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CASE REPORT

Apolipoprotein E Dyslipidemia and Nephrotic Syndrome: A Rare Connection

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Abstract
Severe hyperlipidemia warrants an extensive evaluation. We report a case of a 25-year-old man of Chinese descent seen in the cardiology-lipid clinic. He was found to have a serum low-density lipoprotein cholesterol of 12.12 mmol/L (468 mg/dL) and serum triglycerides of 2.29 mmol/L (203 mg/dL) during routine screening. Work-up revealed nephrotic-range proteinuria, and renal biopsy showed dilated glomerular capillary loops with lipid deposits, pathognomonic of lipoprotein glomerulopathy. Genetic studies showed apolipoprotein E3/E4 phenotype. He was treated with a high-intensity statin and fibrate therapy, which resulted in a marked improvement in dyslipidemia and proteinuria.

Background
Severe hyperlipidemia, especially extremely high serum low-density lipoprotein cholesterol (LDL) greater than 4.92 mmol/L (190 mg/dL), raises the possibility of genetic lipid disorders such as familial hypercholesterolemia (1). Sometimes, significantly elevated LDL levels also may lead to the discovery of an unrecognized secondary cause of dyslipidemia, such as hypothyroidism, Cushing syndrome, nephrotic syndrome, etc., warranting specific work-up and treatment. Lipoprotein glomerulopathy (LPG) is a rare genetic cause of nephrotic syndrome caused by abnormal apolipoprotein E (Apo E) molecules and typically is characterized by severe hypertriglyceridemia. LPG is observed in individuals of East Asian origin, rarely in those of European-American origin, and usually progresses to end-stage renal disease if it remains unrecognized or untreated (2).

Objective
We describe a case of LDL-predominant severe mixed hyperlipidemia and highlight the multidisciplinary approach required in diagnosis and management of LPG.

Case Report
A 25-year-old man was referred to the cardiology-lipid clinic after being diagnosed with significant hyperlipidemia by his primary care physician. He had immigrated from Southeast China. He did not consume alcohol, smoke, or use illicit substances. He reported no family history of cardiovascular, renal, or lipid disorders. He also was diagnosed recently with hypertension and hypothyroidism (serum thyroid-stimulating hormone 8.57 µIU/mL, free T4 9.52 pmol/L). His medications included losartan, 25 mg, hydrochlorothiazide, 25 mg, L-thyroxine, 25 mcg, and atorvastatin, 40 mg.

His blood pressure in the office was 129/75 mm Hg. He had mild bilateral pedal edema, and the rest of his physical examination findings were unremarkable. The lipid panel showed serum total cholesterol (TC) of 14.87 mmol/L (574 mg/dL), serum LDL of 12.12 mmol/L (468 mg/dL), serum

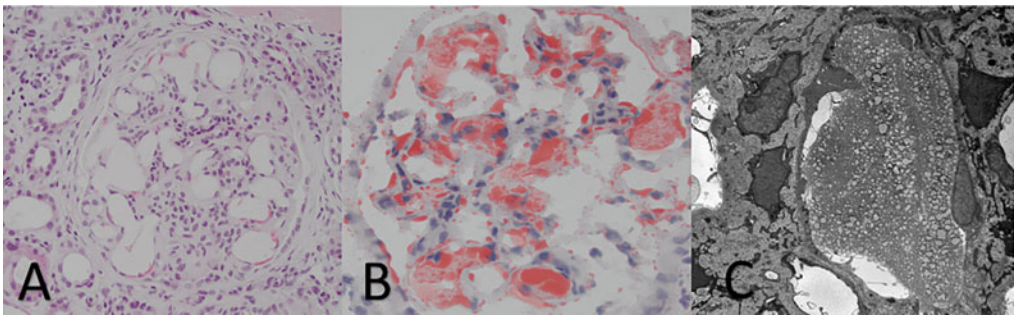

Figure 1. **Histopathology. (A) Dilated glomerular capillary loops with luminal amorphous deposits. (B) Oil Red O stain demonstrating lipid deposition. (C) Luminal amorphous material containing numerous vacuoles on electron microscopy.**

high-density lipoprotein cholesterol (HDL) of 1.37 mmol/L (53 mg/dL), and serum triglycerides (TG) of 2.29 mmol/L (203 mg/dL). Serum creatinine was 109.62 µmol/L (1.24 mg/dL), and serum albumin was 18 g/L (1.8 g/dL). Electrolyte, liver enzyme, and bilirubin levels were normal. Hemoglobin A1C was 5.1%. Urinalysis revealed microscopic hematuria and a urine protein-to-creatinine ratio of 6360 mg/g. Renal ultrasound scan revealed bilaterally enlarged kidneys.

