The Case | Nephrotic syndrome with corneal opacities

Abdullah Ozkok[1], Yesim Onal[1], Isin Kilicaslan[2], Seyhun Solakoglu[3], Huseyin Bayramlar[4] and Ali Riza Odabas[1]

[1]Department of Nephrology, Istanbul Medeniyet University, Goztepe Training and Research Hospital, Istanbul, Turkey; [2]Department of Pathology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey; [3]Department of Histology and Embryology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey; and [4]Department of Ophthalmology, Istanbul Medeniyet University, Goztepe Training and Research Hospital, Istanbul, Turkey

Correspondence: *Abdullah Ozkok, Department of Nephrology, Istanbul Medeniyet University, Goztepe Training and Research Hospital, Kadikoy, Istanbul, Turkey. E-mail: abdullah.ozkok@ismu.edu.tr*

Kidney International (2017) **91,** 515–516; http://dx.doi.org/10.1016/j.kint.2016.07.005

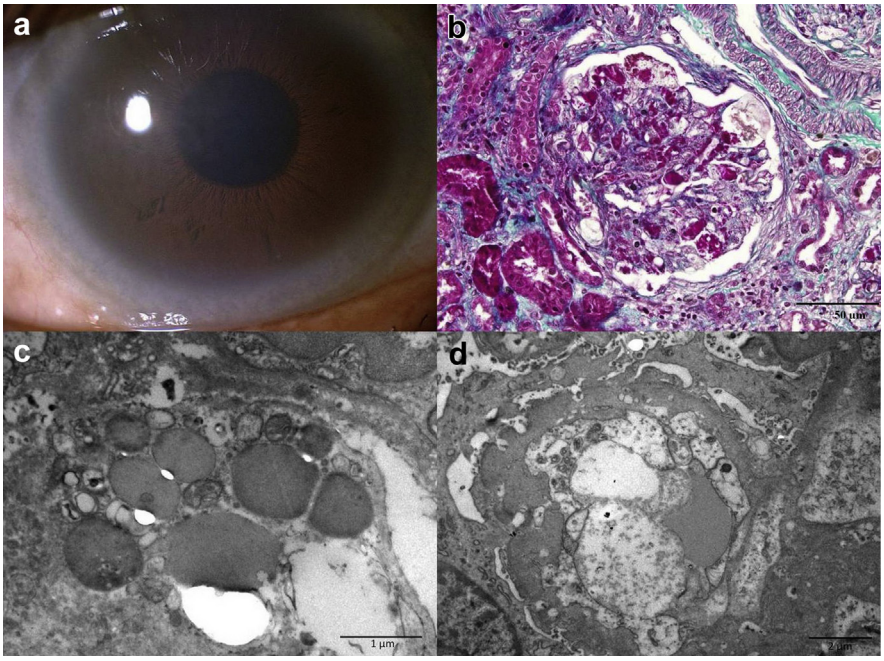

Figure 1 | Ophthalmological and histopathological findings. (**a**) Slit-lamp examination showing corneal arcus and opacities. (**b**) Renal biopsy specimen showing a foamy appearance in endothelial cells and intracapillary periodic acid–Schiff–positive deposits (hematoxylin and eosin, original magnification ×200). (**c**) Electron microscopy showing intramembranous, subendothelial, and mesangial lipid deposits. (**d**) Electron microscopy showing vacuolization in endothelial cells.

A 35-year-old man was admitted with edema in his lower extremities. Physical examination revealed corneal arcus and opacities (Figure 1a) in addition to pitting edema in his legs. He mentioned that he had siblings with similar symptoms such as cloudiness in the eye and kidney disease; however, they refused to seek medical attention. Results of the biochemical analyses performed for our patient were as follows: serum creatinine, 1.43 mg/dl (range, 0.72–1.25 mg/dl); albumin, 2.8 g/dl (range, 3.5–5.2 mg/dl); total cholesterol, 140 mg/dl (<200 mg/dl); and triglyceride, 652 mg/dl (<150 mg/dl). Serum high-density lipoprotein (HDL) levels were unmeasurable. No other abnormality other than mild anemia (hemoglobin, 10.2 g/dl [range, 13–17 g/dl]) was present on laboratory testing. Urine analysis results were 7 g/day (<150 mg/day) proteinuria. Renal biopsy showed that 13 of 31 glomeruli were globally sclerotic. A foamy appearance was noted in endothelial cells and arteriolar walls. Intracapillary periodic acid–Schiff–positive deposits were also present (Figure 1b). Results of Congo red staining were negative. On electron microscopy, intramembranous, subendothelial, and mesangial lipid deposits were observed (Figure 1c), and vacuolization was present in endothelial cells (Figure 1d).

What is your diagnosis?

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The Diagnosis | Lecithin–cholesterol acyltransferase enzyme deficiency

This patient had corneal opacities, nephrotic syndrome, chronic kidney disease, and undetectable HDL levels, which together raised the suspicion of lecithin–cholesterol acyltransferase (LCAT) deficiency. Whole genome sequence analysis revealed a novel homozygote mutation in *LCAT* gene splice site region (IVS1+1G>C[c.154+1G>C]) (MiSeq Sequencing System, Illumina Inc, San Diego, CA). Thus, the diagnosis of LCAT enzyme deficiency was established. The patient is currently being followed with supportive treatment including an angiotensin-converting enzyme inhibitor.

LCAT is an enzyme synthesized in the liver; it esterifies the free cholesterol on lipoproteins. LCAT is important in reverse cholesterol transport, which carries cholesterol from the peripheral tissues to the liver.[1] The *LCAT* gene is localized on chromosome 16 (16q22), and a total of 88 gene mutations have been found in the human *LCAT* gene. Familial LCAT deficiency syndrome is a very rare autosomal recessive disorder (prevalence <1/1,000,000); only 70 cases have been reported worldwide.[2] Clinical manifestations include corneal opacities, hemolytic anemia, and lipid accumulation in various organs including the kidneys, causing proteinuria and renal dysfunction. HDL levels are characteristically very low or undetectable; however, several other diseases may also be associated with low HDL such as Tangier disease and Apo-AI deficiency, which may be considered in the differential diagnosis. Although corneal opacities may also be seen in these diseases, kidney involvement occurs only in LCAT deficiency.

Corneal opacities are apparent in early childhood and are usually the initial finding of LCAT deficiency. These opacities consist of numerous grayish dots in the corneal stroma, giving the cornea a cloudy appearance.[3] Renal dysfunction with proteinuria before the fifth decade is a common feature, which is the major cause of morbidity and mortality. Renal disease associated with LCAT deficiency may progress to end-stage renal disease. In renal pathology, deposition of foamy lipids is observed in the thickened glomerular basement membrane, giving rise to a vacuolated appearance. The mesangium is usually enlarged and may also have a foamy appearance. On electron microscopy, lipid deposits appear as vacuolations in the glomerular basement membrane, Bowman's capsule, and endothelium. The extent of lipid deposition may be an important predictor of the progression to end-stage renal disease.[1]

Currently, there is no specific treatment for LCAT deficiency. Enzyme or gene replacement therapies may be expected in the future. Low-fat/low-calorie diets and angiotensin-converting enzyme inhibitor treatment may be beneficial for the renal disease associated with LCAT deficiency.[1]

LCAT enzyme deficiency should be considered in nephrotic syndrome and chronic kidney disease cases with corneal opacity and very low serum HDL levels.

DISCLOSURE

All the authors declared no competing interests.

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