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Case Report

# Glomerulopathy Associated with Lecithin-Cholesterol-Acyltransferase Deficiency: A Case Report and Literature Review

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## Abstract

Glomerulopathy associated with Lecithin-Cholesterol-Acyltransferase Deficiency (LCAT) is a rare automosal recessive disease. Acquired LCAT deficiency due to inhibitory autoantibodies against LCAT are also described. Lipid profile usually shows variable cholesterol levels but very low HDL levels. Here we describe a 33-year-old man presenting a nephrotic syndrome associated with moderate renal insufficiency for which the pathological analysis allowed to guide toward the diagnosis of LCAT deficiency. Laboratory and genetic data confirmed this diagnosis. Familial history and lipid profile abnormalities are important in the identification of this disease.

**Keywords:** Cholesterol; Electron Microscopy; Glomerulopathy; Lecithin-Cholesterol-Acyltransferase

## Introduction

Lecithin-Cholesterol-Acyltransferase (LCAT) deficiency is a rare autosomal recessive disease characterized by high circulating levels of unesterified cholesterol and oxidized phosphatidylcholine associated in the abnormal "lipoprotein X" [1,2]. Acquired LCAT deficiencies are also described [3]. LCAT is a plasma enzyme which esterifies the free cholesterol in the plasma and allows the reverse transport of cholesterol from the peripheral tissues to the liver. LCAT deficiency leads to the accumulation of phospholipids in organs such as the eye, bone marrow and kidney. Plasmatic lipid profile shows variable cholesterol levels and dramatically reduced levels of High-Density-Lipoprotein (HDL) [2] The prevalence of LCAT deficiency in the general population is unknown, and only case reports were described in the literature [4]. Renal involvement is a major cause of morbidity and mortality [3], and characteristic light- and electron-microscopic findings on renal pathology can lead to the diagnosis of LCAT deficiency. Here we describe a 33-year-old man presenting with a nephrotic syndrome associated with moderate renal insufficiency for whom the pathological analysis paved the way to the diagnosis of LCAT deficiency.

## Case Report

A 33 y-o Italian man, complained of peripheral edema discovered four years earlier. He had no other past medical history, and his parents and five brothers, including a twin brother, were healthy. Blood and urinary (Table 1) analysis showed nephrotic syndrome and anemia.

| | Patient value | Reference range |
|---|---|---|
| Serum albumin | 2.9 g/dL | 3.5 to 5.5 g/dL |
| Proteinuria | 4g/24h | <3.5 g/24 h |
| Hemoglobin level | 10.7 g/dL | 14 to 18 g/dL |

| EGFR | 80 ml/min/1.73 $m^2$ | >60 ml/min/1.73 $m^2$ |
|---|---|---|
| Triglyceridemia | 332 mg/dL | < 150 mg/dL |
| Total cholesterol | 197 mg/dL | < 200 mg/dL |
| Low-density-lipoprotein cholesterol | 100 mg/dL | < 100mg:/dL |
| High-density-lipoprotein cholesterol | 11 mg/dL | > 40mg/dL |
| Apolipoprotein A1 | 47 mg/dL | > 120mg/dL |

**Table 1:** Blood and urinary analysis.

His renal function was normal. Microscopic hematuria was detected. His blood pressure was 125/75 mmHg. His lipid analysis showed hypertriglyceridemia, with normal levels of total cholesterol, Low-Density-Lipoprotein (LDL) cholesterol, and low levels of High-Density-Lipoprotein (HDL) cholesterol and apolipoprotein A1. Esterified cholesterol represented 23 % of total cholesterol. The search for antinuclear antibodies, anti-PLA2R antibodies, cryoglobulinemia and monoclonal gammopathy were negative, complement fractions were normal, and serological markers for hepatitis B, hepatitis C, and HIV were negative.

A renal biopsy was performed. A diffuse mild endocapillary proliferation was observed with coarse heterogenous subendothelial deposits often narrowing capillary loops (Figure 1a).

