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

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INTRODUCTION

Membranous nephropathy (MN) occurs when antibodies target an antigen in the glomerular basement membrane (GBM). Primary membranous nephropathy (PMN) represents 70% of MN cases,[1] with M-Type Phospholipase A2 Receptor (PLA2R) being the target antigen in about 70% of cases, Thrombospondin type-1 domain-containing 7A (THSD7A) in about 1-5% of cases, and about 25% of cases having an unknown target antigen.[2] Recently, nerve epidermal growth factor-like 1 (NELL-1) antigen-antibody has been identified as a rare cause of PMN in PLA2R-negative cases.[2] Lipoic acid, an over-the-counter supplement commonly used to manage neuropathic pain, has been linked to triggering NELL-1-associated MN, resulting in high-grade proteinuria.[3] Discontinuation of lipoic acid showed best results in some patients, as they achieved full remission within six months.[4]

CASE REPORT

A 67-year-old woman with a history of type 2 diabetes mellitus for 16 years, chronic kidney disease, and peripheral neuropathy was referred by her primary care physician due to high-grade proteinuria (4,175 mg/24 hours) and peripheral edema. Her serum creatinine level was 11 mg/dl. The patient had been taking lipoic acid supplements for the past few years to treat her diabetic neuropathy, which provided relief from neuropathy symptoms. Further investigations, including chest x-ray, kidney ultrasound, anti-nuclear antibodies (ANA), serologies for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), anti-PLA2R, and anti-THSD7A antibodies, were inconclusive. A kidney biopsy revealed the characteristic features of NELL-1-associated MN (as shown in Figures 1 and 2). As NELL-1 is associated with malignancy, a thorough screening for cancers yielded negative results.[5] Consequently, the lipoic acid supplements were discontinued, and monthly follow-ups with renal function testing were initiated. After discontinuing lipoic acid, urine albumin excretion improved to 675 mg/24 hours after two months and further decreased to 228 mg/24 hours at five months. The patient's last serum creatinine level was 0.92 mg/dL.

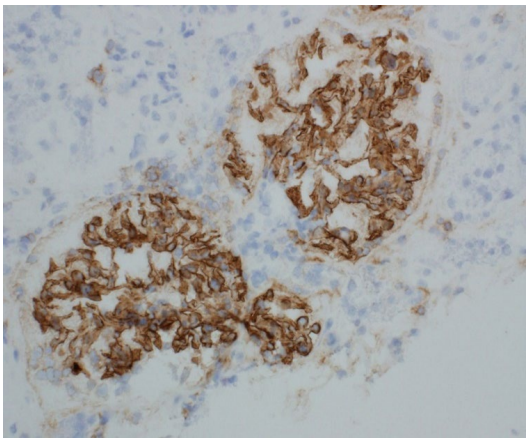

Figure 1. Immunohistochemical staining for NELL-1 shows segmental positivity.

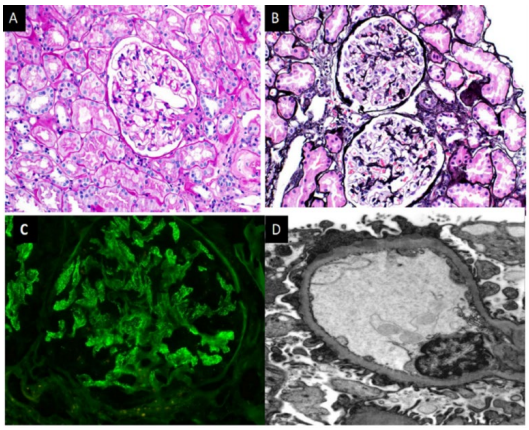

Figure 2. Microscopic features of NELL-1 associated MN. A-Glomerulus on Periodic Acid Schiff stain, showing non-proliferative pattern and prominent capillary loops. B-Spikes and holes along the glomerular capillary loops seen on silver stain. C-Segmental and incomplete global IgG staining in glomeruli on immunofluorescence microscopy. D-Electron-dense deposits along the glomerular capillary loops on Electron microscopy.

DISCUSSION

NELL-1 antigen presence in membranous nephropathy can indicate the development of secondary membranous nephropathy associated with malignancy or serve as an underlying cause for primary membranous nephropathy, specifically NELL-1-associated MN.[5] The latter form is characterized by the presence of autoantibodies targeting the NELL-1 protein within the glomerular basement membrane.[6] Recognition of NELL-1-associated MN cases relies on the identification of distinctive histopathologic features. These features include a granular capillary loop pattern observed during Immunoglobulin G (IgG) and IgG1 subclass staining, exhibiting a segmental to incomplete global distribution.[7] This case report highlights the significance of recognizing NELL-1-associated MN as a distinct clinical entity, as it can inform treatment decisions and provide insights into prognostic factors. Lipoic acid, a potent antioxidant commonly used in the management of diabetic neuropathy and other medical conditions, has been implicated in the development of NELL-1-associated MN, although the precise mechanisms remain unclear.[8] The existing literature is limited, primarily consisting of a few case reports that highlight the association

between lipoic acid and MN. Approximately one-third of patients with NELL-1-associated MN have a history of malignancy, with detectable levels of serum NELL-1-antibodies. However, further investigations are necessary to determine the potential correlation between antibody levels, the presence of proteinuria, and the underlying malignancy.

CONCLUSIONS

This case report suggests that lipoic acid supplementation may trigger the development of NELL-1-associated MN. Patients taking lipoic acid supplements and presenting with symptoms of kidney disease should be evaluated for this rare condition. Further studies are needed to investigate the potential link between lipoic acid and NELL-1-associated MN.

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