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Apolipoprotein A-1-related amyloidosis 2 case reports and review of the literature

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Abstract

Rationale: Apolipoprotein A-1 (ApoA-1)-related amyloidosis is characterized by the deposition of ApoA-1 in various organs and can be either hereditary or nonhereditary. It is rare and easily misdiagnosed. Renal involvement is common in hereditary ApoA-1 amyloidosis, but rare in the nonhereditary form.

Patient concerns: We reported two cases with ApoA-1 amyloidosis, a 64-year-old man suffering from nephrotic syndrome and a 40-year-old man with nephrotic syndrome and splenomegaly. Renal biopsies revealed glomerular, interstitial and vascular amyloid deposits and positive phospholipase A2 receptor staining in the glomerular capillary loop in case 1, and mesangial amyloid deposits in case 2.

Diagnoses: After immunostaining failed to determine the specific amyloid protein, proteomic analysis of amyloid deposits by mass spectrometry was performed and demonstrated the ApoA-1 origin of the amyloid. Genetic testing revealed no mutation of the APOA1 gene in case 1 but a heterozygous mutation, Trp74Arg, in case 2. Case 1 was thus diagnosed as nonhereditary ApoA-1 associated renal amyloidosis with membranous nephropathy, and case 2 as hereditary ApoA-1 amyloidosis with multiorgan injuries (kidney and spleen) and a positive family history.

Interventions: Case 1 was treated with glucocorticoid combined with cyclosporine. Case 2 was treated with calcitriol and angiotensin converting enzyme inhibitors.

Outcomes: Two cases were followed up for 5 months and 2 years, respectively; and case 1 was found to have attenuated proteinuria while case 2 had an elevation of cholestasis indices along with renal insufficiency.

Lessons: Proteomic analysis by mass spectrometry of the amyloid deposits combined with genetic analysis can provide accurate diagnosis of ApoA-1 amyloidosis. Besides, these 2 cases expand our knowledge of ApoA-1-related renal amyloidosis.

Abbreviations: γ-GT = gamma-glutamyltransferase, ALP = alkaline phosphatase, aPLA2R-AB = anti-phospholipase A2 receptor antibody, ApoA-1 = Apolipoprotein A-1, HDL = high-density lipoprotein, HDL-C = high-density lipoprotein cholesterol, LECT2 = leukocyte chemotactic factor 2, LMD and MS-based proteomic analysis = laser microdissection and mass spectrometry-based proteomic analysis, SAP = serum amyloid P component, UPE = urinary protein excretion.

Keywords: amyloidosis, apolipoprotein A-1, case-report, diagnosis

1. Introduction

Amyloidosis is a group of heterogeneous diseases caused by extracellular deposition of amyloid proteins in various organs, resulting in organ failure.[1] Apolipoprotein A-1 (ApoA-1)-associated amyloidosis is characterized by the deposition of ApoA-1 in various organs, resulting in tissue damage and presents with hereditary and nonhereditary forms.[2–21] ApoA-1 is the main protein component of high-density lipoproteins (HDLs), which functions in cholesterol transport. It is synthesized by liver and small intestine and degraded mainly in kidney.[22] The *APOA1* gene located on chromosome 11q23-q24 encodes the 267 residues of the primary ApoA-1 protein. The primary protein has an 18-residue-long signal peptide which is cleaved during secretion, a 6-residue-long propeptide which is cleaved in plasma by protease, resulting in the 243 aa long mature form of ApoA-1.[23] Both wild-type and mutant ApoA-1 proteins are amyloidogenic[2–21] and ApoA-1 deposition in acquired amyloidosis or hereditary amyloidosis are proposed to be pathogenic *in vivo*[18–21] and shown to be cytotoxic *in vitro*.[24]

Hereditary ApoA-1 amyloidosis, usually showing autosomal dominant inheritance, is a rare type of systemic amyloidosis associated with mutations in the *APOA1* gene.[2–17] Only isolated case reports have described this disease. [2–21] Clinical onset varies from the second decade to the sixth decade of life and the penetrance is highly variable.[2–17] Until now, 20 amyloidogenic mutations of ApoA-1 have been reported.[2–17] The mutational hotspots span residues 50 to 93 and 170 to 178. Patients mainly present with chronic renal failure, hepatosplenomegaly, and progressive cardiomyopathy, and usually show

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low plasma levels of ApoA-1 and HDL.[2–17] ApoA-1 amyloidosis always exhibits slow progress in contrast with immunoglobulin light-chain (AL) amyloidosis, which has a median survival time of 6 to 15 months without treatment.[25,26] A nonhereditary form characterized by wild-type ApoA-1 deposition has been reported in the pulmonary vasculature of elderly dogs, in knee joint menisci, in the aortic intima of elderly individuals, and in the peripheral nerve.[18–21] Renal involvement in such conditions has not been reported in contrast with hereditary ApoA-1 amyloidosis in which renal injury is common. Because ApoA-1-associated amyloidosis is an uncommon and multisystemic disease, patients may be misdiagnosed or undiagnosed easily.

