CASE REPORT

A case of acquired lecithin:cholesterol acyltransferase deficiency with sarcoidosis that remitted spontaneously

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Abstract Familial lecithin:cholesterol acyltransferase (LCAT) deficiency is a rare inherited disorder that causes an extremely low high-density lipoprotein cholesterol concentration in serum. Recently, acquired LCAT deficiency caused by IgG antibodies to LCAT, without any LCAT gene mutation, was reported. Here we describe a case of acquired LCAT deficiency occurring in association with sarcoidosis. The patient was a Japanese female aged 70 years, had no mutation in the LCAT gene exon sequence, but had an LCAT inhibitor factor in her serum, detected using lipoprotein-deficient serum. She was diagnosed with acquired LCAT deficiency. Her abnormalities of serum lipoproteins improved spontaneously during three and a half years. Because they require different treatment strategies, distinction between familial lecithin:cholesterol acyltransferase deficiency (FLD) and acquired LCAT deficiency by gene sequencing is warranted, especially in cases without corneal clouding.

Keywords Lecithin:cholesterol acyltransferase (LCAT) deficiency · Familial LCAT deficiency · Spontaneous remission · Renal insufficiency · Foam cells

Introduction

Familial deficiency of lecithin:cholesterol acyltransferase (LCAT) activity is a rare autosomal recessive disorder with a worldwide prevalence below 1:1,000,000 [1]. LCAT catalyzes the esterification of cholesterol in plasma, and deficiency of the enzyme can cause renal damage, hemolytic anemia, and corneal clouding [1]. Since it was first reported in 1967 [2], there have been reports of approximately 70 LCAT mutations of partial or complete deficiency [3]. Two types of deficiency are classified based on their clinical manifestations. One is called fish-eye disease (FED), as its only clinical manifestation is corneal clouding. The other is familial lecithin:cholesterol acyltransferase deficiency (FLD), which is complicated by renal damage and anemia in addition to corneal clouding. Deficiency of the enzyme is caused by LCAT gene mutations. The LCAT gene is on chromosome 16, and approximately 80 mutations have been reported [1]. Eleven mutations causing FLD and three mutations causing FED have been identified in Japanese [4–6]. Recently Takahashi et al. reported a case of acquired LCAT deficiency caused by IgG antibodies to LCAT in the absence of an LCAT gene mutation, which was improved by treatment with prednisolone [7]. Here, we report a case of acquired LCAT deficiency associated with sarcoidosis, whose dyslipidemia improved spontaneously.

Case report

The patient was a Japanese female aged 70 years, in whom bilateral hilar lymphadenopathy was detected on chest X-ray examination. She underwent a mediastinal lymph node biopsy, which revealed non-caseating granulomas

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typical of sarcoidosis. As she had no symptoms, and there were no abnormalities in the blood or urine, she was not given glucocorticoid or immunosuppressive therapy. Two years previously, however, she had been found to have moderate proteinuria, a low high-density lipoprotein cholesterol (HDL-C) level, a high plasma triglyceride (TG) level, and a low low-density lipoprotein cholesterol (LDL-C) level for the first time. On account of leg edema 2 months before her admission, blood and urine tests were performed, which identified high proteinuria, renal function disorder, and anemia. There was no smoking history or drinking habit. She had been treated with valsartan 80 mg/day for hypertension and bezafibrate 400 mg/day for dyslipidemia.

