

A Case of Acquired LCAT Deficiency with the Discrepancy between Spontaneous Resolution of Proteinuria and Continually Low HDL Cholesterol Levels

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A 79-year-old Chinese man was referred for nephrotic syndrome (proteinuria 4.4 g/day). In blood tests, serum high-density lipoprotein (HDL) cholesterol was undetectable, and the esterified cholesterol to total cholesterol ratio was very low. Lecithin: cholesterol acyltransferase (LCAT) activity was also undetectable. Since he had neither corneal opacity nor pathological mutations in the *LCAT* gene and anti-LCAT antibodies were detected in serum, a diagnosis of acquired LCAT deficiency was made. Renal biopsy revealed glomerulopathy associated with LCAT deficiency and membranous nephropathy (MN). Since the patient's proteinuria did not improve despite prescribing an angiotensin II receptor blocker (ARB), we suggested the prescription of prednisolone, but he returned to China due to the expiration of his residence visa for Japan. One year after the initial visit, his proteinuria had improved to 0.9 g/day without immunosuppressive therapy. However, his HDL cholesterol level was still low at around 3 mg/dL, indicating a discrepancy between remission of nephrotic syndrome and lack of improvement in lipid levels.

Of the 11 patients with acquired LCAT deficiency reported to date, 4 with undetectable LCAT activity and MN on renal biopsy required immunosuppressive therapy to alleviate proteinuria. The present patient was prescribed only an ARB according to his preference, which happened to be consistent with the MN treatment guideline that states, "Wait 6 months for spontaneous remission while using maximal antiproteinuric therapy." The clinical course of acquired LCAT deficiency varies, and further case reports are needed to determine the necessity of immunosuppressive therapy.

Key words: Acquired LCAT deficiency, HDL deficiency, Nephrotic syndrome, Membranous glomerulonephritis

Introduction

Lecithin: cholesterol acyltransferase (LCAT) is an enzyme synthesized mainly in the liver that hydrolyzes lecithin into lysolecithin and free fatty acids and synthesizes cholesteryl esters from the free fatty acids and free cholesterol. LCAT plays a crucial role in cholesterol efflux from peripheral cells, particularly in

the formation of high-density lipoprotein (HDL)¹⁻³⁾.

Familial LCAT deficiency (FLD) is an autosomal recessive genetic disorder caused by an LCAT gene mutation and results in markedly decreased serum HDL cholesterol levels. In patients with FLD, lipid deposition in organs occurs, which is complicated by corneal opacity, hemolytic anemia, and renal dysfunction^{1, 3, 4)}. It has been reported that an abnormal lipoprotein

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with a high phospholipid (PL) content, called lipoprotein X (LpX), is involved in proteinuria and renal dysfunction in FLD patients^{5, 6}. FLD is defined as a designated intractable disease by the Ministry of Health, Labor, and Welfare (MHLW) of Japan.

Acquired LCAT deficiency is a disease caused by autoantibodies to the LCAT protein, with no mutations in the *LCAT* gene⁷⁻¹². There have been only a few case reports, mainly from Japan⁷⁻¹⁶. According to some case reports, patients with acquired LCAT deficiency present with proteinuria and nephrotic syndrome, as in FLD, and most of them have stated that immunosuppressive therapy, such as with prednisolone, has been effective^{7-9, 13}. We experienced a case of nephrotic syndrome which improved in the absence of immunosuppressive therapy, although serum HDL cholesterol levels remained low.

Case Presentation

The patient was a 79-year-old Chinese man. He had visited his primary physician in China, who had made the diagnosis of nephrotic syndrome based on his clinical symptoms and laboratory data. He was referred to our hospital at the request of his family, who lived in Japan. He was admitted for further investigation and treatment of nephrotic syndrome.

His medical history was benign prostatic hyperplasia and hyperuricemia at age 70, and he was taking febuxostat 20 mg/day. He had not previously been diagnosed with dyslipidemia or any urinary abnormalities. There was no family history of dyslipidemia and he did not smoke or drink alcohol.