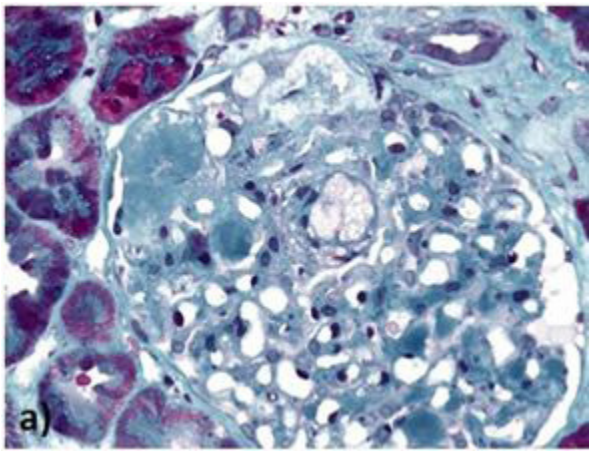


**Figure 1a:** Light microscopy showing a mild proliferation with lucent deposits narrowing capillary loops, Masson trichrome, original magnification x 400.

These deposits were mainly located in the subendothelial space, within the glomerular membrane or in subepithelial areas ((Figure 1b) - silver staining).

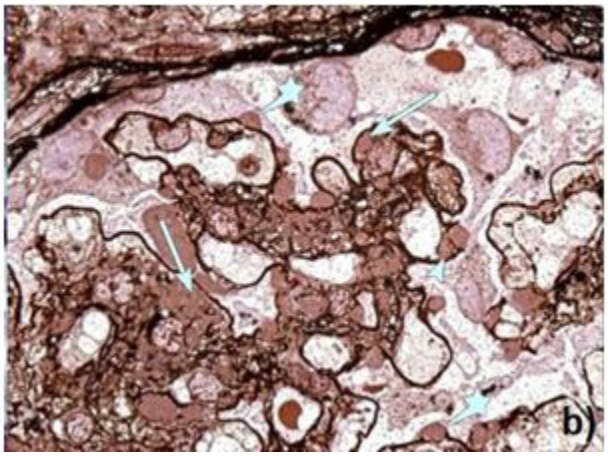


**Figure 1b:** Light microscopy also showing dense deposits in subendothelial (arrows), intramembranous (arrowhead) or subepithelial (stars) areas, Jones staining, original magnification x 1000.

Various sized lipid vacuoles, rare dense deposits and numerous lamellar structures (20-30 nm) were detected by electron microscopy (Figure 1c).

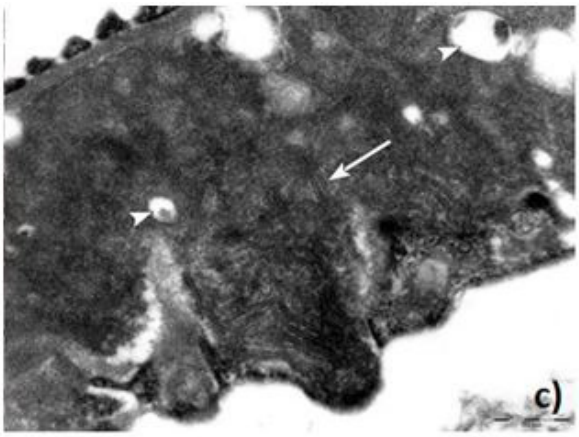


**Figure 1c:** Electron microscopy showing a typical subendothelial area with of lipid lucent vacuoles (arrowheads) and 20-30 nm lamellar structures (arrows), original magnification, x 22 000.

These lesions raised the hypothesis of a glomerulopathy associated with lecithin-cholesterol-acyltransferase (LCAT) deficiency. Sequencing of the LCAT gene identified two pathogenic heterozygotic unknown mutations C.475C>T and C.559del on exons 4 and 5 respectively. Ophthalmologic test showed corneal lesion with a ground glass appearance. The patient progressed to Chronic Kidney Disease (CKD) and End Stage Renal Disease (ESRD) and hemodialysis was initiated 5 years after the diagnosis.

