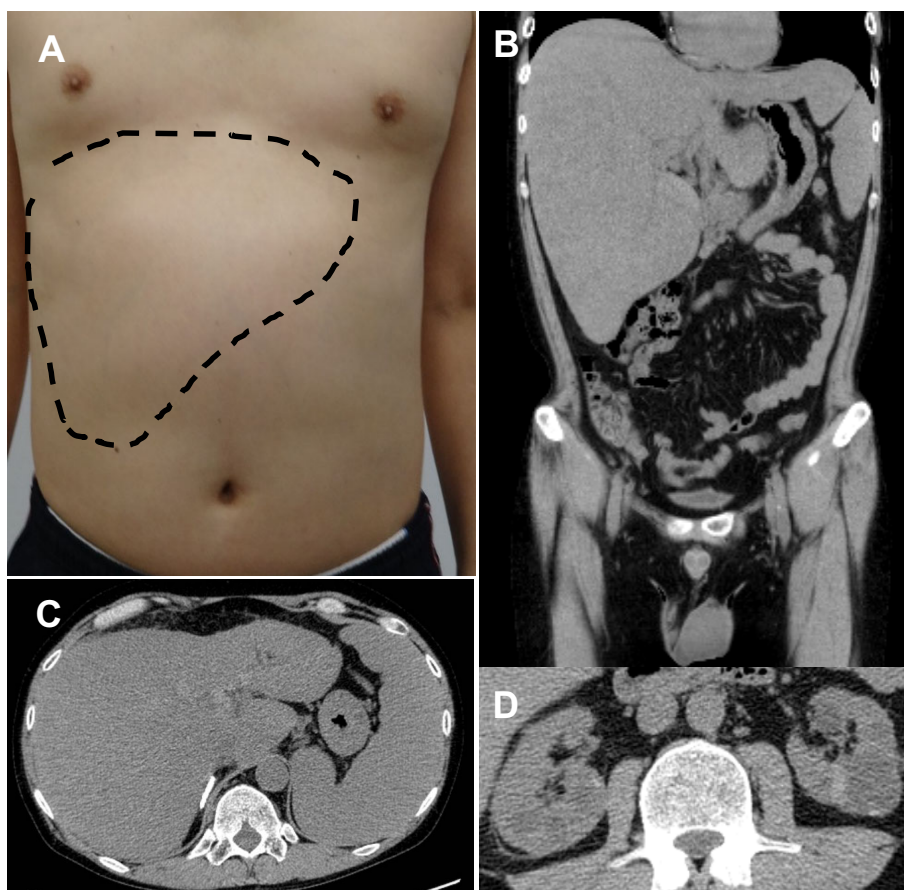
## Discussion

Since the first amyloidogenic apoAI variant (G26R) was identified by Nichols et al. (8), over 20 amyloidogenic APOAI mutations have been reported (3-17). Most of the amyloidogenic mutations are reported in two hot-spot re-

gions: among the 50-93 or 170-178 amino acid residues (5).

The E34K mutation detected in our patient was located outside of these hot-spot regions, and only two cases with the same mutation have been reported (15, 21). The first case described with this variant was a 29-year-old woman who suffered from amyloid nephropathy (15), and the second case was a 26-year-old man who had infertility due to testicular amyloid and amyloid nephropathy (21). Neither of them had apparent clinical amyloid hepatopathy, as was seen in our patient, but the first case was suspected of having amyloid deposits in the liver and spleen by radiolabeled SAP scintigraphy (15). Thus, the E34K variant may be apt to involve the kidney, testis, and liver. Regarding the mutation-phenotype correlation, Eriksson et al. reported that patients with mutations in codons 1-75 (amino terminal) were likely to develop hepatic and renal amyloidosis, while carriers of mutations in residues 173-178 (carboxyl terminal) mainly develop cardiac, laryngeal, and cutaneous amyloidosis (5). This is consistent with our case and the two reported cases with an E34K mutation (15, 21).