His height, body weight, body mass index, and blood pressure were 159.9 cm, 66.9 kg, 26.2 kg/m² and 113/74 mmHg, respectively. Corneal opacity was not observed. The patient had pitting edema in his lower extremities when he visited his primary physician, but upon admission to our hospital, edema was no longer present due to furosemide prescribed at 20 mg/day by his primary physician.

The patient's laboratory data are presented in **Table 1**. He had proteinuria (4.4 g/day) and hypoalbuminemia, resulting in a diagnosis of nephrotic syndrome. Urinalysis results included 3+ for occult blood and sediment containing 30 red blood cells per high-power field. His estimated glomerular filtration rate (eGFR) was 52.5 ml/min/1.73m². Blood examinations revealed severe dyslipidemia with an undetectable HDL-C level. Plasma Apolipoprotein A-I, Apolipoprotein A-II, and low-density lipoprotein (LDL) cholesterol levels were also markedly reduced despite the nephrotic syndrome, and the triglycerides

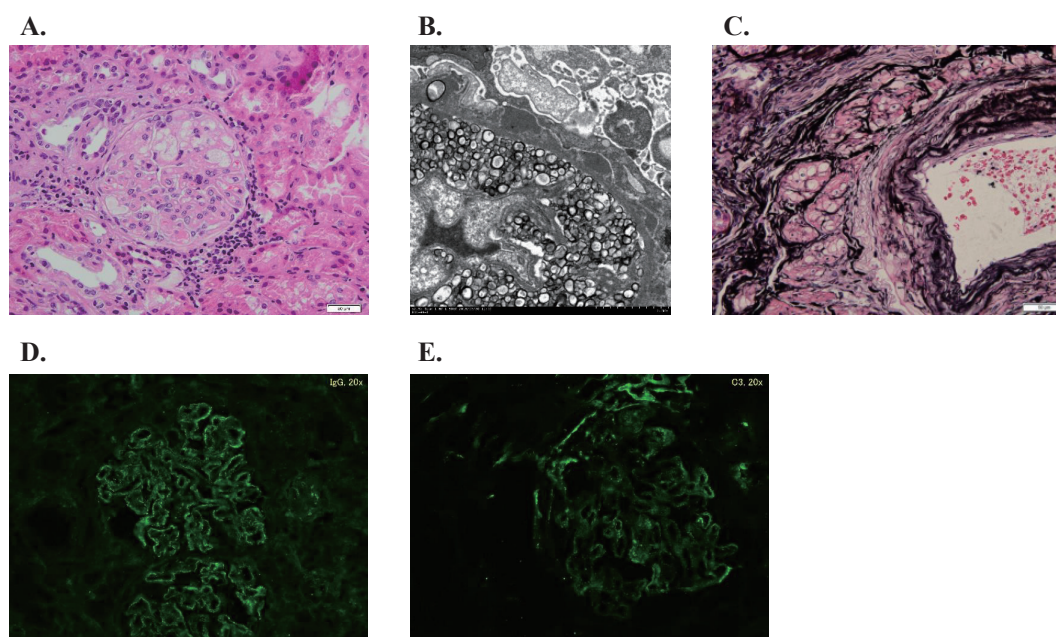
level was elevated. He was not taking any medication to reduce plasma high-density lipoprotein (HDL) cholesterol, such as probucol. On examining the ratio of esterified cholesterol to total cholesterol (CE/TC), we found it to be very low (0.07; normal range, 0.70-0.80), suggesting that esterification of free cholesterol was impaired. Liver and thyroid function tests were normal. The IgG level was not low despite nephrotic syndrome, probably because it was measured early in the onset of nephrotic syndrome. The IgG level first measured was 1698 mg/dL, but had dropped sharply to 1499 mg/dL when remeasured 9 days later, suggesting that IgG was being exposed in the urine. Alternatively, IgG may not be exposed into urine easily in nephrotic syndrome associated with acquired LCAT deficiency because the serum IgG levels of some previous reports of nephrotic syndrome associated with acquired LCAT deficiency whose serum IgG levels were measured were 1600 mg/dL and 1282 mg/dL, which were also not low^{9, 10}. Unfortunately, we did not evaluate the selectivity index in the present patient.

