

# NELL1-ASSOCIATED MEMBRANOUS NEPHROPATHY: A DETAILED CASE SERIES WITH CLINICAL, PATHOLOGICAL, AND IMMUNOLOGICAL INSIGHTS

Asif Sadiq Wani, Zafirah Zahir, Alok Sharma, Anas Hyder



## INTRODUCTION

Membranous nephropathy (MN) is a primary cause of nephrotic syndrome in adults, traditionally categorized as primary or secondary based on clinical and histopathological features. Advances in podocyte antigen discovery—including PLA2R, THSD7A, and NELL1—have redefined MN classification, enabling precise diagnosis and treatment.

- NELL1-associated MN is emerging as a distinct entity, characterized by unique clinical, pathological, and immunological profiles. Studies indicate associations with malignancies and drug exposures, underscoring the importance of comprehensive diagnostic evaluations.
- This case series highlights clinical presentations, biopsy findings, and outcomes of NELL1-MN from a specific geographical region, aiming to contribute to the global understanding of this condition.

## RESULTS

**Sample Size:** 8 patients (4 females; median age: 48 Y).

**Clinical Features:** Median proteinuria: 4.9 g/day; 75% had nephrotic-range proteinuria. Median eGFR: 34 mL/min/1.73 m<sup>2</sup>.

### Biopsy Findings:

- Histopathology: Thickened glomerular basement membranes with mild mesangial proliferation.
- Immunofluorescence: IgG1 predominance.
- Electron Microscopy: Segmental subepithelial deposit

**Outcomes:** 5 complete remissions; 3 partial remissions.

## CONCLUSION

- This case series adds to the growing body of evidence that NELL1-MN is a heterogeneous condition with diverse clinical and pathological features.
- The strong association with malignancies and other secondary causes highlights the need for comprehensive evaluation in these patients.
- While immunosuppressive therapy remains a cornerstone of treatment, addressing underlying etiologies is crucial for optimal outcomes.
- Further studies are needed to elucidate the pathophysiological mechanisms underlying NELL1-MN and to develop targeted therapeutic strategies for this unique subset of MN.

TABLE 1: NELL-1 Associated Membranous Nephropathy – Cases summary

Case	Age/Gender	Clinical Findings	Key Lab Findings	Biopsy Results	Etiology	Treatment	Outcome
1	55/M	Nausea, edema	Cr: 4.3 mg/dl, Prot: 4 g/day	NELL-1+, subepithelial deposits	Lung SCC	Chemo, RT	Partial remission
2	26/F	Edema, periorbital puffiness	Cr: 1.59 mg/dl, Prot: 5.4 g/day	NELL-1+, mild MN	Alpha-lipoic acid	Drug withdrawal	Complete remission
3	65/M	Edema, fatigue	Cr: 2.1 mg/dl, Prot: 4.4 g/day	NELL-1+, MN + FSGS	Prostate CA	Malignancy Rx, steroids	Complete remission
4	48/F	Edema	Cr: 1.8 mg/dl, Prot: 5.8 g/day	NELL-1+, MN	Idiopathic	Modified Ponticelli regimen	Partial remission
5	51/F	Edema	Cr: 3.1 mg/dl, Prot: 5.6 g/day	NELL-1+, MN	Idiopathic	Modified Ponticelli regimen	Partial remission
6	45/M	Facial puffiness, HTN	Cr: 1.9 mg/dl, Prot: 2.9 g/day	NELL-1+, MN	Idiopathic	Telmisartan	Complete remission
7	48/M	Edema, knee pain	Cr: 2.7 mg/dl, Prot: 2.4 g/day	NELL-1+, MN	Ayurvedic meds	Drug withdrawal, steroids	Complete remission
8	32/F	Edema	Cr: 0.8 mg/dl, Prot: 6.8 g/day	NELL-1+, MN	Mercury	Steroids, rituximab, tac, MMF, pred	Complete remission

## DISCUSSION

- Patients typically present at a median age of 66.8 years, with a slight male predominance (58.2%).
- Approximately 35–80% of patients exhibit nephrotic-range proteinuria, often with preserved kidney function.
- Characteristic findings include segmental glomerular capillary loop staining and a predominance of IgG1 subclass deposits.
- NELL1-MN has a higher association with malignancies compared to other MN subtypes, with studies reporting up to 33% of cases linked to cancer.
- Patients often achieve remission upon addressing underlying conditions, such as discontinuing implicated medications or treating associated malignancies.

Caza TN, Hassen SI, Dvanajscak Z, et al NELL1 is a target antigen in malignancy-associated membranous nephropathy. *Kidney international*. 2021 Apr 1;99(4):967-76.  
 Andeen NK, Kung VL, Avasare RS. NELL1 membranous nephropathy: clinical associations provide mechanistic clues. *Frontiers in Nephrology*. 2024 Mar  
 Sethi S. The many faces of NELL1 MN. *Clinical Kidney Journal*. 2023 Mar;16(3):442-6. 26;4:1323432.