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Insights into Therapeutic Strategies and Longitudinal Outcomes: A Retrospective Analysis of NELL1 Positive Membranous Nephropathy Cohort

Abstract

Membranous nephropathy (MN) is a rare autoimmune disease, in which the circulating autoantibodies against antigens attack podocytes. Neural Epidermal Growth Factor like 1 (NELL1) 1-associated MN is the second most common antigen, following phospholipase A2 receptor. Complementary and alternative medicine and malignancies play a pivotal role in the development of NELL1-MN. This retrospective study describes the clinical characteristics, therapeutic strategies, and longitudinal outcomes in patients with NELL1-MN at our center.

Keywords: *Membranous nephropathy, NELL1, PLA2R, Complementary and alternative medicine, CNI*

Introduction

Membranous nephropathy (MN) is a rare autoimmune disease, in which circulating autoantibodies against antigens attack podocytes. It accounts for about 20% cases of nephrotic syndrome in adults.¹ Sethi *et al.* using laser microdissection and tandem mass spectrometry (MS/MS) have recently described six new target antigens in MN that include neural tissue encoding protein with EGF-like repeats [Neural Epidermal Growth Factor like 1 (NELL1)] and others like Exostosin-1, Semaphorin3B.² NELL1 is the second most common antigen implicated in development of MN.³ Emerging evidence suggests that complementary and alternative medicine (CAM) and malignancies may play a pivotal role in the development of NELL1-associated MN (NELL-1 MN).⁴⁻⁶ Many cases of NELL-MN remit following stoppage of the offending agent but some may

require immunosuppression. We examined the clinical characteristics, therapeutic strategies, and longitudinal outcomes of NELL1-MN patients at our center.

Case Series

All adult cases with NELL1-MN diagnosed in Nephrology Department of Sawai Man Singh Medical College & Hospital, Jaipur, India between April 1, 2021 and March 31, 2023 were identified from hospital records and contacted via telephone. Data on demographic parameters, biochemical, and histological characteristics were collected. Immunosuppression and treatment history along with baseline and last available serum albumin, creatinine, and proteinuria were recorded. Those with CKD stage 3 or above at presentation, patients with lupus nephritis or other connective tissue disorders were excluded.

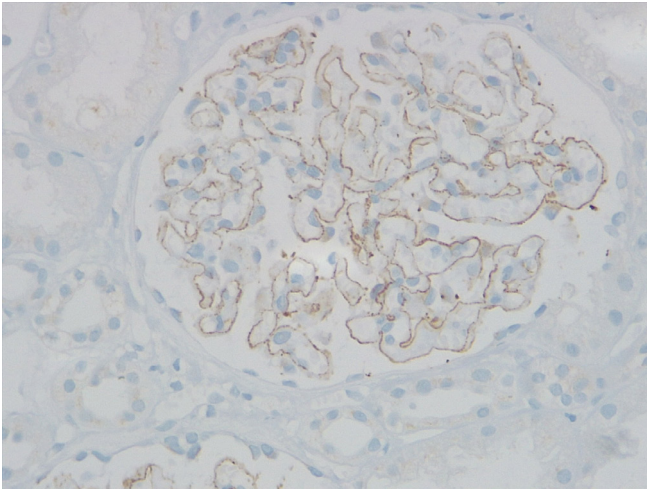


Figure 1: Neural Epidermal Growth Factor like 1 (NELL1) positivity on immunohistochemistry (IHC).

Of the 15 patients with NELL1-MN identified, data of 10 patients were available for analysis as depicted in Table 1. There were 9 females and the mean age was 37.2 ± 15.2 years. The mean duration of follow-up since biopsy was 18.2 ± 6.9 months.

Three patients each had a history of CAM and NSAID intake. None had any history of skin fairness cream use, any identifiable malignancy or autoimmune disease. One patient had history of psoriasis, another of atopy, and two with migraine and another two of hypertension. On histopathology, all patients had IgG1 and IgG4 positivity. C3 positivity was seen in 70% and segmental staining in 30% of cases [Figure 1].

Three cases were managed with conservative management, and all achieved complete remission (CR). Seven patients required immunosuppression with calcineurin inhibitor (CNI) and steroids for 6–12 months. Of these, two achieved CR, four achieved partial remission (PR), and one was CN-resistant, requiring cyclical cyclophosphamide-corticosteroid. There were no deaths in our study, and treatment-related side-effects included diabetes in one patient and hypertension in another.