Nephrology and endocrinology consultations were obtained. Anti-nuclear antibody, C3, C4, antineutrophil cytoplasmic antibody panel, glomerular basement antibody, phospholipase A2 receptor antibody, hepatitis B and C serology, and human immunodeficiency virus testing findings were negative. Serum protein electrophoresis showed no monoclonal protein.

The patient had a renal biopsy, which showed glomerular capillary loop distention with luminal amorphous material and moderate interstitial fibrosis (Figure 1A). Direct immunofluorescence showed no significant staining for IgG, IgA, IgM, C3, C1q, fibrinogen, kappa, and lambda light chains. Oil Red O stain revealed glomerular capillary lipid deposits (Figure 1B). Electron microscopy revealed loss of foot processes, and distended capillary loops with luminal thrombosed amorphous material containing numerous vacuoles (Figure 1C).

Genetic study for familial hypercholesterolemia was negative. Genotyping showed the presence of heterozygous Apo E3/E4 variant. Subsequently, DNA sequencing of was ordered; however, due to financial constraints, the patient declined to undergo this test. Based on clinical, pathognomonic histologic features, and Apo E genotype, a clinical diagnosis of LPG was established, and patient was initiated on treatment.

He was initiated on fenofibrate, 130 mg daily, and atorvastatin was maintained. Losartan was switched to valsartan, and hydrochlorothiazide was discontinued. Levothyroxine was increased to 50 mcg daily due to elevated thyroid-stimulating hormone (6.46 µIU/mL) during follow-up.

Laboratory testing at a 6-month follow-up showed an improved TC of 5.02 mmol/L (194 mg/dL), LDL of 2.98 mmol/L (115 mg/dL), TG of 1.12 mmol/L (99 mg/dL), HDL of 1.58 mmol/L (61 mg/dL), and a decreased urine protein-to-creatinine ratio of 3742 mg/g. A similar trend was observed at 1-year follow-up: TC of 4.20 mmol/L (162 mg/dL), LDL of 2.38 mmol/L (92 mg/dL), TG of 1.02 mmol/L (90 mg/dL), HDL of 1.37 mmol/L (53 mg/dL) (Figure 2), and further decrease in urine protein-to-creatinine ratio to 1994 mg/g.

