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Case Report

Intravascular cardiac lipoproteinosis: extrarenal manifestation of lipoprotein glomerulopathy☆

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ABSTRACT

Intracapillary lipoprotein thrombi are a distinct histopathologic finding described in the setting of lipoprotein glomerulopathy. The disease is associated with mutations in the apolipoprotein E gene and responds well to lipid-lowering treatments. Lipoprotein glomerulopathy is thought to primarily affect the kidneys, and lipoprotein thrombi have never been described in any other organ. Herein we present the first recognized case with extrarenal manifestations in the form of intravascular cardiac lipoprotein deposition.

1. Background

Intracapillary lipoprotein thrombi were first described in the kidney in 1989 by Saito et al. [1], who observed pale-staining amorphous material within the glomeruli of three related individuals presenting with proteinuria and edema. The amorphous material distended capillary loops and stained weakly positive with periodic acid–Schiff (PAS) and pale green with Masson's trichrome. Further testing demonstrated immunoreactivity with antibodies directed against apolipoprotein B and E and a layered, fingerprint-like texture with electron microscopy [2,3]. The constellation of findings was termed *lipoprotein glomerulopathy* (LPG).

Patients typically present with mild to nephrotic range proteinuria, a lipid profile similar to type III hyperlipidemia (i.e., elevations of very low-density lipoproteins and intermediate-density lipoproteins) and variable serum apolipoprotein E (APOE) levels [4–8]. Physical stigmata of hyperlipidemia, such as corneal opacity and xanthomas, are usually lacking. APOE gene mutations have been found in many of these cases, particularly in the LDL-receptor binding domain [2,3,6,8–26]. Inheritance is autosomal dominant in nature.

Since first description, LPG has been reported globally [6,14,18,27]. Extrarenal manifestations have not, to our knowledge, been reported.

2. Case report

2.1. Clinical history

A 50-year-old Caucasian man presented with increasing lower extremity edema and dyspnea. He was known to have systemic hypertension, coronary artery disease (status post myocardial infarction and stent placement), hypercholesterolemia, and chronic obstructive pulmonary disease. His social history included tobacco, marijuana, and alcohol use.

2.2. Physical examination and initial laboratory findings

On examination, he was found to have elevated jugular venous pressure and a third heart sound on auscultation. His liver and spleen were both palpable, and his extremities were severely edematous with pitting. Laboratory testing was remarkable for an elevated B-type natriuretic peptide level at 738 pg/ml (reference range 0–125 pg/ml), a normal serum creatinine at 1 mg/dl (reference range 0.7–1.3 mg/dl), and nephrotic range proteinuria at 7 g/24 h. Cholesterol, triglycerides, and low-density lipoprotein (LDL) levels were all elevated (Table 1).

Serum and urine protein electrophoreses with immunofixation were ordered to further evaluate his proteinuria; an IgG kappa monoclonal gammopathy was identified. Given the presence of a monoclonal gammopathy and echocardiography findings, the patient's heart failure was speculated to be due to cardiac amyloidosis secondary to multiple myeloma. A bone marrow biopsy was performed and was negative for both multiple myeloma and amyloid. An abdominal fat pad biopsy

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Table 1
Patient lipid profile

	Result (mg/dl)	Reference range (mg/dl)
Cholesterol	243	≤200
Triglyceride	202	≤150
dHDL	36	40–60
LDL (calculated)	167	≤99
Apolipoprotein A-1	128	96–178
Apolipoprotein B	178	55–140

was then ordered, but this too was negative for amyloid. At this point, cardiac and renal biopsies were requested for more definitive tissue characterization (see below).

2.3. Imaging findings

Imaging studies demonstrated cardiomegaly and varying degrees of pleural effusions. Transthoracic echocardiography was performed and showed increased left ventricular wall thickness (1.92 cm). Restrictive hemodynamics were observed, along with biatrial dilatation, with preserved ejection fraction (60%). Moderate aortic valve stenosis, trivial mitral valve regurgitation, and mild tricuspid regurgitation were also noted. Myocardial strain was abnormal with distal and apical sparing.

