

Lipoic Acid as a Trigger for NELL-1 Positive Membranous Nephropathy

Tyler Eslinger^{1*}, John S. Hayes^{2,3}

¹Department of Nephrology, Regional Medical Center, The Villages, FL, USA

²Department of Pathology, National Pathology Services, The Villages, FL, USA

³Sunshine Kidney Care LLC, The Villages, FL, USA

Email: *tylereslinger55@gmail.com

How to cite this paper: Eslinger, T. and Hayes, J.S. (2026) Lipoic Acid as a Trigger for NELL-1 Positive Membranous Nephropathy. *Open Journal of Nephrology*, 16, 497-503.

<https://doi.org/10.4236/ojneph.2026.163042>

Received: June 19, 2026

Accepted: September 26, 2026

Published: September 29, 2026

Copyright © 2026 by author(s) and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

Background: Membranous nephropathy occurs when antibodies bind to antigens in the kidney's filtering units. PLA2R is the common target antigen in the main type of MN, while NELL-1 has recently been found to be a target antigen in secondary MN. Alpha-lipoic acid, a common over-the-counter supplement for diabetic neuropathy, may trigger NELL-1-associated MN. **Case Presentation:** We present a case of a 69-year-old white male with type 2 diabetes, obesity (BMI 42), and diabetic peripheral neuropathy. He developed significant proteinuria after starting alpha-lipoic acid supplements (1200 mg daily) in December 2024. Before starting the supplement, his kidney function was stable (creatinine 0.87 - 0.89 mg/dL) and his urine albumin-to-creatinine ratio (UACR) was normal (less than 30 mg/g creatinine). By June 2025, about seven months after he started alpha-lipoic acid, his UACR reached 4,061 mg/g, in the nephrotic range clinically. A kidney biopsy in June 2025 confirmed membranous glomerulopathy. Tests on the biopsy showed IgG, kappa, and lambda staining in the capillary walls. PLA2R was negative, but NELL-1 was positive, confirming NELL-1-associated membranous nephropathy. The biopsy showed 23% of glomeruli globally sclerosed (3 of 13) against a background of diabetic glomerulopathy, Class IIa. The patient stopped taking alpha-lipoic acid right away and was monitored without immune-suppressing medicine. After three months, in September 2025, his UACR dropped to 2,195 mg/g. This was a 46% drop from its highest level, showing good improvement after stopping the drug. **Conclusions:** This case shows a link between alpha-lipoic acid supplements and NELL-1-associated membranous nephropathy. This is supported by the timing, the dosage, and the rapid improvement after stopping the drug. The case shows why it is important to monitor for protein in the urine in patients taking alpha-lipoic acid, especially at higher doses (1200 mg/day or more). Detecting this problem early and discontinuing the drug promptly can

lead to significant improvement without immunosuppressive medication. Since many people use alpha-lipoic acid as a supplement, doctors should be aware of this side effect. They should consider NELL-1-associated MN in patients who develop significant proteinuria while taking this supplement.

Keywords

Membranous Nephropathy, NELL-1, Alpha-Lipoic Acid, Secondary Membranous Nephropathy, Drug-Induced Nephropathy

1. Introduction

Membranous nephropathy (MN) is caused by antibodies against an antigen present in the glomerular basement membrane (GBM). Primary membranous nephropathy (PMN) is responsible for 70% of MN [1], and the target antigen in about 70% of instances is M-Type Phospholipase A2 Receptor (PLA2R), Thrombospondin type-1 domain-containing 7A (THSD7A) in about 1% - 5% of instances, and about 25% of instances have an unknown target antigen [2]. Nerve epidermal growth factor-like 1 (NELL-1) antigen-antibody has also been recently recognized as a secondary cause of MN in PLA2R-negative cases [2]. Over-the-counter lipoic acid, a drug taken to manage diabetic neuropathic pain, has been recognized as a cause of NELL-1-associated MN with resulting high-grade proteinuria [3]. Lipoic acid withdrawal has shown good results in some instances, with the achievement of partial or complete remission within three to six months [4].

2. Case Report

A 69-year-old white male with a history of type 2 diabetes mellitus, obesity (BMI 42), and diabetic peripheral neuropathy was referred for evaluation of worsening proteinuria. The patient had been on alpha-lipoic acid supplements (Nutricost brand, twice a day 600 mg, total 1200 mg/day) since December 2024 for managing his diabetic neuropathy, which had provided symptomatic relief. He was on lisinopril at presentation and denied any prior or current use of SGLT2 inhibitors or mineralocorticoid receptor antagonists (steroidal or nonsteroidal), and had no history of NSAID use. His A1c history was 5.5% to 6.6% (February 2025: 5.5%, November 2024: 5.9%, July 2024: 6.2%, March 2024: 6.6%). Baseline laboratory values were serum creatinine 0.87 - 0.89 mg/dL, BUN 16 - 17 mg/dL, and albumin 3.83 g/dL. His lipid panel was triglycerides 88 - 338 mg/dL, HDL 24 - 25 mg/dL, and LDL 52 - 56 mg/dL. The patient experienced numbness and tingling of both feet with pain.

