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Lamellar Bodies in Podocytes Associated With Compound Heterozygous Mutations for Niemann Pick Type C1 Mimicking Fabry Disease, a Case Report

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Abstract

Rationale: Niemann-Pick type C (NPC) is an autosomal recessive lysosomal storage disease (LSD) caused by mutations in *NPC1* or *NPC2* genes. Mutations result in abnormal cholesterol trafficking, which is manifested by abnormal cholesterol and glycosphingolipid accumulation in lysosomes of various cells.

Presenting Concerns of the Patient: The patient had a history of hyperlipidemia, hypertension, depression, and elevated alkaline phosphatase and initially presented for a workup regarding chronic kidney disease stage G3b/A3 with proteinuria of 1.9 g/day.

Diagnosis: Kidney biopsy revealed numerous lamellar bodies (LB) in podocytes with differential diagnoses of Fabry disease (FD), nail-patella syndrome (which is associated with *LMX1B* gene mutations), and drug-induced phospholipidosis per pathology report. Her workup was negative for a galactosidase-alpha (*GLA*) mutation with normal serum and leukocyte alpha-galactosidase A activity. She was serendipitously discovered to have compound heterozygous mutations in *NPC1* genes (one pathogenic and the other a variant of uncertain significance) from the comprehensive lysosomal storage gene panel as part of her genetic workup for FD. Further studies were done to determine the significance of the *NPC1* mutation and revealed elevated oxysterols. (The profile was consistent with NPC, with elevated cholestane-3beta,5alpha,6beta-triol and 7-ketocholesterol and normal lyso-sphingomyelin.) Sonogram revealed hepatosplenomegaly (liver measuring 20 cm and spleen 15.8 cm). These findings in conjunction with lysosomal lipid accumulation on kidney biopsy were consistent with NPC.

Interventions: She was on 2 cationic amphiphilic agents (CAAs), fluoxetine and atorvastatin, both of which were stopped. There was no significant difference in proteinuria 2 months off CAAs. The treatment of NPC remained supportive care and avoiding medications that can induce seizures or excessive salivary secretion.

Novel Findings: The presence of LB is classically described as a feature of FD which is an LSD. Niemann-Pick type C is another example of an LSD and is typically manifested by neurovisceral symptoms and varies by the age of onset. Renal diseases are typically not described as one of the manifestations of NPC. To our knowledge, there is only one report each for Niemann-Pick disease type A/B and NPC with LB on kidney biopsy. The finding reaffirms that the presence of LB indicates lysosomal lipid accumulation from a variety of etiologies and is not a pathognomonic finding of FD. Niemann-Pick type C should be included as one of the diseases capable of causing renal LB.

Abrégé

Justification: La maladie de Niemann-Pick de type C (NPC) est une maladie lysosomale autosomique récessive (MLAR) causée par des mutations sur les gènes *NPC1* ou *NPC2*. Ces mutations se traduisent par un transport anormal du cholestérol, lequel se manifeste par une accumulation anormale de cholestérol et de glycosphingolipides dans les lysosomes de diverses cellules.

Présentation du cas: Une patiente avec des antécédents d'hyperlipidémie, d'hypertension, de dépression et de phosphatase alcaline (PA) élevée s'étant initialement présentée pour un bilan relativement à une insuffisance rénale chronique (IRC) de stade G3b/A3 avec protéinurie à 1,9 gramme/jour.

Diagnostic: La biopsie rénale a révélé la présence de nombreux corps lamellaires (CL) dans les podocytes avec, selon le rapport pathologique, des diagnostics différentiels pour la maladie de Fabry (MF), l'ostéo-onychodysostose (associée à des mutations du gène *LMX1B*) et la phospholipidose (PL) induite par les médicaments. Le bilan s'est avéré négatif pour une mutation de la galactosidase-alpha (*GLA*) puisque l'activité enzymatique sérique et leucocytaire de celle-ci était normale.

Dans le bilan génétique de la MF, qui comprenait l'ensemble des gènes de stockage lysosomal, on a découvert par hasard que la patiente présentait des mutations hétérozygotes composées dans les gènes *NPC1* (une pathogène et une variante de signification incertaine [VSI]). D'autres examens réalisés pour déterminer l'importance de la mutation *NPC1* ont révélé un taux élevé d'oxystérols. (Le profil était conforme à la NPC, avec des taux élevés de cholestane-3beta, 5alpha, 6beta-triol et de 7-cétocholestérol, et un taux normal de lysosphingomyéline.) L'échographie a montré une hépatosplénomégalie (foie de 20 cm et rate de 15,8 cm). Ces résultats, conjointement à l'accumulation de lipides dans les lysosomes révélée par la biopsie rénale, étaient conformes à une NPC.