2.4. Histologic findings

Histologically, the renal biopsy revealed pale, acellular, silver- and PAS-negative, lamellated eosinophilic material within the glomerular capillaries and a few luminal foam cells (Fig. 1). Two of 16 glomeruli were sclerosed. Glomerular capillary walls were thickened, and double contour formation was apparent in a few segments. There was a mild to moderate increase in mesangial matrix with mild segmental increase in mesangial cellularity.

The endomyocardial biopsy exhibited similar amorphous eosinophilic material filling in small intramyocardial vessels (Fig. 2). The myocardium itself demonstrated nonspecific findings including moderate to marked myocyte hypertrophy and mild interstitial (pericellular-type) fibrosis. There were no acute ischemic changes.

Of note, the intravascular eosinophilic material was Congo red-negative and did not stain with sulfated Alcian blue.

2.5. Ultrastructural findings

Transmission electron microscopy was performed on deparaffinized myocardial tissue. The intravascular material was finely vacuolated and exhibited ultrastructural characteristics in keeping with lipoproteins (Fig. 3).

2.6. Molecular genetic findings

The patient underwent *APOE* genotyping with florescent probes and was found to be homozygous for the ε3 allele. *APOE* gene sequencing has not, to date, been performed.

3. Discussion

Although LPG represents a systemic disease of disordered lipid metabolism, hitherto only renal manifestations have been described. This

