Familial Lecithin-Cholesterol Acyltransferase Deficiency

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Familial lecithin-cholesterol acyl transferase deficiency is an uncommon autosomal recessive disorder from a heritable defect in esterification of plasma cholesterol. In 1968, the disease was described by Gjone and Norum in Norway.

Our case was a 38-year-old woman. Her disease was manifested by presence of lower extremities edema, proteinuria, corneal opacities, increased plasma cholesterol, and hemolytic anemia. Suspicion of the disease was based on renal biopsy, which revealed mesangial expansion and capillary wall widening with clusters of foamy cells in the mesangium. Immunofluorescence study was nonspecific, but specific findings of electron microscopy showed deposition of lipid in the glomerular basement membrane and mesangium. This is the first report of lecithin-cholesterol acyltransferase deficiency in Iran.

The diagnosis was confirmed by a low high-density lipoprotein cholesterol concentration, decreased activity of lecithin-cholesterol acyltransferase in plasma, and positive familial history of the disease.

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Introduction

Lecithin-cholesterol acyltransferase (LCAT) is an enzyme that catalyzes the esterifying reaction of cholesterol in plasma high-density lipoprotein (HDL). Deficiency of LCAT is a rare hereditary disease, characterized by several clinical symptoms such as proteinuria, corneal opacity, and anemia that is due to a shortened life span of erythrocytes.

Case Report

A 38-year-old female patient, from north of Iran, was referred with proteinuria and lower extremities edema. She was admitted to hospital because of proteinuria. On physical examination, she had corneal opacities, anemia, and a high systolic blood pressure (180 mmHg).

Laboratory findings showed a severe anemia with low hematocrit (31 mmHg) and hemoglobin (10 mg/dL) levels. Other laboratory tests showed a creatinine of 3.2 mg/dL, increased cholesterol (320 mg/dL) and triglyceride (450 mg/dL), markedly decreased HDL (22 mg/dL), and 4 g of protein in a 24-hour urine sample.

The patient had proteinuria since three years ago with a high blood pressure, hemolytic anemia (with a history of one unit blood transfusion two months ago), and high levels of cholesterol and triglyceride.

In family history, her younger brother (33 years old) had cataract, high blood pressure, hyperlipidemia, and chronic renal failure.

Renal biopsy was done for the patient. Histopathologic findings by light microscopy showed mesangial expansion with a mild increase in the mesangial cellularity. Glomerular basement membrane was thickened with foamy cells, which showed double contour appearance. Clusters of foamy cells were also observed in the mesangium (Figures 1 and 2).

Immunofluorescence staining for fibrinogen, c1q, IgM, and C3 showed deposition in glomerular basement membrane and very little positive depositions of IgM. IgM was also observed in the mesangium. All of these findings were nonspecific for definite diagnosis. With suspicion of
LPL deficiency, the biopsy specimen was examined by electron microscopy that showed lipid vacuoles in the mesangial matrix and along the glomerular basement membranes and epithelial cells. Glomerular basement membranes had wide and foamy appearance too (Figures 3A and B).

**Discussion**

LPL deficiency is a rare genetic disorder of lipid metabolism with linkage of the genes for alfa-haptoglobin and LPL on the long arm of chromosome 16 that caused by the absence of LPL activity in plasma. The gene for LPL deficiency has been completely sequenced and cloned. The enzyme, LPL, is carried by HDL with apo A-I as a cofactor. It catalyzes the esterification of free cholesterol bound to low-density lipoprotein (LDL).

In 1968, Gjone and Norum reported a familial disorder characterized by proteinuria and corneal opacity. Most of initial patients were of Scandinavian origin. Subsequent reports have been from other countries. Increased concentration of unesterified cholesterol, triglycerides, and phosphatidyl choline are the result of lipid deposition in tissues. Accumulation of lipid component occurs in both intracellular and extracellular sites.

Clinical manifestations include corneal opacities, hemolytic anemia, renal dysfunction, decreased HDL, and low LPL activity in plasma. An increase in the ratio of plasma unesterified cholesterol to esterified cholesterol is observed too. But the triad of anemia, nephritic syndrome, and corneal opacities suggests this disorder. It is not generally accompanied by atherosclerosis in spite of low HDL cholesterol levels. However, there are rare reports of the disease in long-term follow-up or autopsy findings. The incidence of atherosclerosis in LPL deficiency is not clear.

Lipid deposits occur also in liver, spleen, and bone marrow, in which foamy cells (sea blue histiocytes) are present. Renal lesions begin with the glomeruli deposition in the glomerular basement membrane, lipid accumulation in the mesangium, and capillary subendothelium. The progression of renal disease is variable; severe proteinuria in some and mild in others. Hypertension probably appears as an early or late complication of renal insufficiency.

In other studies in histopathologic findings, abnormalities were found mainly in the glomeruli, but arteries and arterioles might also be affected. In glomeruli, mesangial expansion and capillary wall thickening can be seen. Immunofluorescence microscopy is nonspecific and shows that there is typically negative staining for all immunoglobulins and complement components.

By electron microscopy, the most striking features were massive deposition of lipid material in the glomeruli, particularly in the glomerular basement membrane (epimembranous, intramembranous, subendothelial, and mesangial). The glomerular capillary walls are thickened and there is mesangial expansion. Basement membrane appears irregular and often appears to contain bubbles, resembling stage 3 membranous alternations. Double contouring of capillary walls...
is present occasionally. Similar lucencies in the mesangium make a honeycomb appearance. There is no associated glomerular hypercellularity.

We visualized similar changes in our patient's biopsy evaluated by electron microscopy which contained lipid vacuoles in different locations of glomeruli.

On electron microscopy, the lucent areas were visualized as extracellular irregular lucent zones (lacunae) in the mesangial matrix. These contain round, small, and dense structures, either solid or with a lamellar substructure.2,1,4,7

The glomerular changes appear to be similar to that seen in some cases with liver cirrhosis. Lipid material contains a large amount of apolipoprotein-B detected by immunohistology.2,3

Because of the similarity between our patient's symptoms and signs and the findings in light and electron microscopic evaluation with other reports, we confirmed familial LCAT deficiency

**References**