Here we describe 2 cases with ApoA-1-derived amyloidosis, one diagnosed as nonhereditary ApoA-1-related renal amyloidosis combined with idiopathic membranous nephropathy, and the other as hereditary apoA-1 amyloidosis. Both cases were misdiagnosed previously but acquired accurate diagnoses in the present study through laser microdissection and mass spectrometry-based proteomic analysis (LMD and MS-based proteomic analysis). We also review the literature and discuss the diagnosis and treatments of ApoA-1 amyloidosis. This case report was approved by the institutional review board of Jinling Hospital of Nanjing University, and the informed consent was obtained from these 2 subjects.

2. Case report

2.1. Case 1

A 64-year-old Chinese male with no family history of renal disease underwent renal biopsy in local hospital in 2016 because of edema, proteinuria (urinary protein excretion [UPE]: 2.5 g/24 h), and high plasma levels of antiphospholipase A2 receptor antibody (aPLA2R-AB) (181 RU/mL, normal range <20 RU/mL). Renal biopsy revealed amyloid deposition in the mesangium. Immunofluorescence microscopy revealed deposits of immunoglobulin (Ig) G2, IgM and C3 in the glomerular capillary loop. No significant immunostaining was found with antibodies directed against κ-light chain, λ-light chain. He was therefore diagnosed as heavy-chain deposit amyloidosis with membranous nephropathy and treated with tacrolimus. However, his proteinuria still increased to 5 g/day in 3 months.

On October 19, 2016, he was referred to our hospital. Laboratory examinations showed heavy proteinuria (10.06–10.52 g/day), hypoalbuminemia (26.7 g/L), and high levels of plasma aPLA2R-AB (667.88 RU/mL). Serum creatinine (0.87 mg/dL), plasma levels of HDL (1.20 mmol/L, normal range >1.04 mmol/L), and ApoA-1 (3.05 g/L, normal range 1.0–5.0 g/L) were normal. There was no evidence of a plasma cell disorder according to sensitive serum free light chain assay, serum protein electrophoresis, immune fixation electrophoresis, and bone marrow examination. Abdominal ultrasound showed fatty liver. No abnormality was found in the electrocardiogram and echocardiogram. Congo red staining of biopsy tissues taken from abdominal fat, rectal mucosa, and bone marrow was all negative.

Repeat renal biopsy revealed amyloidosis with extensive glomerular, interstitial, and vascular involvement according to the Congo red staining of above-mentioned areas showing the characteristic apple green birefringence under crossed polarized light (Fig. 1A) and the subepithelial deposits as shown by trichrome and methenamine silver (PASM-Masson) staining under a light microscope. Immunofluorescence staining performed on fresh frozen tissue showed the interstitial amyloid deposition with the antibody against ApoA-1 (polyclonal rabbit anti-human ApoA-1, dilution 1:100; Dako, Denmark) (Fig. 1B). Besides, strong staining in a diffuse granular pattern along the glomerular capillary loop with antibodies against PLA2R (Fig. 1C), IgG++, and C3++ was observed. IgG subclass analysis revealed that IgG1, IgG2, and IgG4 were positive, whereas IgG3 was negative. There was no staining with antibodies against single κ-light chain or λ-light chain, lysozyme, β2-microglobulin, transthyretin, and leukocyte chemotactic factor 2 (LECT2). Electron microscopy showed electron-dense subepithelial deposits and massive amorphous deposits with