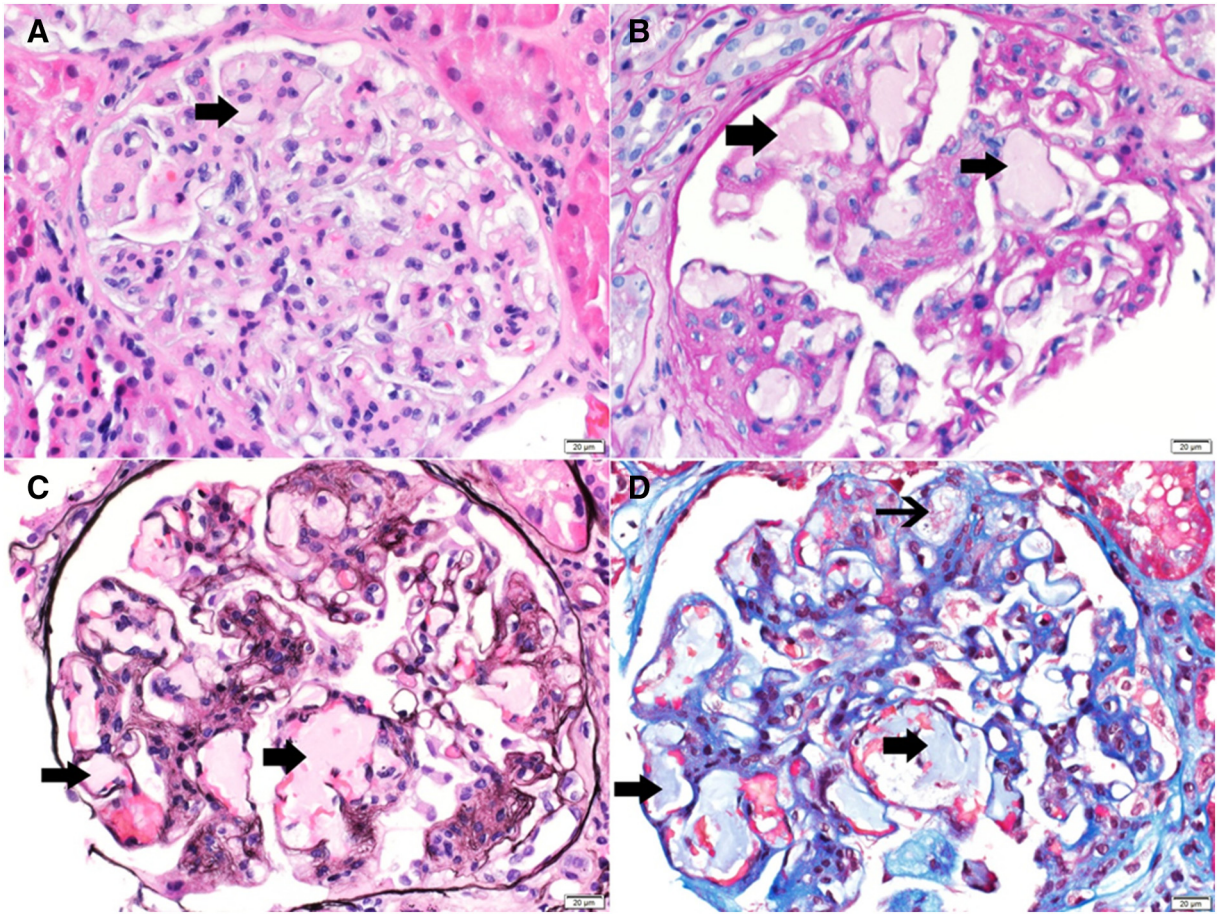

Fig. 1. Renal light microscopic findings. Glomerular capillary loops are distended and contain acellular material (thick arrows) that is PAS and silver negative and appears pale blue on trichrome stain. Foam cells (thin arrow) are also present in the glomerular capillaries. The glomerular capillary tufts exhibit lobular accentuation and show thickened glomerular capillaries with segmental double contour formation (A, hematoxylin & eosin; B, PAS; C, methenamine silver; D, Masson trichrome; original magnification, ×400).

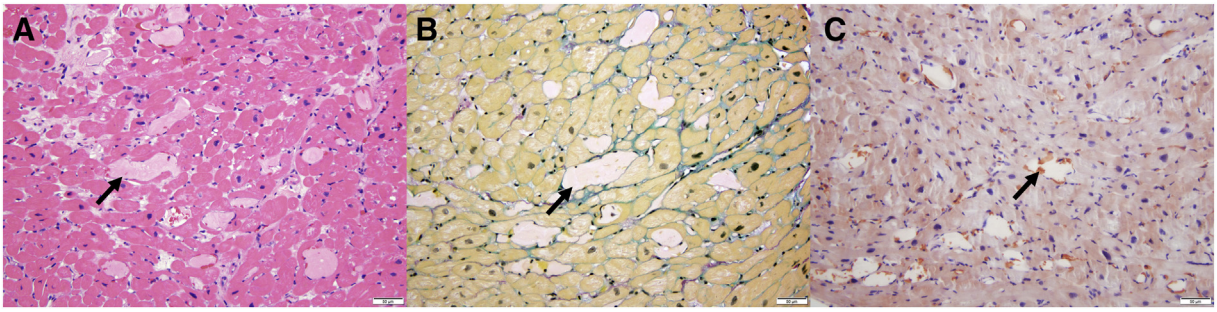

Fig. 2. Cardiac light microscopic findings. Distended intramyocardial capillaries (arrow) filled with amorphous eosinophilic material that is Congo red and sulfated Alcian blue negative. The myocardium is otherwise remarkable for moderate to marked myocyte hypertrophy and mild interstitial (pericellular-type) fibrosis (A, hematoxylin & eosin; B, sulfated Alcian blue; C, Congo red; original magnification, ×200).

report represents the first description of an extrarenal manifestation of LPG. More specifically, it details the light and electron microscopic findings in the heart of a patient with LPG. Additionally, it highlights the clinical difficulty in identifying this disease in the setting of multiple comorbidities and the importance of an interdisciplinary approach in patients with rare diseases.