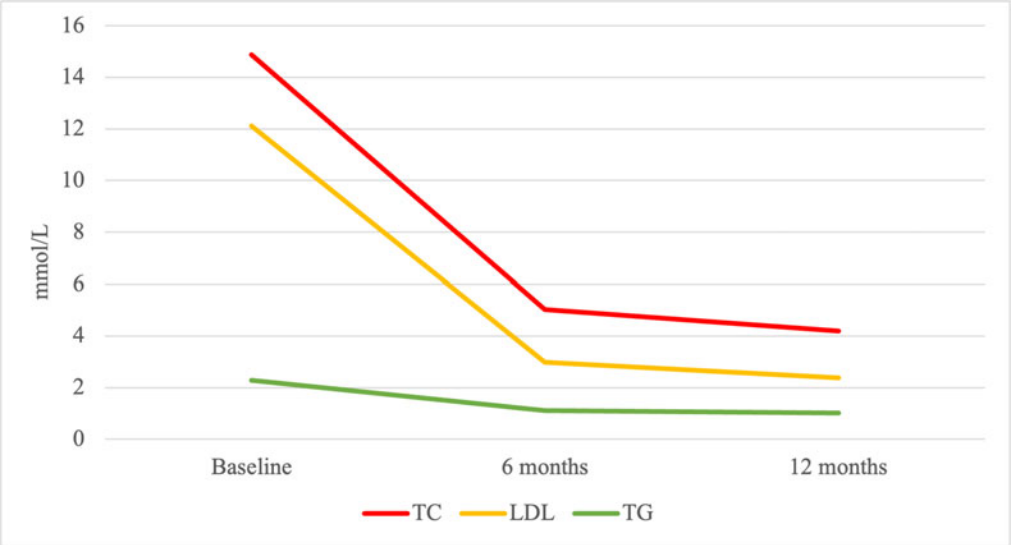

Figure 2. **Change in total cholesterol (TC), low-density lipoprotein (LDL), and triglyceride (TG) levels.**

Discussion

LPG is a rare disorder caused by mutations in the apoE gene and was first described in a Japanese patient in 1989 (3). As in our case, patients with LPG are usually identified during diagnostic evaluation of significant dyslipidemia and/or proteinuria encountered during a routine screening examination, or when they present with features of nephrotic syndrome. It has an autosomal-dominant pattern of inheritance with variable penetrance (4). This disorder usually manifests in adulthood and predominantly affects men (5). Despite similarities in the phenotype of hyperlipidemia in LPG and familial type III hyperlipidemia, xanthomas and atherosclerotic cardiovascular disease have been rarely reported in patients with the former (6). Our case demonstrates an LDL-predominant hyperlipidemia that led to the diagnosis of LPG, differing from the characteristic TG-predominant dyslipidemia pattern described in the literature. Occasionally, normolipidemic cases also are reported (7).

Apo E is a glycoprotein composed of 299 amino acids after cleavage of the 18-amino-acid signal peptide, coded by a gene on chromosome 19, and has 3 major allelic variants (Ɛ2, Ɛ3, and Ɛ4). It serves as a ligand for receptor-mediated uptake via the LDL receptor family and heparan sulfate proteoglycans. It therefore plays a critical regulatory role in the clearance of TG-rich lipoproteins from plasma (8). The mutant Apo E loses its ability to bind to LDLR, resulting in decreased elimination (9), but retains the ability to bind to heparan sulfate proteoglycans, allowing it to adhere to the endothelial surface (10).

The main pathologic feature of LPG is intraglomerular lipoprotein thrombosis. The pathophysiology is poorly understood; however, its unique predilection for the kidney could be possibly related to a favorable glomerular microenvironment: increased concentration of mutant Apo E molecules during ultrafiltration and a greater binding affinity to a negatively charged basement membrane (6). Moreover, impaired macrophage activity due to functional Fc receptor gamma deficiency is implicated in the pathogenesis of LPG (11). Light microscopy shows markedly dilated glomerular capillaries with pale eosinophilic material within the capillary lumen. Staining for Oil Red O or Sudan Red confirms the presence of lipid droplets. Under electron microscopy, lipoprotein thrombosis is characterized by a fingerprint-like concentric lamellar structure with lipid vacuoles (5).

Given the lack of controlled clinical trials because of its rarity, the treatment strategies for LPG have been based on observational studies. The mainstay of therapy is targeted toward lowering Apo E lipoprotein levels with fibrates and statins (12, 13). Treatment in the early phase may result in remission and stabilization of renal function. In refractory cases, LDL-apheresis or immunoadsorption onto staphylococcal protein A may be beneficial (14). In addition, agents like renin–angiotensin–aldosterone system inhibitors and sodium–glucose co-transporter-2 inhibitors may be renoprotective in LPG, as seen in other forms of proteinuric kidney disease. Traditional treatments for nephrotic syndrome such as corticosteroids or immunosuppressive agents are ineffective. The outcome of renal transplantation is poor, as the Apo E abnormality persists and can induce lipoprotein thrombi in the transplanted kidney (15).

In summary, severe hyperlipidemia should warrant further work-up and multidisciplinary collaboration to establish underlying cause. LPG should be suspected in patients presenting with hyperlipidemia and unexplained proteinuria. As the result of greater prevalence among individuals with East Asian ancestry, clinicians should maintain a high index of suspicion in this patient population. LPG remains an under-recognized reno-metabolic disease that requires timely recognition to mitigate adverse consequences.

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