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Case report

Renal findings of partial Lecithin Cholesterol Acyltransferase (LCAT) deficiency: an atypical presentation of an extremely rare cause of nephrotic syndrome in childhood

L.J. De Silva[1], T. Damayanthi[1], S. Gunaratne [2], M.V.C. de Silva[1]

[1] *Department of Pathology, Faculty of Medicine, University of Colombo, Sri Lanka*

[2] *Department of Pathology, Lady Ridgeway Hospital for Children, Colombo, Sri Lanka*

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Abstract

Introduction: Lecithin Cholesterol Acyltransferase (LCAT) is a major enzyme in the cholesterol metabolism pathway. LCAT deficiency (LCATD) is a rare genetic disorder characterized by nephrotic range proteinuria, anaemia and corneal opacities. Two major syndromes, i.e., familial LCATD and partial LACTD, are now considered as one disease spectrum and intermediate phenotypes are not uncommon. This case report highlights the renal findings of two siblings, with genetically confirmed partial LCATD in the elder child, and atypical clinical presentations.

Case report: The two patients were the second and third-born children in a family with second-degree consanguinity. The elder, a six-year-old boy, presented with steroid-resistant nephrotic range proteinuria and hypercholesterolemia at the age of two years, and genetic testing confirmed partial LCATD. He progressed to develop end-stage renal failure and is currently on haemodialysis. His two-year-old sister presented with similar symptoms. Renal biopsies of both showed mostly viable glomeruli and a few partially sclerosed glomeruli. The mesangial matrix was expanded with cells containing pale eosinophilic bubbly cytoplasm. Capillary lumina were obliterated by enlarged mesangial cells in the worst affected glomeruli. The basement membranes were irregular and wrinkled, and the silver stain highlighted their bubbly appearance. Many tubules and some vascular endothelial cells showed cytoplasmic vacuolations. Immunofluorescence was negative for IgA, IgM, IgG and C3. Both patients are being followed up for visual impairment, although the characteristic corneal opacification is not yet established.

Discussion and conclusion: Renal manifestations are a major cause of morbidity in congenital LCATD. The renal findings of LCATD are similar to the late-stage of membranous glomerulopathy, hepatic nephropathy, Alagille syndrome and Nail-patella syndrome. Correlation with clinical, serological, histological, immunohistochemical findings, and electron microscopy if available, is important to arrive at a diagnosis.

Keywords: lecithin cholesterol acyltransferase (LCAT) deficiency, fish-eye disease, nephrotic syndrome, renal biopsy

Corresponding author: Dr Lalani De Silva
Department of Pathology, Faculty of Medicine
University of Colombo, Sri Lanka
lalanidesila7@gmail.com

Introduction

Nephrotic syndrome is a clinical disorder characterized by proteinuria, hypoalbuminaemia, oedema, and hyperlipidaemia (1). Nephrotic syndrome can either be primary due to diseases specific to kidneys, such as minimal change disease, focal segmental glomerulosclerosis and membranous glomerulopathy, or secondary to systemic illnesses affecting kidneys, such as diabetic nephropathy, amyloidosis and some infective/immunological disorders (2). The commonest cause of nephrotic syndrome in childhood is minimal change disease, followed by focal segmental glomerulosclerosis (1).

LCATD is a rare autosomal recessive disease (prevalence < 1: 1,000,000), which can present with nephrotic range proteinuria (3). The other clinical manifestations include dyslipidaemia, anaemia and corneal opacities. LCAT is an enzyme in cholesterol metabolism that is involved in the esterification of cholesterol. Lack of this enzyme results in deranged metabolic pathways and causes abnormal deposition of lipids in organs (3,4). It is a progressive disease resulting in end-stage renal disease in early childhood (4). Two major syndromes associated with LCATD are familial LCATD (complete or Norum disease) and partial LCATD (fish-eye disease), although intermediate phenotypes are reported and remain unclassified (5).

The literature on renal manifestations of LCATD is sparse and there are very few reports on the histopathological evaluation of renal tissue of these patients. Herein we present the histopathological findings of renal biopsies of two siblings in a family with partial LCATD who presented with steroid resistant nephrotic syndrome.