The following timeline summarizes the key laboratory events. On March 11, 2024 (pre-supplement baseline), laboratory values showed WBC 7.4, hematocrit 36.8%, glucose 150 mg/dL, creatinine 0.87 mg/dL, AST 16 U/L, ALT 22 U/L, triglycerides 338 mg/dL, HDL 25 mg/dL, and LDL 56 mg/dL. On July 1, 2024 (ap-

proximately five months before alpha-lipoic acid was initiated), BUN was 17 mg/dL, creatinine 0.95 mg/dL, AST 16 U/L, ALT 28 U/L, UACR 5 mg/g (normal, < 30 mg/g creatinine), total cholesterol 105 mg/dL, HDL 24 mg/dL, triglycerides 221 mg/dL, and LDL 53 mg/dL. Following initiation of alpha-lipoic acid in December 2024, proteinuria rose substantially: UACR was 2520 mg/g on March 14, 2025 (approximately three months after starting supplementation), reaching a peak of 4,061 mg/g on June 27, 2025 (approximately seven months after initiation), the value discussed with the patient at the time of biopsy. Serologic workup for secondary causes was negative, including hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and anti-PLA2R antibodies.

A kidney biopsy was performed on June 27, 2025. Light microscopy of the formalin-fixed specimen revealed tissue consisting of 30% renal cortex with six glomeruli, two of which were globally sclerosed. Glomeruli were mildly expanded mesangially without hypercellularity. Arteries had mild fibrous intimal thickening, and interstitial fibrosis and tubular atrophy were present. Congo red stain for amyloid was negative. Toluidine blue sections revealed arteriolar hyalinosis characteristic of diabetes.

Immunofluorescence microscopy of the Michel's fixative specimen contained seven glomeruli, one of which was globally sclerotic. Subglobal granular peripheral capillary wall staining was identified for IgG (1+), kappa (1+), and lambda (1+). All other immunofluorescence stains were negative in glomeruli. Above all, PLA2R was negative, but NELL-1 was positive, making the diagnosis of NELL-1-associated membranous nephropathy. Electron microscopy was not feasible as no intact glomeruli were available for ultrastructural examination.

The chronicity summary, drawn from both specimen components, identified 13 total glomeruli, with three exhibiting global glomerulosclerosis (23%). Segmental sclerosis, interstitial fibrosis, and tubular atrophy were absent; arterial intimal fibrosis was mild. The final pathological diagnosis was: 1) Membranous Glomerulopathy, NELL-1 Positive, and 2) Diabetic Glomerulopathy, Class IIa.

Because NELL-1 has a malignancy association in roughly one-third of instances, malignancy screening was performed. The patient denied a personal history of cancer. Screening was initiated by obtaining a smoking history, which was negative, and review of imaging results, including a chest radiograph (most recent March 2025), which was unremarkable. His family history was positive for colon cancer in his father, and he is on five-year surveillance for a personal history of adenomatous colon polyps; his most recent colonoscopy in 2023 showed a benign tubular adenoma. His most recent PSA was normal at 0.39 ng/mL. Supplementation with alpha-lipoic acid was discontinued immediately following biopsy. Finerenone (Kerendia), which had been initiated for management of diabetic proteinuria, was continued initially and was subsequently discontinued on October 9, 2025, specifically to establish a finerenone-free proteinuria baseline and clarify the magnitude of alpha-lipoic acid's independent contribution to the proteinuria, rather than because of any adverse effect. All other supplements were also discontinued. Follow-ups monthly with renal function assessment were initiated.

Following cessation of alpha-lipoic acid, the patient showed improvement in proteinuria. UACR at the three-month follow-up on September 9, 2025, was 2,195 mg/g—a decrease of 46% from the maximum of 4,061 mg/g, at a time when finerenone (an agent with well-established antiproteinuric effects) was still being administered; finerenone was not discontinued until October 9, 2025. Therefore, this improvement cannot be attributed solely to alpha-lipoic acid cessation.

