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-3β,5α,6β-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-onchody sostose (associé 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 cholestanol-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 inclue 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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Timeline

- **10/2019**: RUQ ultrasound revealing minimal hepatic enlargement; unremarkable bone scan
- **12/2019**: ALB/Cr ratio approx. 1100 mg/mg Cr
  - 24-hour urine protein approx. 1900 mg/TV
  - Renal biopsy showing lamellar bodies in podocytes
- **10/2020**: Alkaline phosphatase elevated at 192 U/L (40 – 126 U/L)
  - Onset of depression
- **12/2020**: patient presents to nephrology with stage 3 CKD and proteinuria
  - Normal alphagalactosidase A activity
- **02/2021**: Genetic test: negative for GBA mutation; compound heterozygous mutations in NPC1 found
- **03/2021**: CAAs discontinued
- **03/2021**: Elevated liver enzymes found
  - Alkaline phosphatase still elevated at 199 U/L (45 – 117 U/L)
  - Sonogram revealing hepatosplenomegaly
- **End of 03/2022**: Elevated osteosclerosis found
- **06/2022**: 24-hour urine protein 2.4 g/TV
- **07/2022**: Brain MRI unremarkable except for moderate size area of gliosis in the inferior right occipital lobe
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 m² 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.

**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 m² 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 dermatoclasia 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. 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, hydroxychloroquine, amiodarone, ranolazine, sertraline, and carbamazepine. 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. Phospholipidosis due to fluoxetine use has been shown in vitro, in vivo in rats, and furthermore in a patient.

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. 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 and NPC. 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. 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 3.6 and a normal serum Cr at 0.6 mg/dL at the time of biopsy. 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, 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 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.

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. In classic FD, LB are
Table 1. Comparative Features in Renal Phospholipidosis from Selected Etiologies.

| Selected clinical findings | Fabry disease | Drug-induced phospholipidosis | Niemann-Pick type A/B | Niemann-Pick type C |
|----------------------------|---------------|--------------------------------|-----------------------|---------------------|
|                            | Nail-Patella syndrome | Nail-Patella syndrome | Type A or infantile neurovisceral form | Early infantile (2 months to 2 years) |
|                            | Nail-Patella syndrome | Nail-Patella syndrome | Type B | Late infantile (2-6 years) |
|                            | Nail-Patella syndrome | Nail-Patella syndrome | Type C | Juvenile (6-15 years) classical form |
|                            | Nail-Patella syndrome | Nail-Patella syndrome | VSGP | Adolescent and adults (>15 years) |
|                            | Nail-Patella syndrome | Nail-Patella syndrome | Cataplexy | Adults (>15 years) |
|                            | Nail-Patella syndrome | Nail-Patella syndrome | Ataxia | Adults (>15 years) |
|                            | Nail-Patella syndrome | Nail-Patella syndrome | VSGP | Adults (>15 years) |
|                            | Nail-Patella syndrome | Nail-Patella syndrome | Psychosis, depression | Adults (>15 years) |
|                            | Nail-Patella syndrome | Nail-Patella syndrome | Cerebellar ataxia | Adults (>15 years) |
|                            | Nail-Patella syndrome | Nail-Patella syndrome | Dysphagia | Adults (>15 years) |
|                            | Nail-Patella syndrome | Nail-Patella syndrome | NPC1 (95%) NPC2 (5%) | Adults (>15 years) |

| Genetic mutations | GLA (α-galactosidase -A) gene | None | LMX1B | SMPD1 ( sphingomyelin phosphodiesterase ) |
|-------------------|--------------------------------|------|-------|---------------------|
| Transmission      | X-linked recessive              | None | Autosomal dominant | Autosomal recessive |
| Defect            | Decrease in α-galactosidase A | LMX1B encodes an LMH-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 | Muller-Hocker 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 described LB in podocytes. No LB in endothelial cells, mesangial cells, peritubular capillaries, or tubular cells | LB identified in podocytes, tubular epithelial cells, mesangial cells, peritubular capillaries, and peritubular epithelial cells with no inclusions identified in 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 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], cholesterol-3beta,Salpha,6beta-triol 0.135 nmol/mL [<0.070 nmol/mL], 7-ketocholesterol 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**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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