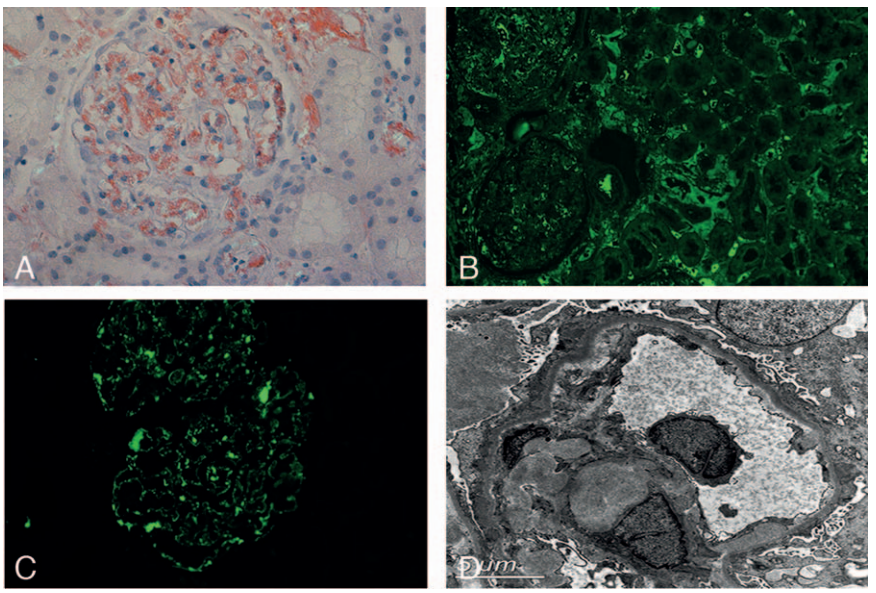

Figure 1. (A) Amyloid with extensive glomerular, interstitial, and vascular involvements and Congo red staining, which yielded characteristic apple green birefringence under crossed polarized light. (Congo red, ×400). (B) The interstitial amyloid deposits stained by an antibody against ApoA-1 (IF, ×200). (C) A granular pattern of strong immunofluorescence staining with an antibody against PLA2R can be seen along the glomerular capillary loop (IF, ×400). (D) Electron microscopy showed electron-dense subepithelial deposits and massive amorphous deposits with low electron density in the mesangium and subendothelial area.

Table 1

Analysis of the proteins in the renal biopsies by mass spectrometry-based proteomics.

	Accession no.	Control number of unique peptides	Peptide count	Case 1 number of unique peptide	Peptide count	Case 2 number of unique peptides	Peptide count	Protein name
1	P02647			16	38	8	16	Apolipoprotein A-I
2	P02768	2	4	15	37	11	28	Serum albumin
3	P01009			13	37	9	25	Alpha-1-antitrypsin
4	P60709	7	16	12	36	10	21	Actin, cytoplasmic 1
5	P25311			15	32	5	18	Zinc-alpha-2-glycoprotein
6	P68871	2	6	9	24	6	31	Hemoglobin subunit beta
7	P69905	1	4	8	20	4	11	Hemoglobin subunit alpha
8	P81605			6	17	4	13	Dermcidin
9	Q9GZZ8			6	16	3	13	Extracellular glycoprotein lacritin
10	P68104	6	10	8	15	5	8	Elongation factor 1-alpha 1

Note: The table shows 10most abundant proteins detected in mass spectrometry-based proteomic analysis of kidney biopsy of control sample, case1 and case 2, respectively. The protein accession no. refers to the protein code in the UniProt database. The higher the number of peptide counts is, the higher the abundance of the protein is. It can be seen that ApoA-I is the most abundant protein in case 1 and case 2, confirming ApoA-I as the major amyloid fibril protein.

low electron density in the mesangium and subendothelial area (Fig. 1D) and with a higher power, unbranched fibrils with a diameter of 8 to 13 nm were viewed. As there were differences between the immunostaining results in glomeruli of the 2 renal biopsies, we analyzed the amyloid deposits in glomeruli by LMD and MS-based proteomic analysis (glomerular tissue was microdissected according to glomerular staining of amyloid deposits by Congo Red). LMD and MS-based proteomic analysis showed that ApoA-1 was the most abundant amyloid protein in the renal biopsy of case 1, whereas there was no enrichment of ApoA-1 in the normal control (Table 1); thus, we presume ApoA-1 being the causative agent of amyloidosis (Table 1). However, no mutation was found in the *APOA1* gene of the patient and his children. He was thus diagnosed as having nonhereditary ApoA-1-associated renal amyloidosis combined with idiopathic membranous nephropathy.

After diagnosis, he was treated with glucocorticoid combined with cyclosporine. After 5 months, the UPE decreased from 10.52 to 2.17 g/24 h, serum creatinine increased from 0.87 to 1.03 mg/dL, and the levels of liver enzymes remained normal.