3. Discussion

NELL-1 antigen in membranous nephropathy can indicate the development of secondary membranous nephropathy following malignancy or exposure to drugs/supplements [5]. NELL-1-related MN cases are diagnosed based on the identification of distinctive histopathologic patterns, including a granular pattern in capillary loops observed with Immunoglobulin G (IgG) staining, with segmental to global involvement [6]. The current case report highlights the significance of recognizing NELL-1-associated MN as a distinct clinical entity, as it could have implications for treatment and prognosis.

Alpha-lipoic acid, a potent antioxidant commonly employed in the treatment of diabetic neuropathy, has been implicated in inducing NELL-1-associated MN, although not the definite mechanisms [7]. Molecular mimicry, hapten-like activity, or adjuvant-like enhancement of immune reactions against the NELL-1 protein on podocytes have been postulated as the etiologic mechanisms [8]. Case reports and small case series reported in the literature include lipoic acid as the etiology of NELL-1 membranous nephropathy [4] [9].

The temporal relationship in this case suggests a possible causal association: stable renal function prior to December 2024, an acute onset of proteinuria during greater than seven months on alpha-lipoic acid therapy, and a 46% reduction in UACR within three months of alpha-lipoic acid cessation. However, finerenone, an agent with well-established antiproteinuric effects, was still being administered at the time this improvement was measured (September 9, 2025) and was not discontinued until October 9, 2025; therefore, the observed improvement cannot be attributed solely to alpha-lipoic acid withdrawal. This temporal sequence is consistent with, but does not definitively establish, drug-induced nephropathy. This case therefore suggests a possible, rather than a confirmed, causal association; the limitations affecting this inference are detailed at the end of this section.

Approximately one-third of NELL-1-associated MN patients have a history of malignancy, with detectable serum titers of NELL-1 antibodies [5]. Therefore, complete cancer-specific screening in each case of NELL-1-positive membranous nephropathy should be performed. The dose used in the current case (1200 mg daily) is in the higher range of commonly administered doses and agrees with dosing in other cases reported in the literature [4] [9], which suggests possible dose dependence of the nephrotoxic effect.

The reversibility established in this instance is valuable prognostically. Although 23% of glomeruli showed global sclerosis on biopsy (consistent with the

Results), indicating a degree of irreversible chronic structural injury, the overall extent of chronicity was limited, and the acute inflammatory underpinning for active proteinuria seemed amenable to withdrawal of the offending agent. Conservative therapy without immunosuppression was successful, without the concomitant risks of infection, metabolic derangement, and worsening diabetes associated with immunosuppressive treatment [10].

Current research has shown that NELL-1 MN with a thiol-containing drug achieves very high remission rates, such as 88% of patients entering remission by 11 months off immunosuppression [11]. This is much higher than other forms of NELL-1 MN and much greater than remission rates for PLA2R MN, likely secondary to the relative ease of exposing and eliminating exposure [11] [12].

Limitations: This case is subject to several important limitations. It is a single-case report, which limits generalizability. The patient had underlying diabetic kidney disease, itself a cause of proteinuria and glomerular injury, representing a potential confounding factor. Finerenone, an agent with established antiproteinuric effects, was co-administered for part of the observation period and was not discontinued until after the initial improvement in proteinuria was documented, confounding attribution of that improvement to alpha-lipoic acid cessation alone. The absence of electron microscopy precluded ultrastructural confirmation of the diagnosis and definitive staging of the membranous nephropathy, limiting the completeness of the pathological characterization. Follow-up after finerenone discontinuation was relatively short, limiting assessment of the durability of improvement. Finally, although malignancy screening was reassuring, it may not have been fully comprehensive, and occult malignancy cannot be entirely excluded. Given these limitations, this case suggests, but does not confirm, a possible association between alpha-lipoic acid and NELL-1-associated membranous nephropathy.

4. Conclusions

This case report suggests a possible association between alpha-lipoic acid supplementation and the development of NELL-1-associated membranous nephropathy. Patients on alpha-lipoic acid supplements, particularly at higher doses (≥ 1200 mg/day), should be screened for developing proteinuria. Patients developing nephrotic-range proteinuria and new-onset renal disease while on alpha-lipoic acid should be evaluated for NELL-1-associated membranous nephropathy with adequate kidney biopsy, including NELL-1 immunofluorescence staining.

Prompt diagnosis and removal of the suspected inciting agent was followed by a 46% reduction in proteinuria within three months in this patient, although concurrent finerenone use limits attribution of this improvement to alpha-lipoic acid cessation alone. Practitioners must be aware, however, that permanent glomerular damage can occur with continued exposure. Due to the association of NELL-1 and malignancy, intensive cancer evaluation must be pursued in all NELL-1-positive individuals.

