Diagnostic Pathology

CASE REPORT

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Normolipidemic lipoprotein glomerulopathy with IgA nephropathy — ApoE Kyoto mutation: a case report

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Abstract

Background Lipoprotein glomerulopathy (LPG), a rare genetic metabolic kidney disease with poor prognosis, is caused by mutations in the apolipoprotein E (ApoE) gene and is usually accompanied by hyperlipidemia. Lipoprotein glomerulopathy can be complicated by other glomerulopathies, such as membranous nephropathy, lupus nephritis, and immunoglobulin A nephropathy (IgAN), which have been mainly reported in Japan. Herein, we present the first case of a patient with LPG with IgAN from Chongqing, China. In contrast to previous cases, this patient lacked hyperlipidemia and ApoE was a Kyoto mutation.

Case presentation A 38-year-old man was admitted to our hospital due to proteinuria and hematuria, which was found during urine examination. Renal function and blood lipid and lipoprotein levels were normal. After renal biopsy, the patient was diagnosed of LPG with IgAN. Analysis of the ApoE gene showed a heterozygous C→T transition in exon 3, resulting in a change in the 25th amino acid from arginine to cysteine (Kyoto mutation). Genetic analysis of the family showed that this mutation was inherited from his father and passed on to his daughter. Serum ApoE was 14.4 mg/dL. Combined with the above findings, the patient was diagnosed with LPG accompanied by IgAN. After 18 months of enalapril treatment without lipid-lowering therapy, the patient's renal function and blood lipid levels were stable and urine protein levels were significantly ameliorated.

Conclusion We presented a rare case of LPG (Kyoto) with IgAN without abnormal blood lipids and other typical clinical manifestations. Therefore, for patients with unremarkable clinical manifestations, renal biopsy is of great value for definite diagnosis of disease.

Keywords Lipoprotein glomerulopathy, IgA nephropathy, ApoE gene, Normolipidemic, Case report

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Background

Lipoprotein glomerulopathy (LPG) is a rare inherited disease caused by mutations in the apolipoprotein E (ApoE) gene [1]. Since it was first reported by Saito et al. [2] in 1989, most cases have been reported in East Asia [3]. The most typical pathological appearance of LPG is dilated capillary lumina with pale staining and thrombus-like substances. Common features include proteinuria, type III hyperlipoproteinemia (HLP)-like lipoprotein profiles, and a marked increase in serum ApoE concentrations. In several cases, LPG is associated with other glomerulopathies, such as immunoglobulin A nephropathy (IgAN), membranous nephropathy, and lupus nephritis [4]. There are a few case reports of LPG in patients with IgAN, mainly in Japan [5]. Herein, we report a case of LPG with IgAN in Chongqing, China. In contrast to previous cases, our patient with ApoE Kyoto lacked hyperlipidemia.

Case presentation

A 38-year-old Chinese man was admitted to our hospital for more than two years with mild proteinuria accompanied by microscopic hematuria during laboratory examination. The patient was asymptomatic. There was no previous history of other diseases, and none of the patient's family member had renal or autoimmune diseases. No history of ingestion of any drug or Chinese herbal medicine. On admission, his blood pressure was 151/81 mmHg, and physical examination revealed no specific signs of hyperlipidemia, such as corneal opacity or xanthomas. At presentation, he had proteinuria (0.94 g/24 h) and hematuria, but no leukocyturia. His estimated glomerular filtration rate (eGFR) was 84 mL/min per 1.73 m^2. Total cholesterol and triglyceride levels were 205 mg/dL and 115 mg/dL, respectively. The immunological indicators, such as serum C3, C4, and IgA levels were normal. The other laboratory parameters are described in Table 1. Immunofluorescence assay showed strong staining for IgA, C3, and ApoE, but negative staining for IgG, IgM, C1q, and C4 (Fig. 1a). Futhermore, double immunofluorescence showed that both KM55 and IgA stained positive in the mesangial region. (Fig. 1b to f). Renal biopsy revealed markedly dilated capillary lumina filled with thrombus-like substances and mesangial proliferation (Fig. 1g). About 12% of interstitial fibrosis with tubular atrophy was also observed. Thrombus-like substances stained positive for Sudan III and ApoE (Figs. 1h and i). Electron microscopy revealed lipid granule deposition in the dilated glomerular capillary lumen, mesangial hyperplasia, and electron-dense deposition in the mesangial area (Figs. 1j and k). These pathological characteristics were consistent with those of LPG with IgAN.