2.2. Case 2

A 40-year-old Chinese man presented with hypertension, edema, and proteinuria (UPE, 2 g/24 h). His father had a history of nephrotic syndrome at age 57 without a renal biopsy. Urine analyses of his mother, brother, sister, and his daughter were all negative. Renal biopsy in local hospital revealed amyloid deposits in the mesangium and immunohistochemistry staining of the amyloid deposits was positive with the antibody directed against fibrinogen Aα-chain but negative with the antibody against lysozyme or transthyretin. He was therefore diagnosed as having fibrinogen Aα-chain amyloidosis and treated with an angiotensin-converting enzyme inhibitor.

One year later, he was referred to our hospital. Laboratory testing showed heavy proteinuria (3.52 g/24 h), hypoalbuminemia (32.3 g/L), low plasma levels of HDL (0.42 mmol /L), and ApoA-1 (0.58 g/L). Serum creatinine was normal. There was no evidence of a plasma cell dyscrasia. Abdominal ultrasound showed splenomegaly. His electrocardiogram revealed sinus bradycardia, left ventricular high voltage, and flat T wave, but echocardiogram and N-terminal pro-B-type natriuretic peptide were normal, suggesting that he was less likely to have cardiac amyloid infiltration. Congo red staining of biopsy tissues taken from abdominal fat, the rectal mucosa, and bone marrow was negative.

His repeat renal biopsy revealed amyloid deposits in the mesangium according to Congo red staining (Fig. 2A), and amyloid deposition was shown by immunofluorescence staining using the antibody against ApoA-1 (Fig. 2B). Electron microscopy showed massive amorphous deposits with medium to low electron densities in the mesangium, and with a higher power, unbranched fibrils with a diameter of 8 to 14 nm were viewed (Fig. 2C). Immunofluorescence staining was found negative with antibodies against lysozyme, β2-microglobulin, LECT2, κ- and λ-light chain, or transthyretin. LMD and MS-based proteomic

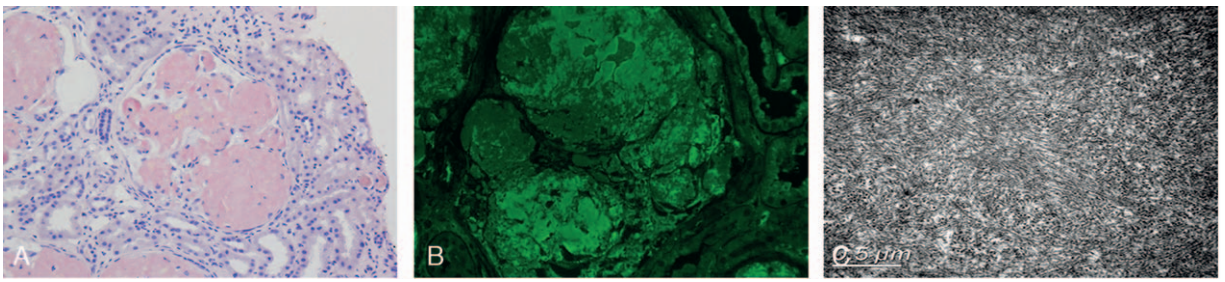

Figure 2. (A) Amyloid deposits in the mesangium (Congo red, ×200). (B) Amyloid deposits in the mesangium stained with an antibody against ApoA-1 (IF, ×400). (C) Electron microscopy showed unbranched fibrils with a diameter of 8 to 14 nm.

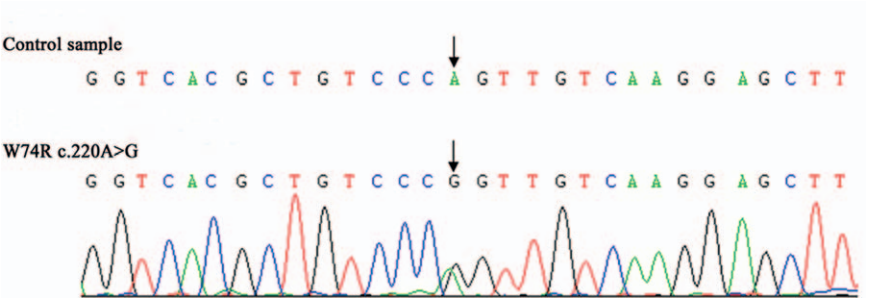

Figure 3. A mutation in the *APOA1* gene of case 2, c.220 A>G in the antisense strand of DNA, is shown (black arrows), which results in amyloidogenic Trp74Arg variant of ApoA-1.