A renal biopsy was performed. In total, 91 glomeruli were observed, and 7 of them were globally sclerosed. The irregular thickening of the glomerular basement membrane (GBM), marked lipid deposition in the GBM and mesangium, and occasional foam cell influx into the capillary lumen observed are characteristic of FLD (**Fig. 1A, B**). In addition, there were foam cell deposits around arterioles (**Fig. 1C**). In electron microscopy, electron-dense deposits were found in the GBM (**Fig. 1B**). Immunohistochemical examination revealed granular deposits of IgG and C3 along capillary loop walls (**Fig. 1D, E**). Our diagnosis was glomerulopathy associated with LCAT deficiency and membranous nephropathy (MN).

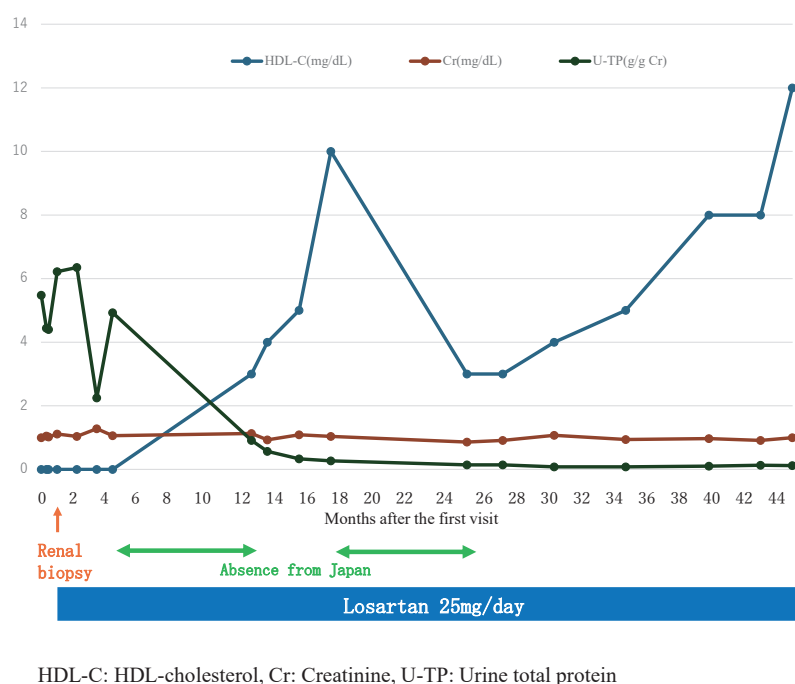
There was no mutation in the patient's *LCAT* gene exon sequence. His serum LCAT activity was below the detection limit. To evaluate LCAT activity in serum, we incubated serum from a patient with an artificial proteoliposome substrate containing tritium-labeled free cholesterol, 1,2-dimyristoyl-sn-glycero-3-phosphocholine, and ApoA-1 for one hour at 37°C. After incubation, esterified cholesterol was quantified as previously described¹⁷. Measurement of autoantibodies against LCAT was performed using the enzyme-linked immunosorbent assay (ELISA) method, which we recently reported¹². Therefore, we diagnosed the patient as having acquired LCAT deficiency. Since MN is often associated with collagen diseases, malignancies, and hepatitis, we performed additional blood tests and imaging studies, but no underlying condition was found to be associated with MN.