Intervention: La fluoxétine et l'atorvastatine, les deux agents amphiphiles cationiques (AAC) que prenait la patiente, ont été cessés. La protéinurie est demeurée pratiquement inchangée deux mois après l'arrêt des AAC. Le traitement de la NPC s'est limité à prodiguer des soins de soutien et à éviter les médicaments pouvant induire des convulsions ou une sécrétion salivaire excessive.

Nouveaux résultats: La présence de CL est généralement décrite comme une caractéristique de la MF, un type de MLAR. La NPC est un autre exemple de MLAR; elle varie selon l'âge du patient à l'apparition et se manifeste généralement par des symptômes neuroviscéraux. Les néphropathies ne sont généralement pas décrites parmi les manifestations de la NPC. À notre connaissance, il n'existe qu'un seul rapport pour la maladie de Niemann-Pick (NPD) de type A/B et pour la NPC avec CL révélés par biopsie rénale. Cette découverte confirme que la présence de CL est indicatrice d'une accumulation de lipides dans les lysosomes à partir d'une variété d'étiologies et qu'il ne s'agit pas d'une preuve pathognomonique de MF. La NPC doit être incluse comme maladie pouvant causer des CL dans les reins.

Keywords

lamellar bodies, Niemann-Pick type C, oxysterols, Fabry disease, renal phospholipidosis

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Introduction

Lamellar bodies (LB) are classically associated with Fabry disease (FD) but have been rarely reported, namely in 1 case of Niemann-Pick type A/B (NPA/NPB) and 1 case of Niemann-Pick type C (NPC). We report a patient whose NPC diagnosis was determined after LB were found on kidney biopsy and a subsequent workup was conducted.

Presenting Concerns

A 51-year-old Caucasian woman presented for evaluation of proteinuria (1.97 g/24 hours) and an abnormal estimated glomerular filtration rate (eGFR).

Clinical Findings

The patient had a medical history of depression since 2020, elevated alkaline phosphatase (AP) since at least 2019 (with unremarkable bone scan and marginal hepatomegaly measuring 15.3 cm from right upper quadrant sonogram), hyperlipidemia, and hypertension. Her medications included amlodipine, atorvastatin, fluoxetine, omeprazole, and valsartan. She also used amitriptyline sparingly for insomnia. Blood pressure was 116/85 mm Hg, and her body mass index (BMI) was 32.58 kg/m^2. Her physical examination was unremarkable for any evidence of skin or nail abnormalities, and she had no abnormal findings on her knees/patella. No abdominal masses or organomegaly were detected on examination. She had normal muscular strength but impaired tandem gait. Renal sonogram was remarkable for slightly echogenic kidneys and a simple-appearing left renal cyst. Serologic studies for proteinuria were unremarkable with normal complement, nonreactive hepatitis B surface antigen and hepatitis C antibody, and antinuclear antibody less than 1:80 (reference range <1:80).

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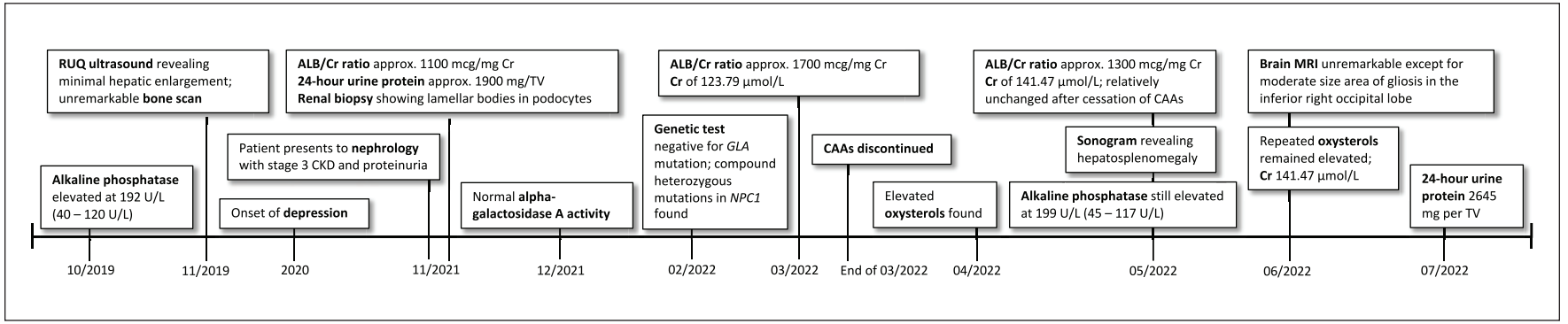
Timeline