analysis of kidney biopsy specimens (Congo Red-stained glomerular areas were microdissected) showed that ApoA-1 was the causative agent of amyloidosis (Table 1). Genetic analysis of case 2 revealed a heterozygous *APOA1* gene mutation (c.220 A>G in the antisense strand of DNA) that resulted in amyloidogenic Trp74Arg variant of ApoA-1 protein (Fig. 3). This mutation is positioned at residue #74 according to the current nomenclature that bases on primary protein of ApoA-1. It is equivalent to previously reported Trp50Arg, whose residue numbering is based on mature form of ApoA-1 protein (lacking 24 residues at amino-terminus) in the previous nomenclature. He was thus diagnosed as having hereditary ApoA-1 amyloidosis and treated with calcitriol and angiotensin-converting enzyme inhibitors.

After 2 years, his proteinuria was attenuated from 3.52 to 3 g/24 h, serum creatinine increased from 0.90 to 3.5 mg/dL. Besides, serum alkaline phosphatase (ALP) and gamma-glutamyltransferase (γ-GT) increased from 94/40 to 289.9/215.5 U/L.

3. Discussion

In our study, case 1 suffered from nephrotic syndrome, whereas case 2 presented with heavy proteinuria, progressive renal insufficiency, splenomegaly, and elevated levels of ALP and γ-GT. Immunostaining of renal biopsies in 2 hospitals revealed totally different results. This is because ApoA-1 is usually not tested in the panel of amyloid typing and immunostaining can be nonspecific or negative, as it may be confounded by background staining and loss of antigenic epitopes in the fibrillar conformation because of mutant protein or proteins with conformational changes.[27] Furthermore, LMD and MS-based proteomic analysis, which is currently considered to be the criterion standard in identifying amyloid protein, demonstrated the ApoA-1 origin of the amyloid in both cases.[27] Therefore, case 2 was diagnosed as having hereditary ApoA-1 amyloidosis with multiorgan injuries (kidney, spleen, and liver), a positive family history and a heterozygous mutation in *APOA1* gene (Trp74Arg). As case 1 had a strong immunofluorescence staining of PLA2R, IgG, and C3, which were diffusely distributed along the glomerular capillary loop but had no underlying diseases found in the clinical screening, case 1 was then diagnosed as having nonhereditary ApoA-1-associated renal amyloidosis combined with idiopathic membranous nephropathy. Alternatively, a systemic amyloidosis may be present in case 1, but we cannot conclude it because of the unavailability of ^{123}I-SAP scintigraphy in China, which is used to diagnose systemic amyloidosis. According to examinations already done, he was less likely to have amyloid infiltration in the organs other than kidney.

The genetic testing of case 2 revealed a heterozygous mutation in *APOA1* gene (c.220 A>G in the antisense strand of DNA) that resulted in Trp74Arg (or Trp50Arg in previous nomenclature) mutation. This is the first report of the mutation in Chinese Han population, and the previous reports were from a Jewish man and a Danish man.[5,28] The major clinical manifestations of the 3 cases include renal amyloidosis and low plasma levels of ApoA-1 and HDL. This may indicate that the Trp74Arg mutation can result in dysfunctional and amyloidogenic ApoA-1 proteins, which mainly targets kidney. In contrast to hereditary ApoA-1 amyloidosis of case 2, no mutations were detected in case 1 in the genetic testing and proteomic analysis. Although the possibility that this patient possesses an alternative abnormal form of ApoA-1 cannot be precluded, it is highly likely that the amyloid in case 1 was derived from the protein product of nonmutated *APOA1* gene because of lack of a family history and normal plasma levels of apoA-1. Amyloid deposition of wild-type ApoA-1 protein has been also detected in the pulmonary vasculature of elderly dogs, the knee joint menisci, the aortic intima of elderly individuals, and the peripheral nerve, which has not been reported in renal amylodosis.[18–21] High m of the ApoA-1 protein is present in kidney probably because kidneys are the major organ of HDL catabolism. Peculiar local conditions, such as low pH and interaction with extracellular matrix (particularly glycosaminoglycans in the glomerular basement membranes, mesangium, and interstitium) may promote fibril formation of the highly concentrated ApoA-1 protein.[1,29] In addition, the factors that are involved in aging-associated amyloid deposition may also play a role in the pathogenesis of ApoA-1 amyloid. It has been shown that senile systemic amyloidosis can be caused by nonmutated transthyretin and wild-type ApoA-1 fibril deposition can be seen in atherosclerotic plaques in elderly individuals.[1,20] Das et al[29] proposed that ApoA-1 misfolding in hereditary and in nonhereditary amyloidosis is triggered by perturbation of ApoA-1 native structure in the amyloid hot spots, leading to misfolding of the protein molecules. However, further studies are required to elucidate the mechanism underlying the misfolding.