Case report

These six-year and two-year-old siblings were the second and third born children of a family with second-degree consanguinity. The six-year-old male child initially presented to the paediatric ward at two years of age with nephrotic range proteinuria, hypoalbuminaemia and hypercholesterolaemia (Table 1). He was initially managed as having minimal change disease. Since he was not responding to the immunosuppressive therapy, a renal biopsy was performed. This initial renal biopsy showed two out of seven glomeruli with mild mesangial expansion, mild tubular atrophy, a patchy chronic interstitial inflammatory cell infiltrate and thickening of vessel walls. These biopsy findings were not diagnostic of any of the clinical differential diagnoses at that time, which included minimal change disease, membranous glomerulopathy and focal segmental glomerulosclerosis. Immunofluorescence studies were not performed due to their unavailability. He was further investigated for persistent hypercholesterolaemia with low HDL levels and found to have partial LCATD on genetic testing. He was managed conservatively, and despite immunosuppressive therapy with cyclophosphamide and rituximab, he progressed to dialysis dependent end-stage renal disease.

The second patient was the third child of the family. She presented at two years of age with a five-week history of persistent nephrotic range proteinuria, which was not responding to steroids. In addition, she had hypoalbuminaemia and hypercholesterolaemia (Table 1). Her clinical presentation and disease progression were similar to her elder brother. The other family members and close relatives denied any symptoms suggestive of renal disease, visual impairment or derangement in lipid profiles.

A renal biopsy was performed on the younger child and the previously reported biopsy of elder child was reviewed. The biopsy findings of younger child done at the age of two years were similar to that of her elder brother done at the age of four years. Most of the glomeruli in these biopsies were viable. There were a few globally sclerosed glomeruli. The viable

glomeruli showed variable mesangial matrix expansion and hypercellularity. The capillary lumina were obliterated in the worst affected segments (Figure 1). The mesangial cells showed expanded cytoplasm with a bubbly, vacuolated appearance that was highlighted in the silver-stained sections (Figure 2). The capillary basement membranes were focally thickened. There was no evidence of leukocyte infiltration, fibrinoid necrosis, epithelial crescents or segmental sclerosis in the glomeruli. Many tubular epithelial cells showed cytoplasmic vacuolation. Some tubules showed epithelial cell sloughing and regenerative changes (Figure 3). There was mild tubular atrophy. The interstitium showed patchy mild to moderate lymphocytic infiltrate and mild to moderate interstitial fibrosis. The large blood vessels were normal. The small capillaries were lined by plump endothelial cells with cytoplasmic vacuolation. Immunofluorescence studies did not show significant staining for IgG, IgA, IgM and C3.

Investigation	**Case 1**	**Case 2**	**Normal value**	**Comment**
Full blood count				
Haemoglobin	11.6 g/dL	10.8 g/dL	11–15 g/dL	
White blood cell count	7800/µL	7143/µL	5000-10000/ µL	
Platelets	594x10^9/L	198x10^9/L	200-490x10^9/L	
Renal function tests				
Blood urea	2.7 mmol/L	5.4 mmol/L	1.5-3 mmol/L	
Serum creatinine	34 µmol/L	30 µmol/L	20-45 µmol/L	
Serum sodium	139 mEq/L	137 mEq/L	135-145 mEq/L	
Serum potassium	4.8 mEq/L	4.6 mEq/L	3.5-5.3 mEq/L	
Urine protein creatinine ratio on spot urine	1280 mg/mmol	1410 mg/mmol	>20 mg/mmol	**Nephrotic range**
Urine albumin	3+	3+		
Liver function tests				
Aspartate aminotransferase	22 U/L	29.5 U/L	10-40 U/L	
Alanine transaminase	17 U/L	21.8 U/L	9-48 U/L	
Serum bilirubin	2 µmol/L	3 µmol/L	3-20 µmol/L	
Serum albumin	23 g/L	19 g/L	34-50 g/L	**Low**
Total cholesterol	10.9 mmol/L	10.82 mmol/L	2.88-5.23 mmol/L	**High**
Triglyceride	3.3 mmol/L	3.02 mmol/L	0.51-2.38 mmol/L	**High**
HDL	0.33 mmol/L	0.48 mmol/L	>0.91 mmol/L	**Low**
Ultrasound scan of abdomen and pelvis	Enlarged kidneys with increased echogenicity	Normal		
Erythrocyte sedimentation rate	82 mm/hr	75 mm/hr	0–10 mm/hr	**High**
C-reactive protein	<5 mg/L	5.3 mg/L	< 10 mg/L	