More research is needed to investigate alpha-lipoic acid-induced NELL-1 nephropathy frequency, identify susceptibility risk factors, identify the pathogenic processes, delineate the best monitoring regimens in patients taking alpha-lipoic acid, and establish long-term outcomes after supplement withdrawal. Medical professionals must exercise vigilance when prescribing alpha-lipoic acid for diabetic neuropathy and initiate other therapies with better-defined safety profiles.

Author Contributions

T.E. compiled the clinical information, conducted the literature search, and wrote the manuscript. J.S.H. performed the pathological testing and reviewed the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

- [1] Salvadori, M. and Tsalouchos, A. (2022) New Antigens Involved in Membranous Nephropathy beyond Phospholipase A2 Receptor. *World Journal of Nephrology*, **11**, 115-126. <https://doi.org/10.5527/wjn.v11.i4.115>
- [2] Sethi, S., Debiec, H., Madden, B., Charlesworth, M.C., Morelle, J., Gross, L., *et al.* (2020) Neural Epidermal Growth Factor-Like 1 Protein (NELL-1) Associated Membranous Nephropathy. *Kidney International*, **97**, 163-174. <https://doi.org/10.1016/j.kint.2019.09.014>
- [3] Caza, T.N. and Larsen, C.P. (2022) Lipoic Acid in Neural Epidermal Growth Factor-Like 1—Associated Membranous Nephropathy: More than a Coincidence? *Kidney International*, **101**, 418-419. <https://doi.org/10.1016/j.kint.2021.12.001>
- [4] Spain, R.I., Andeen, N.K., Gibson, P.C., Samuels, M.H., Morris, C.D., Solomon, A.J., *et al.* (2021) Lipoic Acid Supplementation Associated with Neural Epidermal Growth Factor-Like 1 (NELL1)—Associated Membranous Nephropathy. *Kidney International*, **100**, 1208-1213. <https://doi.org/10.1016/j.kint.2021.10.010>
- [5] Caza, T.N., Hassen, S.I., Dvanajscak, Z., Kuperman, M., Edmondson, R., Herzog, C., *et al.* (2021) NELL1 Is a Target Antigen in Malignancy-Associated Membranous Nephropathy. *Kidney International*, **99**, 967-976. <https://doi.org/10.1016/j.kint.2020.07.039>
- [6] Wang, G., Sun, L., Dong, H., Wang, Y., Xu, X., Zhao, Z., *et al.* (2021) Neural Epidermal Growth Factor-Like 1 Protein-Positive Membranous Nephropathy in Chinese Patients. *Clinical Journal of the American Society of Nephrology*, **16**, 727-735. <https://doi.org/10.2215/cjn.11860720>
- [7] Vallianou, N., Evangelopoulos, A. and Koutalas, P. (2009) Alpha-Lipoic Acid and Diabetic Neuropathy. *The Review of Diabetic Studies*, **6**, 230-236. <https://doi.org/10.1900/rds.2009.6.230>
- [8] Andeen, N.K., Kung, V.L. and Avasare, R.S. (2024) NELL1 Membranous Nephropathy: Clinical Associations Provide Mechanistic Clues. *Frontiers in Nephrology*, **4**, Article ID: 1323432. <https://doi.org/10.3389/fneph.2024.1323432>
- [9] Avasare, R.S., Clark, S., Spain, R.I., Wusirika, R., Rope, R., *et al.* (2024) Characteristics and Outcomes of NELL1 Membranous Nephropathy in Lipoic Acid Users and Non-

users. *Kidney International Reports*, **9**, 1379-1386.

- [10] Rovin, B.H., Adler, S.G., Barratt, J., Bridoux, F., Burdge, K.A., Chan, T.M., *et al.* (2021) Executive Summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. *Kidney International*, **100**, 753-779.
<https://doi.org/10.1016/j.kint.2021.05.015>
- [11] Iwakura, T., Ema, C., Isobe, S., Fujikura, T., Ohashi, N., Kato, A., *et al.* (2022) Prevalence of Neural Epidermal Growth Factor-Like 1- and Exostosin 1/Exostosin 2-Associated Membranous Nephropathy: A Single-Center Retrospective Study in Japan. *Scientific Reports*, **12**, Article No. 2976. <https://doi.org/10.1038/s41598-022-07037-2>
- [12] Sethi, S., Beck, Jr., L.H., Glassock, R.J., Haas, M., *et al.* (2023) Mayo Clinic Consensus Report on Membranous Nephropathy: Proposal for a Novel Classification. *Kidney International*, **104**, 1092-1102.