Both cases presented with nephrotic syndrome. Renal involvement is very common in hereditary ApoA-1 amyloidosis (Table 2), which is characterized by renal interstitial/medulla deposition of amyloid and slow progress, resulting in mild tubular proteinuria and a lowered urinary specific gravity.[2,7,11] Case 2 in this study had amyloid deposits in glomeruli and presented with nephrotic syndrome. He was exclusively diagnosed as having ApoA-1 amyloidosis, which resulted in nephrotic

Table 2

***APOA1* mutations associated with amyloidosis.**

ApoA-I Variant	Age at presentation	Major organ involved	plasma levels of HDL and ApoA-1	Amyloid deposits in kidney biopsy	Prognosis	References
Gly26Arg	26-y-old man with family history	Kidney, peripheral nerves, GI tract	—	Interstitial amyloid deposits in cortex and medulla	ESRD after 18 years	Van Allen et al[2]; Nichols et al[3]
Glu34Lys	29-y-old woman with no family history	kidney, liver, spleen	Normal	amyloid within the kidney	CKD	Rowczenio et al[4]
Trp50Arg	34-y-old man with family history	Kidney, liver, spleen, GI tract	—	Amyloid within the kidney	ESRD after 10 months	Booth et al[5]
Leu60Arg	24-y-old man with family history	Spleen, liver, kidney	—	Amyloid within the kidney	splenectomy	Soutar et al[6]
Leu60-Phe71delins 60Val_61Thr	40-y-old man with family history	Liver, spleen, kidney	↓HDL, ↓ApoA-I	Diffuse interstitial amyloid limited to medulla (autopsy)	Death at 61-y-old due to liver failure	Booth et al[7]
Leu64Pro	58-y-old man with family history	Kidney	↓HDL-C	Amyloid deposits in glomeruli, interstitium and vessels	ESRD after 1 year, good outcome after kidney transplant.	Murphy et al[8]
Glu70_Trp72del	18-y-old woman with family history	Kidney, liver, spleen,choroid vessel	↓ApoA-I	Amyloid within the kidney	ESRD after 5 years. good function of graft after 17 years	Persey et al[9]
Phe71Tyr	51-y-old woman without family history	Liver, palate	—	—	Short follow-up	Rowczenio et al[4]
Asn74LysFs	48-y-old woman and 67-y-old woman	Kidney, uterus ovaries, pelvic lymph nodes, GI tract	—	—	—	Eriksson et al[10]
Leu75Pro	56-y-old female with family history	kidney, liver	—	Diffuse interstitial amyloid deposition limited to the inner medulla	CKD	Gregorini et al[11]
Leu90Pro	54-y-old woman with family history	Skin, heart, larynx	—	—	Progressive heart failure after 6 years	Asl et al[12]
Lys107Del	45-y-old man	Aortic intima amyloid	Normal	—	Heart failure after 23 years	Amarzguioui et al[13]
Ala154fs	58-y-old woman	kidney	—	Glomerular amyloid deposits.	—	Eriksson et al[10]
His155Metfs	77-y-old woman with family history	Kidney	—	glomerular and interstitial deposits of amyloid	CKD	Rowczenio et al[4]
Leu170Pro	52-y-old man without family history	Laryngeal	—	—	—	Eriksson et al[10]
Gln172Pro	70-year-old man with family history	Heart	—	—	Heart failure	Vonberg et al[14]
Arg173Pro	33-y-old woman with family history	Skin, heart	↓HDL	—	Progressive cardiomyopathy	Asl et al[15]
Leu174Ser	42-y-old man with family history	Skin, testes, heart	↓↓HDL-C, ↓↓ApoA-I	—	Heart failure after 6 years; good outcome with heart transplant	Obici et al[16]
Ala175Pro	38-y-old man	Larynx, testes	Normal	—	No progression of organ damage followed up to 43 years	Rowczenio et al[4]
Leu178His	34-y-old woman with family history	Larynx, skin, heart, peripheral nerves	Normal	—	Progressive cardiomyopathy	de Sousa et al[17]