Table 1. Investigation findings of the two patients at their initial presentations

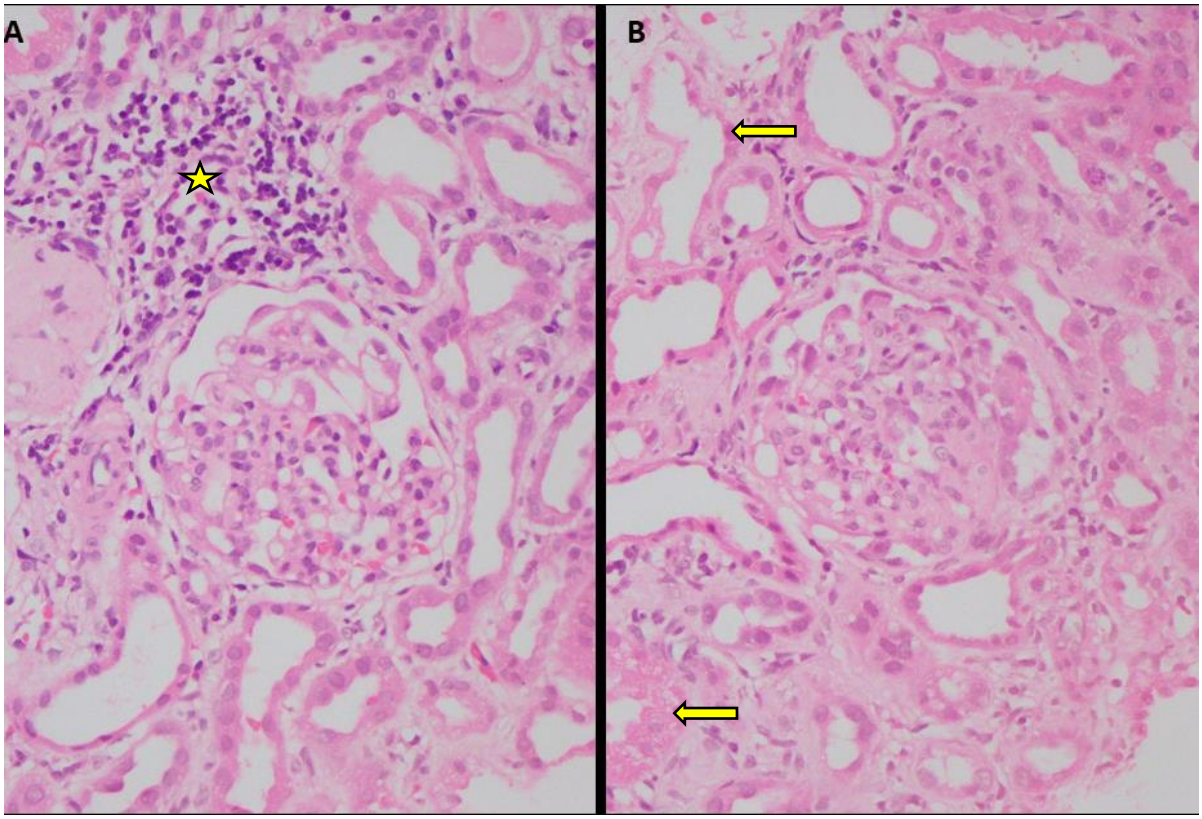

Figure 1. A The renal biopsy of the elder child at 4 years **B.** The renal biopsy of the younger child at 2 years Both biopsies showing viable and sclerosed glomeruli. Viable glomeruli show mesangial expansion with a bubbly, vacuolated appearance. The tubular epithelial cell show vacuolation and flattening (arrow) and there is patchy chronic inflammation in the interstitium (asteric) (H&E x200)