Table 1 Laboratory investigators

Investigators	Results	Normal range
Urine protein	++	-
Microscopic RBC quantification, cells/uL	18	0–10
Microscopic WBC quantification, cells/uL	0	0–5
Urine protein, g/24 h	0.94	0.00–0.10
Total cholesterol, mg/dL	206	120–221
Triglycerides, mg/dL	119	27–151
High density lipoprotein cholesterol (HDL-C), mg/dL	42.53	44.85–54.90
Low density lipoprotein cholesterol (LDL-C), mg/dL	134.92	59.92–120.62
ApoA1, g/L	0.99	1.20–1.96
ApoB, g/L	0.98	0.60–1.38
ApoE, mg/dL	14.40	3.00–5.00
Lipoprotein (a), mg/L	164.00	0–300
Blood urea nitrogen, mg/dL	11.54	8.68–22.4
Serum creatinine, mg/dL	1.10	0.64–1.10
Cystatin C, mg/L	1.10	0.0–1.26
Estimated glomerular filtration rate, mL/min/1.73 m^2	84.03	> 90
Uric acid, mg/dL	7.69	3.50–7.20

RBC, red blood cells; WBC, white blood cells; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

The ApoE gene analysis revealed a heterozygous C→T transition in exon 3, which changed the amino acid at position 25 from arginine to cysteine (Kyoto mutation) (Fig. 2a). Family genotyping showed that this mutation was transmitted from the father to his daughter (Fig. 2b). The serum ApoE was 14.4 mg/dL determined by enzyme-linked immunosorbent assay (LOT: 20210702, JianCheng Bioengineering Institute). Combined with the above findings, the patient was diagnosed with LPG accompanied by IgAN.

After the renal biopsy, the patient was followed-up at the outpatient clinic of Daping Hospital. The plasma lipid level and eGFR were within the normal ranges for 18 months, even without lipid-lowering drugs. The proteinuria improved (fluctuated at + ~ ±; urinary albumin/creatinine ration from 186.06 mg/g Cr to 111.72 mg/g Cr) after administration of 10 mg of enalapril per day. Additionally, we followed-up with his daughter and her urine protein levels remained negative.

Discussion and conclusions

Apolipoprotein E is a glycoprotein composed of 299 amino acids, with a molecular mass of 34 kDa [6]. It can be synthesized by several cell types, including hepatocytes, brain astrocytes, renal mesangial cells, adipocytes, and macrophages. There are two important binding regions in the N-terminal sequence: the low-density lipoprotein (LDL) receptor binding region and heparin sulfate glycoprotein binding region [7]. The C-terminal domain is closely related to lipid binding, and overexpression of the ApoE gene causes excessive production of very low-density lipoprotein