Hypertension, hyperlipidemia, and coronary artery disease are common in the Western population. Given that this patient carried all three of these diagnoses, it is difficult to definitively determine to what extent the coexistent lipoprotein thrombi contributed to his presentation. Nevertheless, the symptoms and findings were deemed out of proportion to what would be expected in this patient based on the severity of these conditions, prompting a closer look that included an endomyocardial biopsy. Indeed, the presence of a monoclonal gammopathy coupled with the strain pattern on echocardiography warranted serious consideration of amyloidosis, which also justified tissue sampling.

Unfortunately, sequencing of this patient's *APOE* gene has yet to be undertaken. Basic genotyping was performed, revealing homozygosity for the ε3 allele—the most common genotype in the general population. Homozygosity for ε3 has been described in association with APOE mutations in the setting of LPG (e.g., $APOE_{Chengdu}$, $APOE_{Kyoto}$, $APOE_{Tsukuba}$, and $APOE_{Chicago}$) [8,9,19,25]. In fact one of the first described cases of

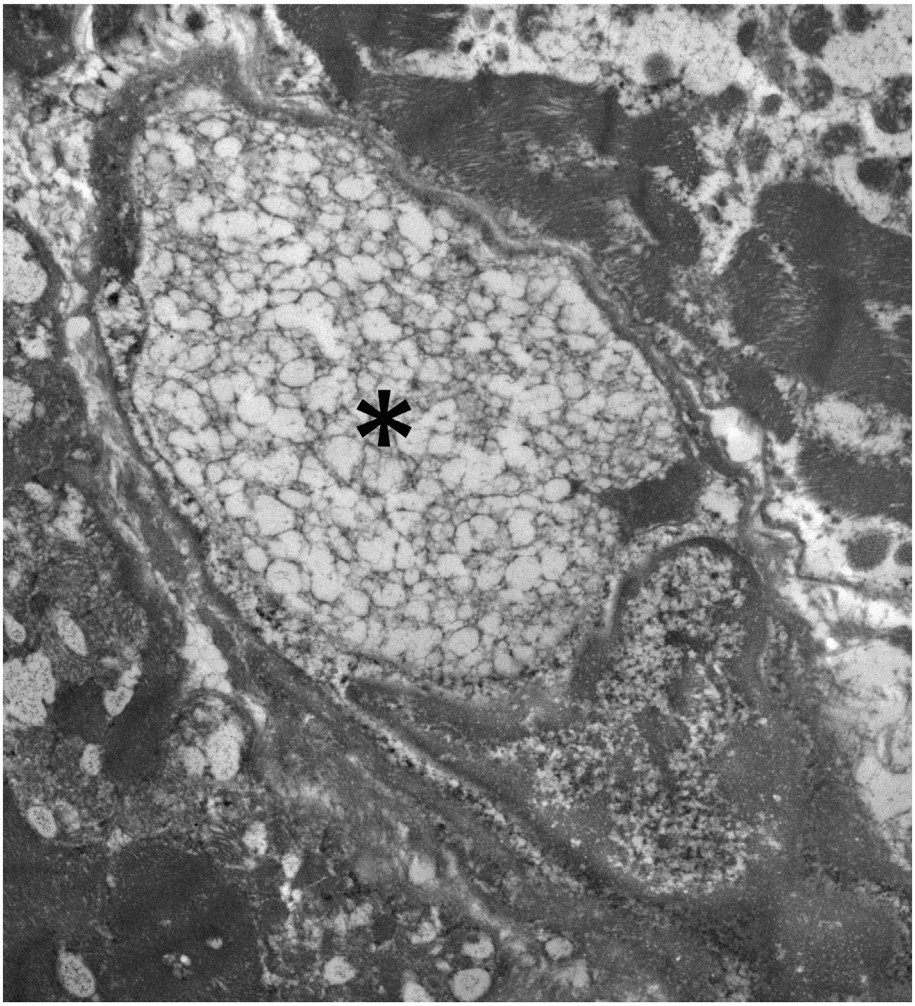

Fig. 3. Cardiac ultrastructural findings. Transmission electron microscopy of an intramyocardial capillary filled with finely vacuolated material (*). Original magnification, ×11000.