Discussion

Our case series adds to the growing literature on NELL1-MN, a relatively new entity and have been linked to cancer, drugs, infections, autoimmune diseases, stem cell transplantation, and use of mercury containing CAM, and skin creams.⁴⁻⁶ In this case series, none of our patients had any signs of malignancy which was similar to a series by Wang *et al.*⁷ three (30%) had a history of consuming CAM, although exact nature of medicines could not be delineated. Kurien *et al.*⁴ reported that approximately 35% of MN cases in India were associated with traditional indigenous medicine use, of which 88% were NELL1-positive. Another three (30%) had history of prolonged NSAID intake for migraine or as an over-the-counter pain

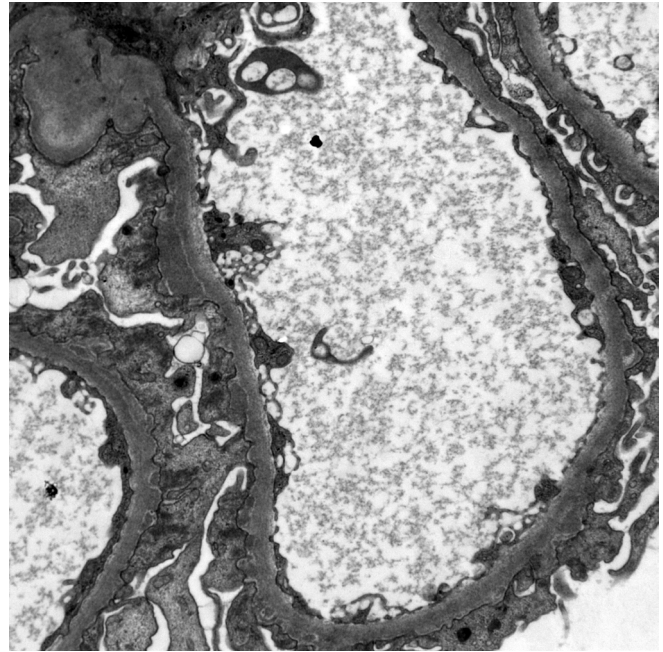


Figure 2: Electron microscopy showing subepithelial deposits.

killer. A possible correlation between heavy metals in CAM or skin fairness creams and incidence of NELL1-MN has been reported in various series recently.^{6,8,9} There was no history of skin fairness cream use in our patients.

In the current study, IgG1 and IgG4 staining was observed in 100% cases, with IgG1 predominance in 20% and IgG1–IgG4 co-dominance in 80%, and segmental IgG staining was observed in 30% and C3 staining in 70% [Figure 2]. Sethi *et al.*² reported that partial or segmental IgG1 staining was predominant in NELL1 MN. The results are also similar to Caza *et al.*,⁵ who found pure segmental staining (IgG) in 45% of the cases and C3 in three-fourths of cases.

Little information is available regarding the optimal treatment and clinical outcomes in patients with non-malignancy-related NELL1-MN. In our study, all but one patient experienced clinical remission with CR in 5 (50%) and PR in 4 (40%). Out of these, three were managed with supportive RAAS inhibition alone and all achieved CR. Those requiring immunosuppression had a mean treatment duration with CNI of 9.3 ± 2.5 months. This was comparable to results of Wang *et al.*,⁷ who reported follow-up data for 12 patients, of whom 10 received immunosuppressive therapy, and 11 achieved clinical remission (CR: 5 and PR: 6). In the study by Caza *et al.*,⁵ only 15 patients (25.42%) received immunosuppressive therapy, with eight receiving CNI, three cyclophosphamide and mycophenolate mofetil combined with steroids each, and one with rituximab therapy. Sultan *et al.*⁸ reported a successful response to cyclical cyclophosphamide-corticosteroids in two patients with skin-whitening cream-associated NELL1-MN. A recent study by Narayanasami *et al.*¹⁰ examined the clinical characteristics and remission rates of NELL1-MN

Table 1: Baseline characteristics, biopsy findings, and therapeutic outcomes in NELL1-MIN patients