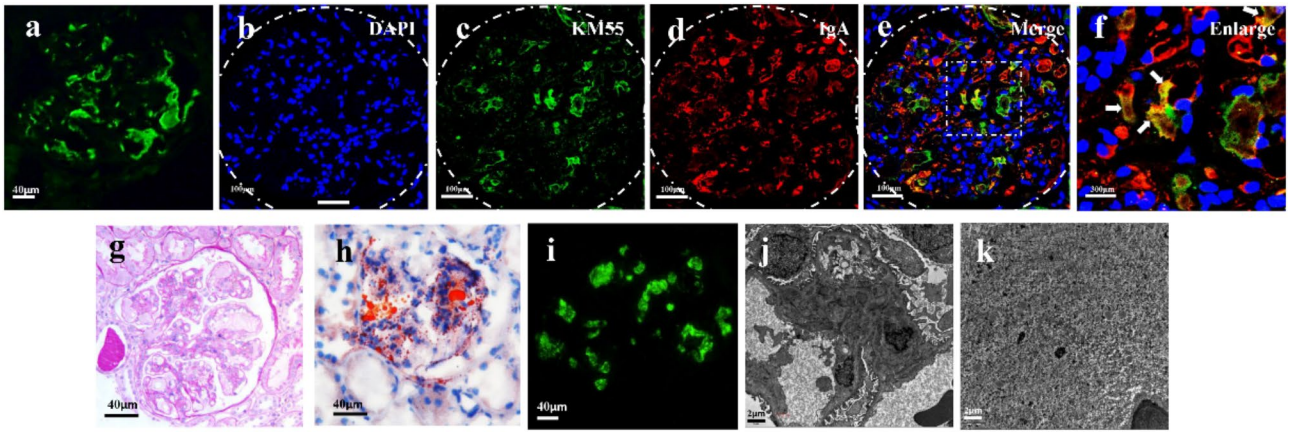

Fig. 1 (**a**) Immunofluorescence showed that IgA was primarily presented in the mesangial area. Scale bar, 40 μm. (**b**) - (**f**) Double immunofluorescence with KM55 and IgA. The circular dotted line indicated the glomerulus, and the arrow indicated the area where KM55 and IgA merged. Scale bar, 100 μm and 300 μm. (**g**) PAS staining showed glomerular capillary filled with amorphous pale-staining thrombus-like substances and mesangial proliferation. Scale bar, 40 μm. (**h**) Sudan III staining. Scale bar, 40 μm. (**c**) (**i**) Immunofluorescence showed that ApoE was primarily presented in the capillary lumina. Scale bar, 40 μm. (**j**) Electron micrograph showed electron dense deposition in the mesangial area. Scale bar, 2 μm. (**k**) Electron micrograph showed lipid granules in a dilated capillary lumina and glomerular capillary lumen was occupied with lipoprotein thrombi. Scale bar, 2 μm