— = unreported, ↓↓ = decrease degree that is >50% of the normal plasma level of HDL or ApoA-1, ↓ = decrease degree that is <50% of the normal plasma level of HDL or ApoA-1, CKD = chronic renal failure, ESRD = end-stage renal disease, GI = gastrointestinal, HDL-C = high-density lipoprotein-cholesterol.

syndrome. In contrast, case 1 additionally suffered from idiopathic membranous nephropathy. Renal biopsy of case 1 revealed extensive glomerular, interstitial, and vascular amyloid deposits and subepithelial deposits, marked ApoA-1 amyloid deposits in interstitium, and PLA2R, IgG, and C3 deposits along the glomerular capillary loop. In addition, proteomic analysis demonstrated the ApoA-1 origin of the amyloid in glomeruli. Based on these findings, we consider that both ApoA-1-related renal amyloidosis and membranous nephropathy contributed to the renal disease and proteinuria of case 1. Besides, the proteinuria of case 1 in the follow-up decreased from 10.52 to 2.17 g/24 h under steroids/cyclosporin therapy, nephrotic syndrome in case 1 may be mainly attributed to membranous nephropathy and ApoA-1-related renal amyloidosis partially resulted in proteinuria. ApoA-1 amyloidosis complicated with certain membranous nephropathy or IgA nephropathy was previously found in patients with ApoA-1 Leu75Pro variant.[30] It is important to identify other types of kidney diseases accompanied for appropriate treatment.

Diagnosis of ApoA-1 amyloidosis is challenging given that AopA-1 amyloidosis is rare and is usually not tested in amyloid typing. Clinical presentation varies widely depending on the organs involved. As ApoA-1 amyloidosis is diagnosed histologically, biopsies from target organs are required.[1,31] Congo red staining remains the criterion standard for defining amyloid.[1] Conventional methods such as immunohistochemistry and immunofluorescence can identify the amyloid subtype but can be confounded by background staining caused by serum contamination and loss of antigenic determinants in the fibrillar conformation.[27] Studies have shown that LMD and MS-based proteomic analysis can provide accuracy rates ranging from 98% to 100% in the diagnosis of the subtypes of amyloidosis,[32] which are higher than those by immunohistochemistry staining (38%–87%)[33] and immunofluorescence (65%–87%).[33] In addition, genetic testing can differentiate between hereditary and nonhereditary amyloidosis, but the results must be interpreted combined with other findings (e.g., immunohistochemical or proteomic typing of the amyloid). Low plasma levels of ApoA-1 and HDL owing to the dysfunctional proteins can serve as an indicator of hereditary ApoA-1 amyloidosis.[34] Besides, as serum amyloid P component (SAP) binds to all amyloid deposits, ^{123}I-SAP scintigraphy can locate amyloid deposits in the body.[35] Thus, combinations of the detailed clinical evaluation, histology, immunohistochemistry, proteomics, genetic analysis, and biochemical investigations are necessary for establishing the diagnosis of ApoA-1 amyloidosis.

ApoA-1 amyloidosis is a slowly progressive disease. The 2 patients in the present study were treated with glucocorticoid combined with cyclosporine and calcitriol combined with angiotensin-converting enzyme inhibitors, respectively. During follow-up, renal function of case 1 remained stable, whereas case 2 had an elevation of cholestasis indices and renal insufficiency. Presently, there is no effective drug for hereditary apoA-1 amyloidosis. Supportive treatment and organ transplantation are the major therapeutic approaches.[36] New therapies targeting associated amyloid proteins show great potential in hereditary and localized amyloidosis.[37] A phase 1 trial of CPHPC ((R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid), which can delete SAP from the plasma followed by an anti-SAP antibody, revealed major reduction in liver amyloid with no serious adverse effect in a patient of apoA-1 amyloidosis, which provides a new treatment for apoA-1 amyloidosis.[38]

In summary, we have described 2 cases of ApoA-1-related renal amyloidosis in Chinese Han population presenting with hereditary and nonhereditary forms. Besides, our study has demonstrated the usefulness of mass spectrometry in identifying the compositions of amyloid deposits, which will provide further insights into the ApoA-1-associated renal amyloidosis.

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