The patient was admitted to our hospital for further examination. On admission, her height, body weight, body mass index, blood pressure, and pulse rate were 152.5 cm, 49.8 kg, 21.4 kg/m², 118/72 mmHg and 87 beats/min, respectively. Her palpebral conjunctiva indicated anemia. She did not have bulbar conjunctival jaundice, neck lymphadenopathy, skin lesions, or corneal clouding. She had

pitting edema in her lower extremities. Her laboratory data are shown in Table 1. She had severe proteinuria (5.6 g/g Cr) without urinary red blood cells, and normocytic anemia with low haptoglobin, indicating hemolytic anemia. She also had low plasma total cholesterol (119 mg/dL), very low HDL-C (2 mg/dL), an abnormally low proportion of cholesteryl esters (14.6 %), low LCAT activity (62.5 nmol/mL h (37 °C), 260.0–560.0), and high plasma TG (243 mg/dL). Her estimated glomerular filtration rate (eGFR) was 32.2 mL/min/1.73 m². There were no abnormalities in an electrocardiogram, and no significant carotid atherosclerosis on carotid ultrasound. As no morphological abnormality was detected by renal ultrasound, a kidney biopsy was performed. All glomeruli showed accumulation of foam cells (Fig. 1, arrow 1), mesangiolysis (Fig. 1, arrow 2) and focal sclerosis (Fig. 1, arrow 3). In some glomeruli, the glomerular basement membrane (GBM) showed a double contour (Fig. 1b, arrow 4). The granulomatous lesion which was characteristic of sarcoidosis was not found. Immunofluorescence did not reveal the presence of immunoglobulin or complement. Electron microscopy

Table 1 The patient's laboratory data on admission

<i>Blood</i>			
Complete blood count		Serum chemistry	
White blood cell	4500/μL	Total protein	6.8 g/dL
Red blood cell	289 × 10 ⁴ /μL	Albumin	3.9 g/dL
MCV	99.6 fL	Total bilirubin	0.9 mg/dL
Hemoglobin	9.6 g/dL	Aspartate amino transferase	34 U/L
Hematocrit	29.9 %	Alanine transaminase	19 U/L
Platelet count	21.5 × 10 ⁴ /μL	Lactate dehydrogenase	344 U/L
Serology		Blood urea nitrogen	27 mg/dL
CRP	0.07 mg/dL	Creatinine	1.26 mg/dL
IgG	1282 mg/dL	eGFR	32.2 mL/min/1.73 m ²
IgA	224 mg/dL	Sodium	140 mEq/L
IgM	76 mg/dL	Potassium	5.4 mEq/L
CH50	47 U/mL	Chloride	106 mEq/L
C3	120 mg/dL	Total cholesterol	119 mg/dL
C4	23 mg/dL	Triglyceride	243 mg/dL
Antinuclear antibody	40 times	HDL-C	2 mg/dL
Rheumatoid factor	<12 U/mL	LDL-C	39 mg/dL
<i>Urine</i>		HbA1c	3.7 %
Urinalysis		Haptoglobin	<9 mg/dL
Protein	3+	Ferritin	222 ng/mL
Blood	1+	LCAT activity	62.5 nmol/mL h (37 °C) (260–560)
Urinary sediments		Free form cholesterol	96 mg/dL (30–60)
Red blood cell	<1/HPF	Ester form cholesterol	14 mg/dL (90–200)
White blood cell	<1/HPF	Cholesterol ester ratio	14.6 % (65–80)
Cast	(–)	ACE	16.8 IU/L/37 °C
Urine chemistry			
Selectivity index	0.37		

Fig. 1 Histological findings of the renal biopsy. Accumulation of foam cells (**a** and **b**, arrow 1), mesangiolysis (**a** and **b**, arrow 2) and focal sclerosis (**a** and **b**, arrow 3). The glomerular basement membrane (GBM) showed a double contour (**b**, arrow 4)

Fig. 2 Electron microscopy findings. Abnormal lipid accumulation in subendothelial space (arrow 1) and foam cells in mesangial region and sub-endothelial space (arrow 2)

showed that there was abnormal lipid accumulation in subendothelial space (Fig. 2, arrow 1) and foam cells in mesangial region and the sub-endothelial space (Fig. 2, arrow 2).