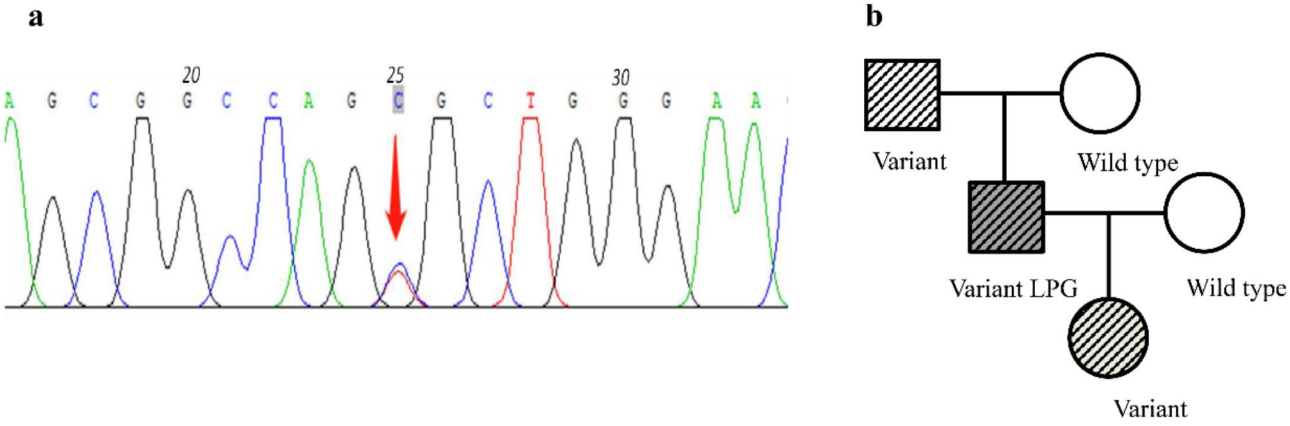

Fig. 2 (**a**) The ApoE sequence in the patient has a heterozygous C→T transition in exon 3 (arrow). (**b**) Family pedigrees for the patient indicated the presence of ApoE Kyoto genotype (either wild-type or C→T variant) in family members for whom DNA was available. Men are represented by squares and women by circles. The shaded squares indicate the patients with LPG

(VLDL) and triacylglycerol, leading to hypertriglyceridemia [8]. Therefore, ApoE plays a central role in lipoprotein metabolism. The human ApoE gene has three alleles (ε 2, ε 3, and ε 4), which are expressed as ApoE isoforms E2, E3, and E4, respectively [6, 7]. The ApoE3 isoform is the most common subtype, accounting for more than 70% in the normal population, and does not affect lipoprotein metabolism. Thus, ApoE3 carriers are typically normolipidemic. However, approximately 15% of ApoE4 isoform preferentially binds to VLDL, leading to downregulation of LDL receptor function and an increase in LDL levels [9]. Interestingly, the lipid levels in our patient with genotype E3/E4 were normal.

Mesangial cells are a major source of ApoE in the kidney, and mesangial cell proliferation and matrix formation are increased in ApoE-null mice [10]. Apolipoprotein E inhibited mesangial proliferation induced by different stimuli, including growth factors and LDL, and prevented apoptosis induced by oxidized low-density lipoprotein. Increasing matrix heparan sulfate proteoglycans is a probable mechanism by which ApoE can be anti-proliferative to mesangial cells. In ApoE-null mice, severe hyperlipidemia is accompanied by glomerular inflammation, as demonstrated by the presence of foam cells, macrophage recruitment, and endothelial cell activation [10]. This evidence suggests that ApoE is closely associated with kidney disease. The mutation of ApoE-Sendai (Arg145Pro), which is the 145th arginine of the ApoE gene, was replaced by proline and was discovered for the first time by Oikawa et al. in 1997 [11]. By introducing the ApoE-Sendai mutation into APOE-deficient mice, both increased lipid levels and LPG-like renal pathology were observed in the mice, suggesting that a single gene mutation causes LPG [12]. To date, 17 ApoE variants associated with LPG have been reported. ApoE Kyoto (Arg25Cys) is the most frequent mutation in LPG worldwide, including

Table 2 Cases with lipoprotein glomerulopathy combined with other glomerulopathies

Case	Authors and reference	Age and gender	Urine protein, g/day	Ccr, mL/min	Plasma TG, mg/dL	Plasma TC, mg/dL	Plasma ApoE, mg/dL	ApoE phenotype	Other glomerulopathies	Follow-up
1	Abo et al. [5]	10, F	1–2	105	450	266	29.8	E2/3	IgAN	ND*
2	Amenomori et al. [25]	54, F	2.2	78	1019	720	38.8	E2/2	IgAN	5 years, ameliorated
3	Yagi et al. [5]	45, M	0.5	75	134	134	18.3	ND*	IgAN	1 year, unchanged
4	Yomogida et al. [5]	69, F	9	76	126	235	16.1	E2/4	MN	5 years, ameliorated
5	Muso et al. [5]	52, F	8	73	570	314	16.6	E2/4	LN	2 years, renal failure
6	This patient	38, M	0.94	104	119	206	14.4	E3/4	IgAN	18 months, ameliorated

*ND, not described; IgAN, immunoglobulin A nephropathy; F, female; M, male; TG, triglyceride; TC, total cholesterol; MN, membranous nephropathy; LN, lupus nephritis

South-Western China, Japan, France, and the USA [3]. The pathological manifestations of the ApoE Kyoto murine model are similar to those of LPG in patients, and ApoE concentration is significantly elevated, while cholesterol and triglycerides are not [13]. Furthermore, an increase in the binding of triglyceride-rich lipoproteins to endothelial cells may promote lipid deposition in glomerular capillaries [14].