Table 1. Patient's laboratory data on admission

Blood			Reference range		
Total protein	5.4 g/dL	6.7-8.3	CRP	0.14 mg/dL	0-0.3
Albumin	2.3 g/dL	4.0-5.0	IgG	1698 mg/dL	870-1700
Total bilirubin	1.1 mg/dL	0.3-1.2	IgA	414 mg/dL	110-410
Direct bilirubin	0.5 mg/dL	0-0.4	IgM	90 mg/dL	33-190
Aspartate aminotransferase	40 U/L	13-33	CH50	47.6 U/mL	25.0-48.0
Alanine transaminase	20 U/L	8-42	C3	99.8 mg/dL	65.0-135.0
eGFR	52.5 ml/min/1.73 m ²	≥90	C4	29.3 mg/dL	13.0-35.0
Blood urea nitrogen	20 mg/dL	8-22	Antinuclear antibody	40	<40
Creatinine	1.05 mg/dL	0.60-1.10	White blood cells	8200/μL	4000-9000
Sodium	143 mEq/L	138-146	Red blood cells	362×10 ³ /μL	420-550 ×10 ³
Potassium	4.2 mEq/L	3.6-4.9	Hemoglobin	11.5 g/dL	13.5-18.0
Haptoglobin	76 mg/dL	25-176	Hematocrit	34.5%	36.0-54.0
HbA1c	3.6%	4.6-6.2	Platelet count	19×10 ⁴ /μL	15-35 ×10 ⁴
Total cholesterol	123 mg/dL	128-219	Urine		
Triglyceride	260 mg/dL	30-149	Urinalysis		
HDL-C	<2 mg/dL	40-96	Protein	4+(4.44 g/day)	
LDL-C	56 mg/dL	<140	Blood	3+	
Ester from cholesterol	9 mg/dL	80-200	Urinary sediments		
Cholesterol ester ratio	7%	70-80	Red blood cells	30-49/HF	
ApoA-1	53 mg/dL	119-155	White blood cells	1-4/HF	
ApoA-2	7.2 mg/dL	25.9-35.7	Granular cast	1+	
ApoB	34 mg/dL	73-109	Erythrocytic cast	1+	
ApoC-2	4.7 mg/dL	1.8-4.6	Urine M-protein	negative	
ApoC-3	9.8 mg/dL	5.8-10.0			
ApoE	6.8 mg/dL	2.7-4.3			
LCAT activity	undetectable				
LCAT antibodies	Positive				

**Fig. 1.** Histological findings of renal biopsy

(A) Periodic acid-Schiff staining. Glomerular basement membrane (GBM) was irregularly thickened. There were foam cells in the GBM and mesangium infusing into capillary lumen.
 (B) Electron microscopy findings. There was lipid deposition in the GBM and mesangium. Electron-dense deposits were found in the GBM.
 (C) Periodic acid-methenamine silver staining. Foam cells were observed around arterioles.
 (D, E) Immunohistochemical examination showed granular deposits of IgG (D) and C3 (E) along capillary loops.



HDL-C: HDL-cholesterol, Cr: Creatinine, U-TP: Urine total protein

Fig. 2. Clinical course of patient

Proteinuria was reduced to 0.91g/g Cr at 12 months, 0.27g/g Cr at 17 months, and maintained below 0.3g/g Cr after that. HDL-C level became detectable at 12 months and had increased up to 10mg/dL at 17 months. However, it decreased again after 25 months, while it was still detectable. HDL-C had still not reached the normal level at 44 months.

We used losartan 25 mg/day to reduce proteinuria because it was reported that angiotensin II receptor blockers (ARBs) delayed the progression of renal failure in patients with FLD¹⁸⁾, and renin-angiotensin system inhibitors reduced proteinuria in nephrotic syndrome patients including those with MN¹⁹⁻²¹⁾. However, four months after starting losartan, the proteinuria had not decreased, and serum HDL cholesterol levels remained undetectable. We therefore recommended that he be treated with prednisolone, but due to the impending expiration of his visa to stay in Japan, he was unable to begin treatment. He returned to China and revisited our hospital one year after the initial visit. Interestingly, at the time of the return visit, the urinary protein level had spontaneously decreased to 0.91 g/g Cr and the serum HDL cholesterol level had recovered to a measurable level of 3 mg/dL. Therefore, we decided to observe the patient without using prednisolone. At 17 months, the HDL-C level had increased to 10 mg/dL, and proteinuria had decreased to 0.27 g/g Cr. At 30 to 34 months, proteinuria was further reduced, up to 0.08 g/gCr. Nephrotic syndrome remained in remission up to 44 months. However, after 25 months, HDL-C levels were reduced again, at 3-5 mg/dL. His serum HDL cholesterol level did not eventually rise to within the normal range, indicating

a discrepancy between resolution of proteinuria and the continually low HDL cholesterol levels (**Fig. 2**). Since our patient could not visit our hospital regularly before 25 months, we examined LCAT activity and anti-LCAT antibodies on admission, at 25 months, and at 34 months. **Table 2** shows that LCAT activity was detectable, rising to 24.5 ± 0.7 nmol/hr/mL at 25 months and had further recovered, to 46.6 ± 2.3 nmol/hr/mL at 35 months, though it was still not in the normal range. LCAT antibodies were still positive at 25 and 35 months. However, LCAT antibody concentrations were reduced compared to the time of admission (**Table 2**). During the period he stayed in China and was unable to visit our hospital, there were no significant changes in his lifestyle and no events of other diseases, and he continued taking the same medication.