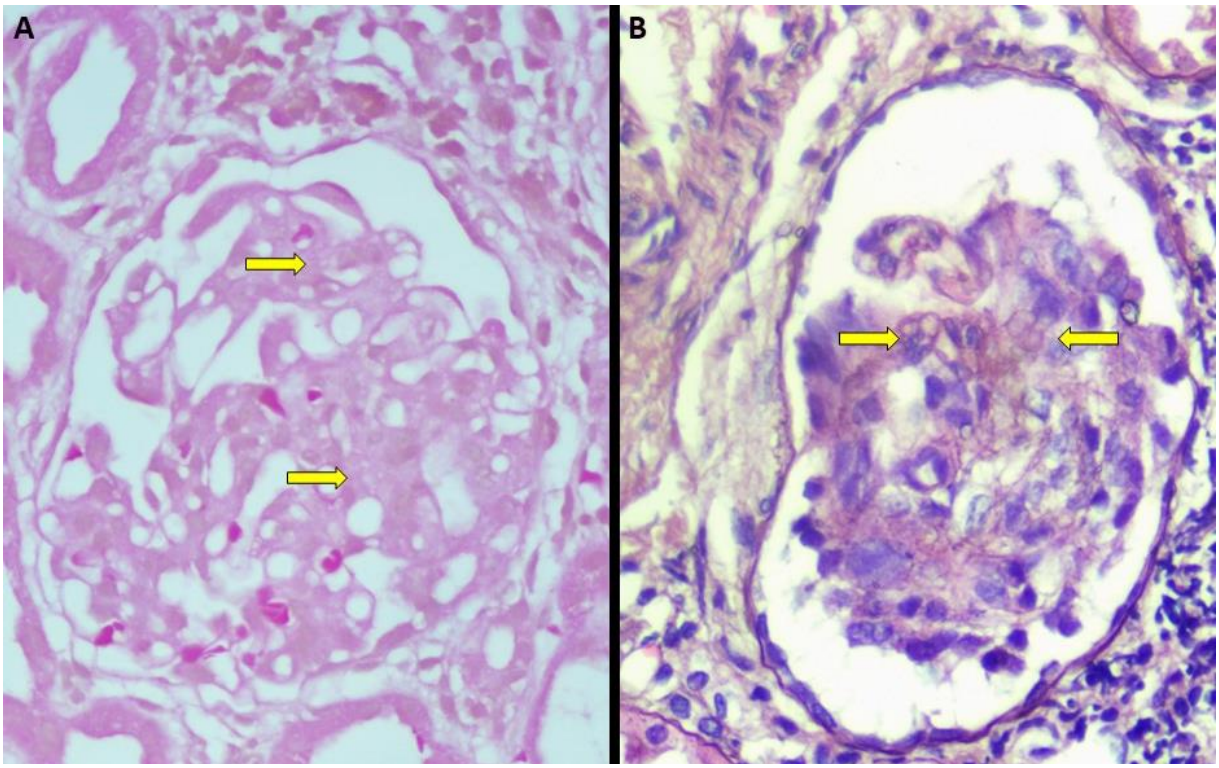

Figure 2. A. The mesangial cells show bubbly cytoplasm (arrows) (H&E x 400)
B. Silver-stained sections highlight the bubbly appearance (arrows) (Methenamine silver stainx400)