Previous studies have reported cases of LPG combined with IgAN, membranous nephropathy, lupus nephritis, and other glomerular diseases; their characteristics are listed in Table 2 [4, 5]. Although there is no definitive evidence that LPG causes mesangial IgA deposition or IgAN, LPG-induced ApoE variants and lipoprotein abnormalities interact with the intrinsic glomerular factors. However, Fc receptors may be responsible for IgAN [3, 4].Earlier case reports suggested that there were no beneficial effects from immunosuppressants [11, 15, 16] or transplantation [17–21]. Aggressive lipid-lowering therapy is recommended for patients with type III HLP. Several case reports and small clinical trials have shown that fenofibrate significantly delays LPG progression [22, 23]. Plasma exchange and immunoadsorption also have certain effects. Previous studies reported that urinary protein and serum lipid levels decreased for a while in LPG patients treated with statins or fibrates, angiotensin receptor blockers (ARB), and plasma exchange [24]. Approximately 50% of LPG patients eventually progress to chronic renal failure [4]. The rate of eGFR decline in LPG patients in the partial remission group (50% reduction in proteinuria from baseline) was slower, indicating that proteinuria may be a risk factor for renal function deterioration [24]. In this patient, the plasma lipid level and eGFR were within the normal ranges for 18 months, even without lipid-lowering drugs. Proteinuria improved (fluctuated at + ~ ±; urinary albumin/creatinine ration from 186.06 mg/g Cr to 111.72 mg/g C) after administration of 10 mg of enalapril per day.

In conclusion, we reported the case of a patient with proteinuria and hematuria without abnormal blood lipid levels. After renal biopsy, ApoE gene analysis, and serum ApoE level detection, the final diagnosis was LPG (Kyoto) with IgAN. After 18 months of enalapril treatment without lipid-lowering therapy, the patient's renal function and blood lipid levels were stable and urine protein levels were significantly ameliorated. Therefore, for patients with unremarkable clinical manifestations, renal biopsy is of great value for definite diagnosis.

Abbreviations

LPG	Lipoprotein glomerulopathy
ApoE	Apolipoprotein E
IgAN	Immunoglobulin A nephropathy
HLP	Hyperlipoproteinemia
eGFR	Estimated glomerular filtration rate
RBC	Red blood cells
WBC	White blood cells
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
LDL	Low-density lipoprotein
VLDL	Very low-density lipoprotein
TG	Triglyceride
TC	Total cholesterol
MN	Membranous nephropathy
LN	Lupus nephritis
ARB	Angiotensin receptor blockers

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13000-025-01636-z.

Supplementary Material 1

Acknowledgements
We appreciate the patient for participating in this study.

Author contributions
XY analyzed the patient data and drafted the final manuscript. LB performed the histological examination of the kidney. KC acquired the patient data. YH and JC substantively revised the manuscript. All authors read and approved the final manuscript. All authors reviewed the manuscript.

Funding
This research was supported and funded by the Chongqing Science and Health Joint Medical Research Project-Youth Project (2023QNX011), Youth Cultivate Project of Army Medical University (2019XQN15) and National Natural Science Foundation of China (82270768) mainly used for the cost of testing and article publication. The funders played a role in the collection analysis and interpretation of the data.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The participant signed a letter of informed consent to allow his data to be stored, as required by Daping Hospital.

Consent for publication
Written informed consent was obtained from this patient prior to the use of his data for publication.

Competing interests
The authors declare no competing interests.

Received: 21 November 2023 / Accepted: 24 March 2025
Published online: 05 April 2025

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