Various forms of hereditary systemic amyloidosis have

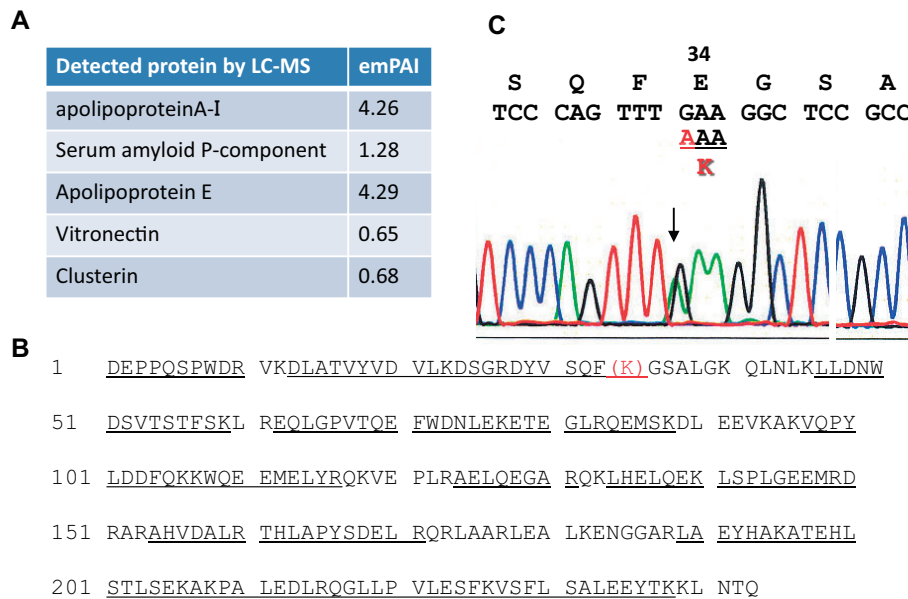


**Figure 2.** A picture of the patient's abdomen (A) and abdominal CT scan images (B-D). His markedly enlarged liver was palpable, as indicated by the dotted line (A). Coronal section CT showed a markedly enlarged liver and an enlarged left testis (B). Axial section CT showed severe hepatosplenomegaly (C) and bilaterally atrophic kidneys with some cysts (D).

been reported globally (1), and in Japan, hereditary neuropathic amyloidosis is common [hereditary ATTR amyloidosis (TTR-related familial amyloid polyneuropathy (FAP)) and gelsolin-related amyloidosis (AGel amyloidosis)]. Until a patient with fibrinogen-related amyloidosis (AFib amyloidosis) was reported in 2015 (19), no case of hereditary non-neuropathic systemic amyloidosis had been reported in Japan. As for AApoAI amyloidosis, only one patient with two apoAI variants (L202R and K262N) has recently been described (17). A 63-year-old Japanese woman underwent renal transplantation due to amyloid nephropathy (17). The clinical features of AApoAI amyloidosis are heterogeneous, and many systemic organs are involved, including the skin, larynx, and testis. However, the most commonly affected sites are the kidney, liver, and heart (3-17). These organs can be also involved in patients with AL amyloidosis (18, 22) or AA amyloidosis, usually induced by inflammatory disorders. As for hepatic amyloidosis in Japan, the vast majority are ascribed to AL or AA amyloidosis (23), and in particular, hepatomegaly is often observed in AL amyloidosis patients (22). Therefore, hepatic amyloidosis patients without clear family histories can easily be misdiagnosed with systemic AL amyloidosis or AA amyloidosis due to its clinical similarity, as was the case with our patient.

However, the progression rate of hepatic involvement in AApoAI amyloidosis may be slower than that in AL amyloidosis. In our patient, the liver function at the diagnosis of AApoAI amyloidosis (42 years old, Table) was well-preserved even 3 years after massive amyloid deposits had initially been detected at 39 years old. A previous study also reported the characterization of hepatic AApoAI amyloidosis, with patients remaining stable and asymptomatic for many years until portal hypertension and liver failure later develop (24). However, in some AL amyloidosis patients with hepatic involvement, the liver function rapidly deteriorates, and patients require immediate treatment intervention, including liver transplantation (25, 26). Therefore, a slow disease progression in hepatic amyloidosis patients without serum or urine monoclonal protein may be an important characteristic suggestive of AApoAI amyloidosis. In addition, as symptomatic testicular amyloidosis is rarely seen in AL and AA amyloidosis (22, 27), infertility or testicular swelling associated with amyloidosis may also be a diagnostic clue for AApoAI amyloidosis.

Finally, even in Japan, patients with hereditary amyloidosis aside from hereditary ATTR and AGel amyloidosis certainly exist. However, most of them may have been misdiagnosed with other types of systemic amyloidosis. Recently,



**Figure 3.** Results of the proteomics analysis (A, B) and *APOA1* gene analysis (C). **A:** LC-MS/MS-based proteomic analysis shows the presence of abundant apoAI. The emPAI is the exponentially modified protein abundance index, which is used as an index for estimating relative protein quantification in mass spectrometry-based proteomic analyses (31). **B:** Amino acid sequence of apoAI with a substitution of K for E at position 34 (as shown in red). The peptides detected by LC-MS/MS are indicated by underlining. Several tryptic peptides derived from apoAI were detected. The amino acid at position 34 was only variant K. **C:** A DNA sequence analysis of the *APOA1* gene exon 3 demonstrated a heterozygous c.172G>A (E34K) mutation. No other mutations were detected. LC-MS/MS: liquid chromatography-tandem mass spectrometry, apoAI: apolipoprotein A-I

several effective therapies have been established, especially for AL amyloidosis or AA amyloidosis (27-29). In AApoAI amyloidosis, organ transplantation, including that of the kidney, liver, or heart, has been performed as a promising therapy (30). Thus, it is very important to distinguish AApoAI amyloidosis from AL amyloidosis because the strategies used to treat these conditions are completely different. A proteomic analysis using LMD-LC-MS/MS was quite useful for correctly diagnosing the present patient.

The authors state that they have no Conflict of Interest (COI).

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Tsuneaki Yoshinaga and Nagaaki Katoh contributed equally to this work.

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