LPG in the Caucasian population was homozygous for the ε3 allele [28]. Furthermore, in vitro studies that demonstrate increased aggregation of mutant *APOE* were conducted on ε3 mutants [29]. Unfortunately, without sequencing, an underlying mutation cannot be excluded.

This report expands the understanding of LPG and documents histopathologic evidence of extrarenal involvement. In light of this, the term *lipoprotein glomerulopathy* is probably too limiting of a term, as the extent to which other organs may be involved has not been carefully evaluated. Prior descriptions of this finding were believed to be unique to the kidneys and thought to be related to the possibility that ultrafiltration plays a key role in the formation of thrombi [30]. That notion is also brought into question by this report.

References

[1] Ando M, Sasaki J, Hua H, Matsunaga A, Uchida K, Jou K, et al. A novel 18-amino acid deletion in apolipoprotein E associated with lipoprotein glomerulopathy. Kidney Int 1999;56:1317–23.

[2] Boumendjel R, Papari M, Gonzalez M. A rare case of lipoprotein glomerulopathy in a white man: an emerging entity in Asia, rare in the white population. Arch Pathol Lab Med 2010;134:279–82.

[3] Chen HP, Liu ZH, Gong RJ, Tang Z, Zeng CH, Zhu MY, et al. Lipoprotein glomerulopathy: clinical features and pathological characteristics in Chinese. Chin Med J 2004; 117:1513–7.

[4] Chen S, Liu ZH, Zheng JM, Zhang X, Li LS. A complete genomic analysis of the apolipoprotein E gene in Chinese patients with lipoprotein glomerulopathy. J Nephrol 2007;20:568–75.

[5] Cheung CY, Chan AO, Chan YH, Lee KC, Chan GP, Lau GT, et al. A rare cause of nephrotic syndrome: lipoprotein glomerulopathy. Hong Kong Med J 2009;15:57–60.

[6] Hagiwara M, Yamagata K, Matsunaga T, Arakawa Y, Usui J, Shimizu Y, et al. A novel apolipoprotein E mutation, ApoE Tsukuba (Arg 114 Cys), in lipoprotein glomerulopathy. Nephrol Dial Transplant 2008;23:381–4.

[7] Hu Z, Huang S, Wu Y, Liu Y, Liu X, Su D, et al. Hereditary features, treatment, and prognosis of the lipoprotein glomerulopathy in patients with the APOE Kyoto mutation. Kidney Int 2014;85:416–24.

[8] Katsarou M, Stratikos E, Chroni A. Thermodynamic destabilization and aggregation propensity as the mechanism behind the association of apoE3 mutants and lipoprotein glomerulopathy. J Lipid Res 2018;59:2339–48.

[9] Kinomura M, Sugiyama H, Saito T, Matsunaga A, Sada KE, Kanzaki M, et al. A novel variant apolipoprotein E Okayama in a patient with lipoprotein glomerulopathy. Nephrol Dial Transplant 2008;23:751–6.

[10] Konishi K, Saruta T, Kuramochi S, Oikawa S, Saito T, Han H, et al. Association of a novel 3-amino acid deletion mutation of apolipoprotein E (Apo E Tokyo) with lipoprotein glomerulopathy. Nephron 1999;83:214–8.

[11] Liberopoulos E, Siamopoulos K, Elisaf M. Apolipoprotein E and renal disease. Am J Kidney Dis 2004;43:223–33.

[12] Luo B, Huang F, Liu Q, Li X, Chen W, Zhou SF, et al. Identification of apolipoprotein E Guangzhou (arginine 150 proline), a new variant associated with lipoprotein glomerulopathy. Am J Nephrol 2008;28:347–53.

[13] Magistroni R, Bertolotti M, Furci L, Fano RA, Leonelli M, Pisciotta L, et al. Lipoprotein glomerulopathy associated with a mutation in apolipoprotein e. Clin Med Insights Case Rep 2013;6:189–96.