## Discussion

LCAT deficiency can be suspected in front of clinical signs associated with serum lipid abnormalities such as low plasma HDL-cholesterol, and the pathological analysis of an organ affected by phospholipid accumulation, such as the kidney [1,3]. In clinical practice, the age of onset is variable, but most patients are diagnosed in adulthood. Extra-renal manifestations include corneal lipoid arcus or corneal greyish spots (called fish eye syndrome), and normocytic anemia accompanied by prominent target cell formation, red cell osmotic fragility due to lipid abnormalities in erythrocyte membrane [1,4]. Serum and red cell lipids tend to normalize in vivo when LCAT is provided by infusions of normal plasma [1,3]. Renal involvement is frequent and may lead as in this case to end stage renal failure within the fifth decade [3]. Proteinuria is variable, ranging from minimal to nephrotic syndrome. Interestingly, the nephrotic syndrome itself can decrease LCAT activity [5]. Renal biopsies show glomerulopathy evolving toward sclerosis with diffuse lipid deposits within the glomerular tuft or in the wall of the interstitial blood vessels [1,6]. Immunoglobulins deposits are classically missing except in acquired LCAT deficiency (IgG and C3 staining of glomerular capillary walls) [3]. Electron microscopy are key to the diagnosis: lipid deposits are seen as small dark, irregular, granular, electron-dense, or electron-lucent particles. Intramembranous and mesangial regions can be involved. Glomerular basement duplication are also described [3].

Differential diagnoses include lipoprotein glomerulopathy, lipid deposits in few syndromic diseases such as Alagille syndrome, or advanced membranous glomerulopathies with extensive secondary focal segmental sclerosis with numerous foamy cells [1].

Familial history and lipid profile abnormalities are important in the identification of this rare disease.

The enzyme LCAT is encoded by a gene located on 16q22 and composed of six exons [4]. To date, more than 88 mutations of the LCAT gene have been identified [6]. Shoji, et al. [7] suggest that a translational or post-translational mechanism may be involved. The presence, in the heterozygous state, of the R135W mutation has been reported in the literature [8]. It is leading to an open reading frame frame-shift and a protein truncation. Molecular defects result in various LCAT activity levels and enzymatic specificities leading to different clinical phenotypes, from the fish-eye-disease (also called "partial LCAT deficiency") without renal involvement and residual activity except against HDL, to the classical familial LCAT deficiency ("complete LCAT deficiency") with complete loss of activity [1,2,5]. Acquired LCAT deficiency was also described recently and is due to inhibitory auto-antibodies against LCAT [9,10], associated with auto-immune diseases such as Sjogren's syndrome, or with lymphomas [9,10]. These auto-antibodies can be detected in the serum by mixing test and co-immunoprecipitation study. In that case, a treatment with corticosteroids can lead to the disappearance of the foam cells within the glomeruli [9].

Renal disease is the major cause of morbidity and mortality in patient with LCAT deficiency. Treatment of LCAT deficiency aims at correcting dyslipidemia and delaying and preventing the development of CKD [11] and progression to ESRD.

The mechanisms of development of the renal lesions are not precisely understood yet. Lynn, et al. [12] proposed that lipoprotein-X can stimulate monocyte infiltration through a mechanism involving monocyte chemoattractant protein-1 secretion by mesangial cells. The infiltrating monocyte could contribute in the pathogenesis of glomerulosclerosis and subsequent renal failure by forming foam cells, and producing cytokines and growth factors. In our case, the electron microscopy showed numerous areas containing lamellar structures. These structures are thought to be the consequence of abnormal cell membranes renewal [13] and may explain the nephrotic syndrome. This case underlines the interest of pathology in the LCAT deficiency diagnosis.

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