Patient	Baseline parameters (at presentation)		Associated features	Renal biopsy findings	Follow-up (months)	ACEi/ARB	24-hr UP after 3-6 mo (mg/d)	Immunosuppression (months)	Latest parameters Outcome				
	S. Cr (mg/dL)	24-hr UP (g/dL)							S. Cr	24-hr S. Alb UP			
43/M	1.3	-	2.2	None	IFTA 20-25%, IgG 3+, C3 2+	Excluded (Lost to follow-up)	-	-	-	-			
68/M	0.9	2800	2.8	Psoriasis, HTN, CAM	IFTA 10-15% IgG1, IgG4 3+ granular along capillary wall, C3 1+	33	Yes (33 mo)	1300	No	0.8	281	3.8	CR
27/F	0.7	12,000	1.8	None	IFTA 10-15% IgG1, IgG4 3+ segmental & capillary wall, granular, C3 1+	27	Yes (27 mo)	10070	CNI + P (12 mo)	1.3	211	3.5	CR
42/F	0.9	2190	2.8	None	IFTA 10-15% IgG1 3+, IgG4 3+ capillary wall, granular, C3 -ve	24	Yes (24 mo)	1584	No	0.5	127	3.8	CR
31/F	0.82	14,767	2.6	CAM intake	IFTA 10-15% IgG1 3+, IgG4 1+ capillary wall, granular, C3 1+	19	Yes (12 mo)	12600	CNI + P (6 mo) Modified Ponticelli (6 mo)	2.9	2190	2.4	GFR decline
32/F	0.65	8800	2.87	Migraine, NSAID intake	IFTA 10-15% IgG1 3+, IgG4 3+ capillary wall, granular, C3 -ve	15	Yes (15 mo)	9800	CNI + P (12 mo)	0.7	420	3.9	PR
22/M	1.25	2130	2.6	None	IFTA 10-15% IgG1 3+, IgG4 1+ capillary wall, granular, C3 2+	14	Yes (14 mo)	354	No	0.9	82	4.1	CR
64/M	0.94	4490	2.6	HTN, Osteoarthritis, NSAID use	IFTA 10-15% IgG1 3+, IgG4 2+ capillary wall, granular, C3 1+	13	Yes (13 mo)	5420	CNI + P (10 mo)	0.6	291	3.8	CR
28/F	0.6	7120	2.3	Chronic Headache, NSAID intake	IFTA 10-15% IgG1 3+, IgG4 3+ capillary wall, granular, C3 1+	13	Yes (13 mo)	6800	CNI + P (10 mo)	0.8	380	4	PR
36/M	5.4	-	2.2	CKD, HTN	Glom- 38% globally sclerosed, IFTA 35-40% IgG 2+, capillary wall, granular, C3 1+	Excluded (eGFR <60)	-	-	-	-	-	-	-
30/M	0.8	7640	2.1	None	IFTA 10-15% IgG1, IgG4 3+ segmental & capillary wall, granular, C3 1+	12	Yes (12 mo)	10880	CNI + P (9 mo)	0.7	795	3.6	PR
28/F	0.75	3090	2.72	Atopy, Old Pulmonary TB, CAM	IFTA 10-15% IgG1, IgG4 3+ segmental & capillary wall, granular, C3 -ve	12	Yes (12 mo)	3800	CNI + P (6 mo)	1.1	660	3.4	PR
34/F	0.8	-	2.4	Multiple food allergies	IFTA 10-15% IgG 3+ capillary wall, granular, C3 2+	Excluded (<1 year follow up)	-	-	-	-	-	-	-
57/F	0.9	-	2.6	None	IFTA 10-15% IgG 3+ capillary wall, granular, C3 3+	Excluded (<1 year follow up)	-	-	-	-	-	-	-
30/F	1	-	2	Rash, alopecia	IFTA 10-15% IgG 3+ capillary wall, granular, C3 2+	Excluded (<1 year follow up)	-	-	-	-	-	-	-

ACEi: Angiotensin converting enzyme inhibitor, Alb: Albumin, ARB: Angiotensin receptor blockers, CAM: Complementary and Alternative Medicine, CKD: Chronic Kidney Disease, CNI: Calcineurin inhibitor, CR: Complete remission, Cr: Creatinine, C3: Complement factor 3, eGFR: estimated Glomerular Filtration Rate, HTN: Hypertension, IFTA: Interstitial fibrosis and tubular atrophy, IgG: Immunoglobulin G, NSAID: Non-Steroidal Anti-Inflammatory Drug, P: Prednisolone, PR: Partial remission, TB: Tuberculosis, UP: Urine Protein

and compared them with unidentified antigen-associated MNs. Immunosuppression was less frequently required in NELL1 group and, there was no difference in remission rates between cyclical cyclophosphamide-corticosteroid and rituximab-treated patients. In present study, one patient (10%) was CNI-resistant, requiring cyclical cyclophosphamide-corticosteroid. This patient did not respond to immunosuppression and had progressive eGFR decline.

Although this study delineates the etiological and longitudinal outcomes of NELL1-MN, it has certain limitations. These encompass a retrospective nature, small sample size, brief follow-up duration, a dearth of information regarding the nature of CAM, non-usage of rituximab, and absence of antibody monitoring.

Nonetheless, the present study suggests that oral CNI with steroids could prove efficacious in managing patients without spontaneous remission or non-responsive to RAAS inhibition, and if ineffective, modified Ponticelli regimen could serve as an effective alternative.

NELL1-associated MN demonstrates an association with CAM and NSAID intake, with possible role of heavy metals, and not with malignancy, as previously thought. Some patients may undergo spontaneous or CR with elimination of inciting factor or effective RAAS inhibition. We document good response to CNI therapy, thus, pointing to avoidance of cytotoxic agents and biologics as first line, to prevent unnecessary side effects. Long-term response, remission, and relapse rates need further studies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Conflicts of interest

There are no conflicts of interest.

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