RUQ ultrasound revealing minimal hepatic enlargement; unremarkable **bone scan**
ALB/Cr ratio approx. 1100 mcg/mg Cr
24-hour urine protein approx. 1900 mg/TV
Renal biopsy showing lamellar bodies in podocytes
ALB/Cr ratio approx. 1700 mcg/mg Cr
Cr of 123.79 µmol/L
ALB/Cr ratio approx. 1300 mcg/mg Cr
Cr of 141.47 µmol/L; relatively unchanged after cessation of CAAs
Brain MRI unremarkable except for moderate size area of gliosis in the inferior right occipital lobe
Patient presents to **nephrology** with stage 3 CKD and proteinuria
Genetic test negative for *GLA* mutation; compound heterozygous mutations in *NPC1* found
CAAs discontinued
Sonogram revealing hepatosplenomegaly
Repeated **oxysterols** remained elevated; **Cr** 141.47 µmol/L
Alkaline phosphatase elevated at 192 U/L (40 – 120 U/L)
Onset of **depression**
Normal **alpha-galactosidase A activity**
Elevated **oxysterols** found
Alkaline phosphatase still elevated at 199 U/L (45 – 117 U/L)
24-hour urine protein 2645 mg per TV
10/2019
11/2019
2020
11/2021
12/2021
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03/2022
End of 03/2022
04/2022
05/2022
06/2022
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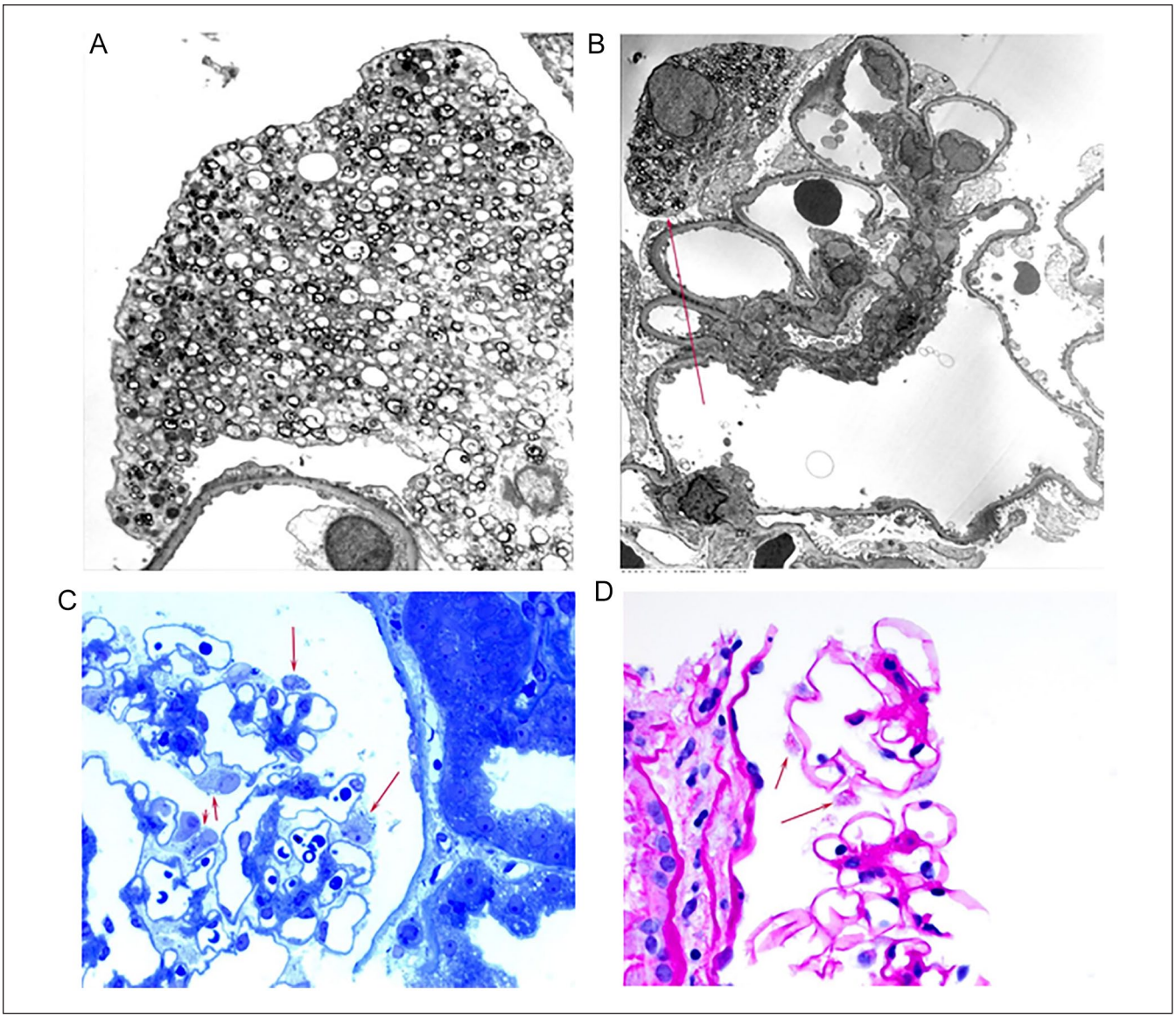