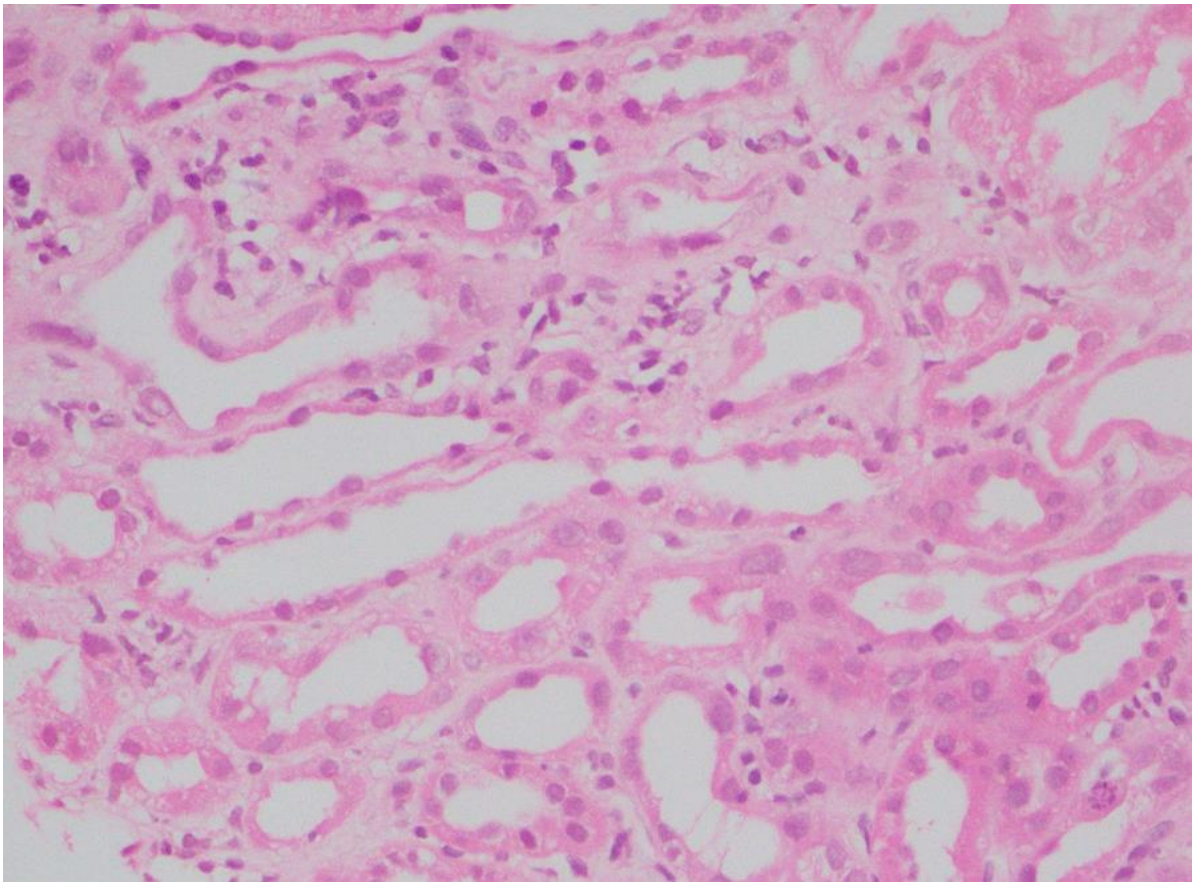

Figure 3. The tubular epithelial cells show vacuolated bubbly cytoplasm.

Considering the findings of the genetic studies of the elder child and the similar morphological and immunofluorescence findings of the renal biopsies, LCATD was the most likely cause of the renal manifestations in these patients. Genetic confirmation was not performed in the younger child due to financial constraints.

Currently, both patients are on regular renal replacement therapy.

Discussion

LCAT is a key enzyme involved in reverse cholesterol transport from the peripheral tissues to the liver, which converts free cholesterol into cholesterol esters and facilitates the conversion of nascent high-density lipoproteins (HDL) into mature HDL (6). The deficiency of LCAT impairs the esterification of free cholesterol in the plasma, leading to accumulation of phospholipids, including lecithin, in organs (6).

LCATD can be congenital due to genetic mutation in chromosome 16q22 or acquired due to inhibitory autoantibodies directed to LCAT (6,7). The congenital form is inherited in an autosomal recessive pattern and is further categorized into familial LCATD and partial LCATD (fish-eye disease) (6,7). The familial LCATD results in virtually absent plasma alpha and beta LCAT activity due to missense mutation. In partial LCATD, the enzyme remains active on the cholesterol particles in very low-density lipoproteins (VLDL) and low-density lipoproteins (LDL) but not in HDL (6,7).

The major clinical manifestations of LCATD are corneal opacification, anaemia and proteinuria with renal impairment. Less common symptoms include atherosclerosis, hepatomegaly, splenomegaly and lymphadenopathy. The characteristic corneal opacification develops due to the deposition of fatty material in the cornea. This feature is

more frequent in partial LCATD than complete LCATD, and it is named fish-eye disease because the cornea resembles the eyes of a boiled fish (3,4,8). The index cases have not yet developed corneal opacity and are under close ophthalmology follow-up.