To determine the cause of the low LCAT activity, we obtained informed consent to performed LCAT gene analysis by the next-generation sequence method. However, there was no mutation in the LCAT gene exon sequence of the patient. No mutation in LCAT gene suggested that she would be an acquired LCAT deficiency. To examine the existence of the LCAT inhibitory factors including anti-LCAT antibody, we prepared a lipoprotein deficient serum (LPDS) from this patients and normal control. If serum contains LCAT inhibitory factors, the LCAT activity is low in patient's LPDS added recombinant LCAT (rLCAT) or normal serum than in normal control LPDS added rLCAT or normal serum. In this patient case, the LCAT activity was low in her LPDS added rLCAT

Fig. 3 To look for anti-LCAT antibodies or other LCAT inhibitors, we prepared lipoprotein-deficient serum (LPDS). LCAT activity was lower in the patient's LPDS with added rLCAT than in normal LPDS with added rLCAT (**a**). LCAT activity was also lower in the patient's LPDS with added normal serum than in normal LPDS with added normal serum (**b**)

(Fig. 3a) or normal serum (Fig. 3b) than in normal control LPDS added rLCAT or normal serum. Then, to conform the existence of IgG which had reactivity with rLCAT in her serum, we performed immunoprecipitation test. As shown in Fig. 4, rLCAT was immunoprecipitated with anti-LCAT antibody [rabbit monoclonal antibody (mAb)] and with patients IgG refined from her LPDS. From these results, patient's LPDS had anti-LCAT antibody which partially inhibited LCAT activity.

Based on these results, we diagnosed her disorder as acquired LCAT deficiency with anti-LCAT-antibodies in her serum.

Fig. 4 Immunoprecipitation study. rLCAT was immunoprecipitated with anti-LCAT antibody [rabbit monoclonal antibody (mAb)] and with patients IgG. IP-WB immunoprecipitation–western blotting, HDL-C high density lipoprotein

Because the leg edema gradually decreased after admission and there was no significant carotid atherosclerosis, we started a diet composed of lipid and protein restrictions, after which her leg edema and proteinuria gradually decreased. Three and a half years later, her LCAT activity had increased to 118 nmol/mL h (37 °C), and her dyslipidemia (total cholesterol 151 mg/dL, TG 101 mg/dL, HDL-C 37 mg/dL, LDL-C 90 mg/dL), and anemia (Hb 13.2 g/dL) had all improved. Urine protein became negative.

Discussion

LCAT is a 416 amino acid glycoprotein that is produced mainly in the liver. It exists in plasma on lipoproteins, and plays an important role in the transfer of surplus cholesterol from peripheral cells to the liver via HDL [8, 9]. The enzyme catalyzes the transacylation of the sn-2 fatty acid of lecithin to the free 3-OH group of cholesterol, generating cholesteryl ester and lysolecithin [10]. Consequently, in LCAT deficiency, free (i.e., non-esterified) cholesterol is increased and HDL-C is reduced. Increases in free cholesterol and phosphatide produce red blood cell abnormalities and hemolytic anemia [11]. Free cholesterol also accumulates in the cornea and the kidney. Both FED

and FLD are usually associated with HDL-C values of less than 5–10 mg/dL. The differences in clinical manifestations between FLD and FED are caused by differences in LCAT activity [11]. FED is characterized by partial enzyme deficiency, whereas in FLD there is complete deficiency. Recently Kuroda et al. reported abnormal lipoprotein subfractions highly associated with renal damage in FLD patients [12]. On the other hand, Guerin et al. reported the renal damage in FLD patients were caused by lipoprotein called lipoprotein-X (Lp-X) [13].