Figure 1. Renal biopsy revealing lamellar bodies in podocytes (A and B) and foamy podocytes (C and D). (A and B) Electron microscopy. (C) Toluidine blue stain. (D) Hematoxylin/Eosin stain. Red arrows in (B) indicate podocytes with lamellar bodies and in (C) and (D) indicate foamy podocytes. (Note: Biopsy photos obtained from online result portal. Several attempts made to obtain the magnification for electron microscopy and light microscopy from the attending pathologist were unsuccessful despite providing the relevant patient information and rationale.)

Diagnostic Focus and Assessment

She underwent a kidney biopsy for an evaluation of proteinuria (1970 mg/24 hours) in the setting of chronic kidney disease (CKD) stage G3b/A3 with eGFR of 36 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) study equation. Her automated urinalysis showed 1+ hematuria, 3-8 red blood cells per high-power field (HPF) (reference range, 0-5/HPF), and negative casts. A kidney biopsy was performed. Light microscopy revealed occasional foamy enlarged podocytes. Twelve out of 13 glomeruli were globally sclerotic. No hypercellularity or necrotizing lesions were observed. There was severe intimal fibrosis and arteriolar hyalinosis. Immunofluorescence revealed kappa and lambda light chains staining equally in small casts and in tubulointerstitial regions. The remaining stains were essentially negative. Electron microscopy (EM) showed numerous LB in podocytes without mention of the presence of LB in other cell types. No mesangial electron-dense deposits were noted. The pathology diagnosis was arterionephrosclerosis, acute tubular injury, and enlarged podocytes that contained lysosomal bodies (Figure 1) with differential diagnoses of FD, iatrogenic cationic amphiphilic agent (CAA)-associated phospholipidosis (PL), and nail-patella syndrome.

Slit-lamp examination was negative for cornea verticillata. Her eye examination otherwise was significant for dermatochalasis and 1+ nuclear sclerosis; cherry-red spots in fundi were not mentioned in the report. Serum alpha-galactosidase was normal at 0.135 U/L (normal range, 0.074-0.457 U/L). Leukocyte alpha-galactosidase was normal (no reference range provided), and galactosidase-alpha (*GLA*) gene mutation for FD was not detected using a comprehensive lysosomal storage disorders panel (screening for 58 lysosomal storage disease [LSD] genes; Invitae, San Francisco, California). Serendipitously, she was found to have 2 mutations in *NPC1* genes from this panel: c.2474A>G(p. Tyr825Cys) (heterozygous) which is a pathogenic variant and c.1301C>T(p. Pro434Leu) which is a variant of uncertain significance (VUS) for NPC. Allele segregation was performed by testing her mother and son for *NPC1* mutations. Both of them tested positive for the same pathogenic variant and negative for VUS. The finding suggests that the patient's *NPC1* pathogenic variant and the VUS were likely located on opposite alleles (biallelic mutations).