[14] Matsunaga A, Saito T. Apolipoprotein E mutations: a comparison between lipoprotein glomerulopathy and type III hyperlipoproteinemia. Clin Exp Nephrol 2014;18: 220–4.

[15] Matsunaga A, Sasaki J. Apolipoprotein E. Nihon Rinsho 1999;57:104–6 Suppl.

[16] Matsunaga A, Sasaki J, Komatsu T, Kanatsu K, Tsuji E, Moriyama K, et al. A novel apolipoprotein E mutation, E2 (Arg25Cys), in lipoprotein glomerulopathy. Kidney Int 1999;56:421–7.

[17] Meyrier A, Dairou F, Callard P, Mougenot B. Lipoprotein glomerulopathy: first case in a white European. Nephrol Dial Transplant 1995;10:546–9.

[18] Murano T, Matsumura R, Misawa Y, Ozaki H, Miyashita Y, Yoshida S, et al. Interaction of endothelial cells and triglyceride-rich lipoproteins with apolipoprotein E (Arg–> Cys) from a patient with lipoprotein glomerulopathy. Metabolism 2002;51:201–5.

[19] Oikawa S, Suzuki N, Sakuma E, Saito T, Namai K, Kotake H, et al. Abnormal lipoprotein and apolipoprotein pattern in lipoprotein glomerulopathy. Am J Kidney Dis 1991;18:553–8.

[20] Oikawa S, Matsunaga A, Saito T, Sato H, Seki T, Hoshi K, et al. Apolipoprotein E Sendai (arginine 145–>proline): a new variant associated with lipoprotein glomerulopathy. J Am Soc Nephrol 1997;8:820–3.

[21] Rovin BH, Roncone D, McKinley A, Nadasdy T, Korbet SM, Schwartz MM. APOE Kyoto mutation in European Americans with lipoprotein glomerulopathy. N Engl J Med 2007;357:2522–4.

[22] Saito T, Sato H, Kudo K, Oikawa S, Shibata T, Hara Y, et al. Lipoprotein glomerulopathy: glomerular lipoprotein thrombi in a patient with hyperlipoproteinemia. Am J Kidney Dis 1989;13:148–53.

[23] Saito T, Ishigaki Y, Oikawa S, Yamamoto TT. Etiological significance of apolipoprotein E mutations in lipoprotein glomerulopathy. Trends Cardiovasc Med 2002;12:67–70.

[24] Saito T, Matsunaga A, Oikawa S. Impact of lipoprotein glomerulopathy on the relationship between lipids and renal diseases. Am J Kidney Dis 2006;47:199–211.

[25] Sam R, Wu H, Yue L, Mazzone T, Schwartz MM, Arruda JA, et al. Lipoprotein glomerulopathy: a new apolipoprotein E mutation with enhanced glomerular binding. Am J Kidney Dis 2006;47:539–48.

[26] Takasaki S, Matsunaga A, Joh K, Saito T. A case of lipoprotein glomerulopathy with a rare apolipoprotein E isoform combined with neurofibromatosis type I. CEN Case Rep 2018;7:127–31.

[27] Tokura T, Itano S, Kobayashi S, Kuwabara A, Fujimoto S, Horike H, et al. A novel mutation ApoE2 Kurashiki (R158P) in a patient with lipoprotein glomerulopathy. J Atheroscler Thromb 2011;18:536–41.

[28] Toyota K, Hashimoto T, Ogino D, Matsunaga A, Ito M, Masakane I, et al. A founder haplotype of APOE-Sendai mutation associated with lipoprotein glomerulopathy. J Hum Genet 2013;58:254–8.

[29] Tsimihodimos V, Elisaf M. Lipoprotein glomerulopathy. Curr Opin Lipidol 2011;22: 262–9.

[30] Wu H, Yang Y, Hu Z. The novel apolipoprotein E mutation ApoE Chengdu (c.518TC, p.L173P) in a Chinese patient with lipoprotein glomerulopathy. J Atheroscler Thromb 2018;25:733–40.