These patients can be recognized as having atypical presentations of partial LCATD, as corneal opacification, which is the characteristic presentation of partial enzyme loss is not yet developed in these children. However, a decade ago, Calabresi et al. proposed that the two major clinical syndromes are rather different manifestations of one disease spectrum. This was further proven by the finding of the similar biochemical phenotype of both conditions despite a different esterification profile (9,10). Further, 21.5% of genetically proven LCAT deficient patients remain as unclassified because of atypical phenotypes (11).

The exact mechanism of renal injury is not yet elucidated. Deposition of lipid particles in the glomerular basement membrane (GBM), mesangium and sub-endothelial tissue and direct toxicity of lipid particles to endothelial cells are considered potential mechanisms (4).

The prognosis of LCATD is variable, and the majority develop end-stage renal disease by the fourth decade of life. Visual impairment, atherosclerotic events and renal failure are the major causes of morbidity and mortality (4, 6,7). Currently, there is no specific treatment modality for LCATD, and the disease can recur in the renal allografts. LCAT gene replacement and enzyme replacement therapy are potential future therapeutic options (12).

Renal biopsy findings include both glomerular and tubulointerstitial changes. The glomeruli appear acellular with an eosinophilic matrix accumulating in areas of segmental sclerosis. The mesangium contains foamy cells. Silver-stained sections highlight the irregularities with vacuolation of the GBM and double contouring resembling late-stage membranous glomerulonephritis. Tubular epithelial cells and capillary endothelial cells appear bubbly, vacuolated or honeycombed in appearance. Immunofluorescence studies are usually negative. Sometimes IgM and/or C3 entrapment can be detected. Electron microscopic features are characteristic and show glomerular epimembranous, intramembranous, subendothelial, and mesangial lipid deposits. The lipids are partly deeply osmiophilic with cross-striated curvilinear serpiginous fibrils, rounded lamellar densities and granular densities. Densely osmiophilic GBM deposits resemble the glomerular alterations of dense deposit disease (3,4,8,13). However, facilities for electron microscopic examination are not available in the local setting.

The renal abnormalities, although easily recognizable, are not diagnostic because similar lipid deposits occur in kidneys of patients with chronic liver disease, who also have elevated serum lipoproteins. Other possible differential diagnoses for this histological appearance of the renal biopsy include membranous nephropathy, Alagille syndrome and Nail-patella syndrome.

Hepatic glomerulopathy, also called hepatic glomerulosclerosis is a secondary sclerosing glomerular lesion associated with liver disease and shows deposition of lipid particles similar to those seen in LCATD, but usually with less severity. Hepatic glomerulopathy occurs in the context of liver failure and cirrhosis. The possibility of liver disease was excluded by clinical, serological and radiological findings in these patients.

The light microscopic appearance of GBM changes on the silver stain can mimic stage III membranous nephropathy. Positive family history, hypercholesterolemia, negative immunofluorescence and lipid deposits recognized in electron microscopy favour LCATD over membranous nephropathy.

Alagille syndrome is an autosomal dominant disease caused by mutations in either *JAG1* or *NOTCH2* genes, involving 94%

and 0.8% of probands, respectively (14). This disorder can affect multiple organs, including the liver, heart, skeleton, eye, face, and kidneys. Renal dysplasia is present in most patients with Alagille syndrome, and the most striking pathological finding in advanced disease is the presence of numerous lipid vacuoles (lipidosis) embedded within the GBM, which is identical to the appearance of LCATD. In addition, prominent lipid particle deposits can be present in the mesangium. However, the autosomal dominant pattern of inheritance and the presence of cholestasis, and cardiac, skeletal, ocular and facial abnormalities differentiate Alagille syndrome from LCATD (14).

Nail-patella syndrome is a rare autosomal dominant disease with variable penetrance. Renal involvement is the most common and serious manifestation of the disease that is seen in 40% of the affected individuals. The glomerular changes by light microscopy are non-specific, comprising variable focal and segmented sclerosis and often segmental thickening of the capillary walls. Sometimes, the GBM can show a moth-eaten appearance similar to the findings in LCATD (15).

Conclusion

LCATD is a rare genetic disorder leading to nephrotic range proteinuria, which gives characteristic histological findings in renal biopsies. However, atypical presentations, as in these cases, are not uncommon. It is always important to correlate histopathological findings with patient demographics, presenting features, family history and radiological investigations prior to confirming the diagnosis.

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