As the patient had compound heterozygous mutations in *NPC1* genes, an oxysterol assay (Mayo Clinic, Rochester, Minnesota) was performed to determine the significance of mutations. Cholestane-3beta,5alpha,6beta-triol was elevated at 0.117 nmol/mL (normal range <0.070 nmol/mL), 7-ketocholesterol was elevated at 0.240 nmol/mL (normal range <0.100 nmol/mL), and lyso-sphingomyelin was within the normal range at 0.010 nmol/mL (normal range <0.100 nmol/mL). The findings of the assay were consistent with NPC.

Discussion

The 2 primary differential diagnoses for renal PL, identified as LB on biopsy, include drug-induced PL and FD, although there are sporadic reports of LB on kidney biopsy in other conditions including Niemann-Pick disease (NPD) types A/B and C, nail-patella syndrome, silicosis, and radiocontrast agent use.

Drug-induced PL, namely with CAAs, can mimic FD. Cationic amphiphilic agents are a group of drugs composed of compounds containing both hydrophobic and hydrophilic regions.[1] A number of CAAs have been identified as causative agents in cases of PL, and reports of drug-induced *renal* PL, specifically, exist for CAAs such as chloroquine,[2] hydroxychloroquine,[3] amiodarone,[4] ranolazine,[5] sertraline,[6] and carbamazepine.[7] Our patient was on 2 CAAs, atorvastatin and fluoxetine. Both of these medications are capable of causing PL but have not been reported to cause renal PL in humans. Statins have been linked to cases of *pulmonary* PL.[8] Phospholipidosis due to fluoxetine use has been shown in vitro,[9] in vivo in rats,[10] and furthermore in a patient.[11]

Fabry disease is one example of a heritable LSD. Niemann-Pick disease is another and is due to a deficiency in the enzyme acid sphingomyelinase, leading to a buildup of sphingomyelin in lysosomes for NPA and NPB. Niemann-Pick type C is actually a distinct entity compared with NPA/NPB. In NPC, mutations in *NPC1* or *NPC2* genes do not result in a specific enzymatic defect but instead result in alteration of cellular cholesterol trafficking in the late endosomal stage from loss-of-function variant resulting in glycosphingolipids and cholesterol accumulation in lysosomes.[12] Manifestations of NPC vary by age of onset but include jaundice, hepatosplenomegaly, supranuclear vertical gaze palsy, cerebellar ataxia, gelastic cataplexy, and various psychiatric diseases. Renal involvement has been rarely reported in NPA, NPB, or NPC. To our knowledge, there was one report each for myelin bodies in NPA/NPB[13] and NPC[14] patients. In the case of NPA/NPB, the patient was diagnosed with NPD type A/B at the age of 6 months when she was found to have hepatosplenomegaly and low sphingomyelinase level. She developed CKD with creatinine (Cr) clearance of 41 mL/min, and a kidney biopsy was performed when she was 14 years old with concerns about cyclosporin-induced renal toxicity.[13] Proteinuria was not documented in the paper, but it was documented that she had no hematuria. The patient was on fluoxetine, although the implications of fluoxetine in renal PL were not mentioned in the paper. In the NPC case, a 21-year-old woman, who was diagnosed with NPC in childhood with neurologic and respiratory manifestations, underwent a kidney biopsy for nephrotic range proteinuria, with a urine protein/Cr ratio of 5.6 and a normal serum Cr at 0.6 mg/dL at the time of biopsy.[14] In both reports, foamy podocyte's cytoplasm was demonstrated by light microscopy, and numerous LB were demonstrated by EM. Our patient had 2 biallelic heterozygous mutations in *NPC1* genes: a pathogenic variant and a VUS for NPC1. The elevated oxysterols and renal LB suggest that the VUS for NPC might actually be a pathogenic variant as well. According to Niemann-Pick Disease Consensus Conference,[15] a filipin test is recommended for definitive diagnosis in a patient with elevated oxysterols in the setting of 1 pathogenic variant and 1 VUS. We propose that the LB on her kidney biopsy provide sufficient evidence of lysosomal lipid accumulation to diagnose NPC in her case without performing the logistically challenging filipin staining.