Discussion

In this report, we describe a case of acquired LCAT deficiency with nephrotic syndrome in which proteinuria spontaneously resolved, while HDL deficiency remained. Similar to several previous studies⁷⁻¹²⁾, autoantibodies against LCAT were detected in our patient with acquired LCAT deficiency.

Table 2. Clinical course of LCAT activity and LCAT antibody concentrations

	on admission	at 25 months	at 34 months
LCAT activity (nmol/hr/mL)	undetectable	24.5 ± 0.7	46.6 ± 2.3
LCAT antibody concentration (μg/mL)	1.85 ± 0.05	0.115 ± 0.004	0.140 ± 0.008

LCAT activity: 415 ± 5 nmol/hr/mL (healthy control)

LCAT antibody concentration: Owing to the lack of a standard human antibody, we used an existing standard antibody and converted the concentrations obtained with it. Calibration curves were prepared using an anti-LCAT rabbit monoclonal antibody (clone #EPR1384Y; Abcam Ltd., Cambridge, UK).

Since renal insufficiency defines the life prognosis of FLD patients²², proteinuria and renal function trends are considered clinically meaningful in patients with acquired LCAT deficiency. However, the mechanism of renal failure in LCAT deficiency is not fully understood. Some mechanisms of renal failure in FLD patients that have been suggested are: accumulation of oxidized phospholipids in the glomeruli²³, and entrapment in capillary loops of abnormal lipoprotein particles, namely LpX, consisting of phospholipids and unesterified cholesterol. Although LpX appears to be accompanied by reduced LCAT activity and migrates toward the cathode during agarose gel electrophoresis²⁴, we found no evidence for presence of LpX in the present case. A large TG-rich LDL fraction (Lp8), which was detected recently in high-performance liquid chromatography with a gel filtration column, was reported to be associated with progression of renal dysfunction²⁵.

In FLD, accumulation of lipid components is a characteristic feature of renal lesions, and it occurs both intracellularly and extracellularly. FC and PL deposition in the GBM, subendothelial lesions of blood vessels and accumulation of foam cells lead to thickening of the GBM^{5, 6}. In the present case, renal biopsy revealed not only a lipid deposition characteristic of FLD but also that characteristic of MN: electron-dense deposition at the epithelial side of GBM and IgG deposition along capillary loops (Fig. 1D).

Based on previous case reports, including ours, we discuss the relationship among severity of proteinuria, LCAT activity, and serum HDL cholesterol levels. We compared 7 cases in which proteinuria was 3.5g/day or more and 5 cases in which it was lower than 3.5g/day. There was no difference in HDL-C levels or CE/TC ratio. However, LCAT activity was likely lower in the former cases (Table 3A) than in the latter cases (Table 3B). Next, among patients with proteinuria of 0.5 g/gCr or more, we compared 6 patients who received immunosuppression therapy or did not recover and 3 patients in whom

proteinuria spontaneously resolved. In the former (Table 3C), LCAT activity was likely lower than in the latter (Table 3D). Moreover, in 2 cases other than the present case in which proteinuria spontaneously resolved, there were no findings of MN in renal biopsies (Table 3D). From these comparative analyses, low LCAT activity and pathological diagnosis of MN were considered to be characteristics of severe cases requiring immunosuppressive therapy. However, in the present case, proteinuria spontaneously resolved despite the undetectable LCAT activity and findings of MN (Table 3D). The clinical course of the present case suggests that immunosuppression therapy may not be necessary for improvement of nephrotic syndrome in acquired LCAT deficiency. However, in a younger patient not receiving immunosuppression therapy, end stage renal disease developed¹⁴, so further case reports on characteristics that determine the need for immunosuppressive therapy are needed.