In our case, the clinical manifestations were like those of FLD, although some LCAT activity was detectable. To our knowledge, three cases of acquired LCAT deficiency have been reported in English [7, 14, 15]. The first case was a LCAT deficiency without mutations in the coding sequence. Her clinical manifestation was similar to FLD with corneal opacities, normocytic anemia, dyslipidemia, and proteinuria progressing to chronic renal failure [14]. The second was a patient with non-Hodgkin lymphoma and autoantibodies to LCAT [15]. Her LCAT activity recovered after complete lymphoma remission. However, clinical manifestations other than severe HDL-C deficiency were not described. The third case also had anti-LCAT antibodies and extremely low HDL-C [7]. She presented with nephrotic syndrome due to glomerular lipid deposition with prominent accumulation of foam cells, similar to the histological findings of FLD. However, the presence of irregular thickening of the GBM with subepithelial electron-dense deposits suggested the coexistence of membranous nephropathy. Treatment with prednisolone and azathioprine resulted in complete remission of the nephrotic syndrome, and additionally normalization of serum LCAT activity and HDL-C. Our case is similar to the third case, who presented with proteinuria but no corneal clouding. Although we did not prove the presence of anti-LCAT antibodies directly, tests carried out with LPDS from the patient and a normal control strongly suggested the existence of either anti-LCAT antibodies or another LCAT inhibitory factor in her serum.

The mechanism by which autoantibodies against LCAT can develop is unclear. The first case was associated with hyperthyroidism. The second case was associated with non-Hodgkin lymphoma, and the third case with Sjögren's syndrome, and our case with sarcoidosis, indicating that some immunological disorder might play an important role.

In general, patients with secondary LCAT deficiency, due for example to hepatic disease or sepsis, do not show corneal clouding. The first case had corneal clouding, however, her mother and elder sister had cornea opacities, but not had dyslipidemia and LCAT deficiency. The cause of cornea opacities of this patient may not be due to the LCAT deficiency. These facts suggest that corneal clouding may not be a clinical feature of acquired LCAT deficiency.

The dyslipidemia in the second and third patients remitted during treatment of their complications. In our case, it improved gradually without specific medications. Our patient had sarcoidosis. In half of all cases of sarcoidosis, the disease resolves spontaneously within 2 years, and in the remaining cases it often resolves within five years [16]. In our case, the absence of symptoms or involvement of any organ during the clinical course suggests that active sarcoid disease might decrease LCAT activity, and that the latter improves as the disease resolves.

The pathological abnormalities of the kidney in FLD are mainly in the glomeruli [17]. Light microscopic examination reveals enlargement of the mesangium, vacuolation of the loop wall, and speculation, double contouring and deposition of foamy lipid in the GBM. Immunofluorescence is typically negative for immunoglobulin and complement. Electron microscopic findings are lipid deposition, visualized as small vacuolations of various sizes on the epimembranous, intramembranous, and subendothelial aspects of the GBM [17]. In the third report of acquired LCAT deficiency, electron microscopy revealed subepithelial electron-dense deposition as well as glomerular lipid deposition. In our case, electron microscopy did not show subepithelial electron-dense deposition. These findings seem to indicate that the electron microscopic findings in the kidney in cases of acquired LCAT deficiency are almost the same as those in FLD, and that subepithelial electron-dense deposition is not an invariable pathologic feature of the kidney in acquired LCAT deficiency.

Because they require different treatment strategies, distinction between FLD and acquired LCAT deficiency by gene sequencing is warranted, especially in cases without corneal clouding.

Compliance with ethical standards

Conflict of interest Honoraria: Jitsuo Higaki (Pfizer Inc, Asters Co, Takeda Pharm Co, Boehringer-Ingelheim Japan Co, Daiichi-Sankyo Co, MSD Co, Mochida Pharm Co, Novartis Pharm Co, and DaiNihon-Sumitomo Co), Research funding: Jitsuo Higaki (Pfizer Inc, Asters Co, Takeda Pharm Co, Boehringer-Ingelheim Japan Co, Daiichi-Sankyo Co, MSD Co, Mochida Pharm Co, Novartis Pharm Co, and DaiNihon-Sumitomo Co). The other authors have no conflicts of interest with regard to the content of this article.

Human and animal rights This article does not contain any studies with human participants performed by any of the authors.

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