The mechanism of renal injury in *NPC* is not well defined because there was only 1 prior case report. Patel et al[14] proposed that the abundant podocyte LB in their case suggested that lysosomal lipid accumulation was responsible for the clinical features of nephrotic syndrome and podocyte injury. Accumulation of undigested substrate in lysosomes can lead to enlargement and loss of function of organelles.[16]

Although the morphology and location of LB can be difficult to distinguish in FD and non-FD patients (Table 1), non-FD patients tend to have focal LB predominantly in podocytes; furthermore, there are certain characteristic findings with use of certain drugs, such as curvilinear inclusion bodies in vascular smooth muscle cells and podocytes in chloroquine-induced renal PL and in podocytes in hydroxychloroquine-induced renal PL.[2,19,20] In classic FD, LB are

Table 1. Comparative Features in Renal Phospholipidosis from Selected Etiologies.

	Fabry disease	Drug-induced phospholipidosis	Nail-Patella syndrome and isolated LMX1B-associated nephropathy in the absence of extrarenal manifestations[17]	Niemann-Pick type A/B	Niemann-Pick type C
Selected clinical findings	• Angiokeratoma • Acroparesthesia • Proteinuria • Kidney failure • Cardiomyopathy • Cornea verticillata • Cardiac arrhythmia • Elevated globotriaosylsphingosine (LysoGb3)	• Cornea verticillata (in amiodarone case). • Proteinuria • Kidney failure	• **Nail-Patella** syndrome • Usually apparent at birth or during early childhood • Nails dysplasia (98%) • Aplasia or hypoplasia of patellae • Glaucoma • Lester's sign (cloverleaf shape discoloration of iris) • Nephropathy (30%-50%) • Hematuria • Kidney failure (5%) • **Isolated LMX1B-associated nephropathy in the absence of extrarenal manifestations** • Microscopic hematuria • Proteinuria	**Type A or infantile neurovisceral form** with very low acid sphingomyelinase activity and usually fatal by the age of 3 **Type B** Hepatosplenomegaly Thrombocytopenia Interstitial lung disease Neurological involvement	**Early infantile (2 months to 2 years)** Hepatosplenomegaly Neurologic involvement such as delay developmental milestone and central hypotonia **Late infantile (2-6 years)** Isolated splenomegaly Hepatosplenomegaly Neurologic involvement VSGP Epilepsy **Juvenile (6-15 years) classical form** Isolated splenomegaly (rarely hepatosplenomagaly) VSGP Cataplexy Ataxia **Adolescent and adults (>15 years)** splenomegaly VSGP Psychosis, depression Cerebellar ataxia Dysphagia
Genetic mutations	GLA (α-galactosidase -A)gene	None	LMX1B	SMPD1 (sphingomyelin phosphodiesterase1)	NPC1 (95%) NPC2 (5%)
Transmission	X-linked recessive	None	Autosomal dominant	Autosomal recessive	Autosomal recessive
Defect	Decrease in α-galactosidase A activity	Chloroquine has been shown to cause direct suppression of α-galactosidase A activity. Amiodarone been shown to inhibit phospholipase A1 and A2 activity in vitro	LMX1B encodes an LIM-homeodomain protein critical for limb, kidney, and eye development	Decrease in acid sphingomyelinase A activity	Impairment in processing and utilization of endocytosed cholesterol
Electron microscopic findings	LB are more extensively present in various types of renal cells including podocytes, tubular epithelium, vascular endothelial cells, and medial smooth muscle cells	Müller-Höcker et al described curvilinear inclusions in podocytes and vascular smooth muscle cells in chloroquine case Curvilinear inclusions also found in podocytes, tubular cells, glomerular endothelium, and vascular smooth muscle cells in hydroxychloroquine case In amiodarone case: LB identified in podocytes, mesangial cells, and tubular epithelial cells with no inclusions identified in endothelial cells LB in various renal cell types were described in other cases of drug induced renal phospholipidosis	Pinto e Vairo et al[18] described LB in podocytes. No LB in endothelial cells, mesangial cells, peritubular capillaries, or tubular cells	LB identified in podocytes, tubular epithelial cells, peritubular capillaries, endothelial cells, and many small nerves. LB were not present in glomerular endothelial cells	LB identified in most podocytes and focal tubular epithelial cells and not present in other cell types in the tissue available for electron microscopy

Note. The bold letter signified a different entities. VSGP = vertical supranuclear gaze palsy; GLA = galactosidase-alpha; LB = lamellar bodies.

more extensively present in podocytes, renal tubular cells, mesangial cells, vascular smooth muscle cells, and endothelial cells. However, the distribution of LB in renal cells between FD and non-FD can be similar, and in such cases, genetic mutations, alpha-galactosidase activity, and plasma globotriaosylsphingosine (LysoGb3) can be useful.[20,21]