Strategies for treating idiopathic MN may be helpful in the choice of treatment for acquired LCAT syndrome. In this regard, measurement of anti-phospholipase A₂ receptor (PLA₂R) antibody titers is used in practice to diagnose idiopathic MN²⁶. Like LCAT, PLA₂ is an enzyme that hydrolyzes the ester bond at the sn-2 site of glycerophospholipids, and PLA₂ and LCAT have structural homology. In addition, the Kidney Disease Improving Global Outcome (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases notes that approximately 30% of patients with idiopathic MN will resolve spontaneously within 2 years and that low-risk patients with progressive loss of kidney function can be managed with renin-angiotensin system inhibitors alone²⁶. Furthermore, the guideline states that it is reasonable to wait 6 months for spontaneous remission, while the use of maximal antiproteinuric therapy and immunosuppressive therapy is considered if proteinuria does not improve after 6 months of conservative treatment. We await further case accumulation to help determine whether the treatment guideline for idiopathic MN can be adapted to acquired LCAT deficiency as well.

Table 3. Previously reported cases of acquired LCAT deficiency and present case

A. Patients with proteinuria of 3.5 g/day or more							
Reference	7	8	13	9	14	10	Present case
Age/Gender	67/M	63/F	62/M	70/M	33/M	70/F	79/M
Country	Japan	Japan	Japan	Japan	Italy	Japan	China
Proteinuria (g/gCr or day)	6.38	4.1	5	7.7	4	5.6	4.4
Cr (mg/dL)	1.18	0.58	0.9	1.15	N/A	1.26	1.05
HDL-C (mg/dL)	7	3	11	3	11	2	<2
CE/TC ratio	0.11	0.11	0.05	N/A	0.23	0.15	0.07
LCAT activity	undetectable	undetectable	undetectable	undetectable	N/A	62.5 ^{*1}	undetectable

^{*1} 62.5 nmol/ml/h (normal range; 260-560)

B. Patients with proteinuria of lower than 3.5 g/day					
Reference	9	15	16	11	12
Age/Gender	74/M	53/F	36/F	71/F	59/F
Country	Japan	Japan	Japan	Italy	Japan
Proteinuria (g/gCr or day)	^{*2}	1.6	0.2	N/A	Negative
Cr (mg/dL)	1.41	0.50	0.7	N/A	0.5
HDL-C (mg/dL)	1	2.5	2	5	2
CE/TC ratio	0.02	N/A	0.15	0	0.26
LCAT activity	undetectable	22.9 ^{*3}	10 ^{*4}	N/A	9.3 ^{*5}

^{*2} Urine albumin was around 1400 mg/gCr

^{*3} 22.9 U (contrast; 408.2)

^{*4} 10 UI/mL (normal range; 53.5-95.5)

^{*5} 9.3 nmol/hr/mL (normal pooled serum; 375 ± 4.9)

C. Patients who received immunosuppression therapy or did not recover						
Reference	received treatment				did not recover	
	7	8	13	9	9	14
Age/Gender	67/M	63/F	62/M	70/M	74/M	33/M
Immunosuppression therapy	PSL	PSL	PSL	PSL	none	none
Clinical course	remission			improved	not improved	ESRD
Renal biopsy	FLD+MN				N/A	FLD+MN
Proteinuria (g/gCr or day)	6.4	4.1	5.0	7.7	^{*2}	4.0
HDL-C (mg/dL)	12	3	11	3	1	11
LCAT activity	undetectable	undetectable	undetectable	undetectable	undetectable	N/A

PSL: prednisone, ESRD: end stage renal disease, FLD: foam cells in GBM and mesangium, MN: findings of membranous nephropathy-like electron-dense deposits at epithelial side of GBM

D. Patients in whom proteinuria spontaneously resolved			
Reference	10	15	Present case
Age/Gender	70/F	53/F	79/M
Clinical course	remission		
Renal biopsy	FLD		FLD+MN
Proteinuria (g/gCr or day)	5.6	1.6	4.4
HDL-C (mg/dL)	2	2.5	<2
LCAT activity	62.5 nmol/ml/h (normal range; 260-560)	22.9 U	undetectable (contrast; 408.2)

FLD: foam cells in GBM and mesangium, MN: findings of membranous nephropathy-like electron-dense deposits at epithelial side of GBM