As renal disease is not classically considered to be a feature of NPC, our case is quite unique, considering the patient's initial presentation of proteinuria that led to a subsequent diagnosis of NPC at the age of 51. Additional workup for other clinical features of NPC revealed hepatosplenomegaly (liver 20 cm, spleen 15.8 cm on sonogram). Retrospectively, she was discovered to have a marginally enlarged liver of 15.3 cm about 2 years prior to her presentation. She then developed depression and was started on antidepressants several months prior to her first renal evaluation. She did not have any neurologic complaints but had difficulty performing tandem gait, and her brain magnetic resonance imaging showed a moderate area of gliosis in the inferior right occipital lobe. Altogether, it appeared that she had underlying NPC manifested 2 years prior to her first renal evaluation, with subtle hepatomegaly associated with elevated AP, followed by psychiatric manifestation. The diagnosis of NPC was not made until after the finding of LB and comprehensive genetic/biochemical analysis. By this time, she had progression in organomegaly and developed subtle neurologic findings.

In addition to isolated reports of FD-associated PL and CAA-induced PL, an interesting case involving drug-induced PL in a patient *with* FD provides a unique consideration of PL in this setting. Fine et al present a case of worsening cardiac function in a 54-year-old patient with FD upon initiation of amiodarone, a CAA, with improvement in cardiac function upon cessation of the drug. They suggest caution when prescribing amiodarone in this patient population.[21] Pintavorn and Cook reported a case of amiodarone-induced renal PL. In that case, amiodarone was shown to be associated with transient reduction in alpha-galactosidase A level (which was normalized a few months after its discontinuation),[4] and the finding of an effect of amiodarone on alpha-galactosidase A level is supportive of the recommendation in the paper by Fine et al. A comparison may potentially be drawn between these patients and ours, with atorvastatin and fluoxetine (both CAAs) as possible culprits promoting the renal manifestations in our patient. However, discontinuation of these 2 agents did not result in any changes in proteinuria, serum Cr, and oxysterols 2 months afterward (urine protein 2645 mg/24 hour, serum Cr 141.47 umol/L [normal range, 53.05-114.96 umol/L], cholestane-3beta,5alpha,6beta-triol 0.135 nmol/mL [<0.070 nmol/mL], 7-ketochloesterol 0.300 nmol/mL [<0.100 nmol/mL], and lyso-sphingomyelin 0.011 [<0.100 nmol/mL]). Her blood pressure had been similar before and after discontinuation of CAAs (105/71 mm Hg on follow-up) with unchanged antihypertensive regimen. Although arterionephrosclerosis can cause proteinuria, her degree of proteinuria was more than expected from chronic hypertension with well-controlled blood pressure on angiotensin-converting enzyme inhibitor. The mechanistic relationship between renal PL and proteinuria is not entirely clear.

Therapeutic Focus and Assessment

Treatment for NPC includes mainly supportive care and avoiding medications that can potentially cause worsening in clinical manifestations of the disease.

Follow-up and Outcomes

The patient's urinary protein excretion, serum Cr, and oxysterols failed to improve after discontinuation of CAAs, and we believe that renal PL was related to NPC rather than drug-induced renal PL.

Conclusion

Lamellar bodies were detected in a retrospective analysis in 32 of 4400 renal biopsies at the University of Rochester from 2010 to 2021, only 6 of which were attributed to FD.[22] Drug-induced LSDs are thought to be responsible for some of the other cases. There are numerous CAA agents; some of these (such as statins, antidepressants, and amiodarone) are commonly prescribed, yet only a small fraction of kidney biopsies revealed LB. It is plausible that mutations in other lysosomal storage genes might be the cause or might play a synergistic role in renal PL in those patients using CAA because hereditary-induced and drug-induced-LSDs might not be mutually exclusive. Our case illustrated that NPC should be considered as one of the causes of renal PL and NPC genetic testing should be considered in non-FD patients. We would not have been able to make the correct diagnosis if we had just performed *GLA* genetic testing and would have erroneously concluded that this is a case of CAA-induced renal PL.

Ethics Approval and Consent to Participate

The patient provided written consent to use her clinical information and biopsy photographs for publications in anonymized form.

Consent for Publication

The patient has provided written informed consent to publish this case in deidentified form and was shown the manuscript for approval prior to submission.

Availability of Data and Materials

Not applicable.

Declaration of Conflicting Interests

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