So, what was the reason for the discrepancy between resolution of proteinuria and lack of an increase HDL cholesterol in the present case? As our first hypothesis, we speculate that there are differences between the threshold of LCAT activity at the onset of HDL deficiency and that of MN. In most previous reports of acquired LCAT deficiency, onset of nephrotic syndrome was preceded by HDL deficiency, and there was resolution of nephrotic syndrome if HDL deficiency was preceded by nephrotic syndrome. The clinical course of LCAT activity in our case supported this hypothesis (Table 2). However, in some cases, resolution of nephrotic syndrome has been followed by HDL deficiency, so this hypothesis does not always hold good. Our second hypothesis is that there is an optimal ratio of antigen and antibody when deposits that occur in MN develop. It has been reported that the antigen to antibody ratio is important in one of the mechanisms regulating the development of subepithelial immune deposits in MN²⁷⁾. In the present case, when the nephrotic syndrome reached remission, the patient was still positive for LCAT antibodies but their concentration was reduced (Table 2, Fig. 2), which supports this hypothesis. The third hypothesis is that MN was coincidentally accompanied by acquired LCAT deficiency in the present case. At the time, we could not examine anti-PLA2R antibody titers and immunohistochemical examination of PLA₂ and LCAT was not performed. However, this hypothesis is unlikely to be correct and we consider that secondary MN associated with LCAT deficiency is more likely than primary MN in the present case. It is because immunohistochemistry and immunofluorescence detected LCAT along parts of the glomerular capillary walls in some previously reported cases of MN accompanied with LCAT deficiency^{7, 8)}, suggesting that LCAT was an antigen responsible for the MN. Moreover, in the present patient, the onsets of HDL deficiency and nephrotic syndrome were considered to have occurred nearly simultaneously and both urinary protein and serum HDL cholesterol level were showing signs of improvement when the patient returned for a follow-up visit 13 months after the initial visit.

This case report has several limitations that should be taken into consideration. First, the present patient did not bring a referral letter detailing his medical history and progress with his primary physician in China. Hence, the details of the clinical data in China were unclear. Second, given that LCAT activity was assessed at only three sample points, fluctuations of LCAT activity might have occurred during unmeasured intervals. Third, because some

previously reported cases of acquired LCAT deficiency had underlying diseases such as lymphoma and sarcoidosis, there remains a possibility that an underlying disease may be identified in the present patient subsequently.

In conclusion, we report a patient who had acquired LCAT deficiency with severe HDL deficiency and nephrotic syndrome. This novel case is interesting because the pathology indicated MN and only proteinuria spontaneously resolved without recovery in LCAT activity or serum HDL cholesterol level. Although immunosuppressive therapy could not be administered in view of the expiration date of the patient's residence visa, the natural history of the kidney in this case was similar to that of low-risk cases of idiopathic MN. Further case reports and discussions are needed.

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Conflicts of Interest

Masatsune Ogura has received honoraria from Amgen, Kowa Company, and Ultragenyx Japan. Masayuki Kuroda has received patent royalty and licensing fees from CellGenTech, Inc. Mariko Harada-Shiba holds stock of Liid Pharmaceuticals, and has received speaking honoraria from Amgen, MEDPACE, Kowa, BML, Protosera, and Novartis. Koutaro Yokote has received honoraria from MSD K.K., Kowa Company, Ltd., Sanofi K.K., Sumitomo Pharma Co., Ltd., Daichi Sankyo Company, Limited, Taisho Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Boehringer Ingelheim International GmbH, Novartis Pharma K.K., Novo Nordisk Pharma Ltd., Bayer Yakuhin, Ltd., and Pfizer Japan Inc., as well as clinical research funding from CellGenTech, Inc. KY has also received scholarship grants from Abbot Japan LLC, Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Kowa Company, Ltd., Sumitomo Pharma Co., Ltd., Taisho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Limited, Mitsubishi Tanabe Pharma Corporation, TEIJIN PHARMA LIMITED, Eli Lilly Japan K.K., Boehringer Ingelheim International GmbH, and MOCHIDA PHARMACEUTICAL Co., Ltd.. The other authors have no conflicts of interest to declare.

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