Section: General Medicine

Case Series

BEYOND NEPHROTIC SYNDROME: THREE DISTINCT FACES OF MEMBRANOUS NEPHROPATHY IN THE ERA OF ANTIGEN-BASED DIAGNOSIS

Bhuvaneswari Kothendaraman[1], Kavitha B[2], Seetharaman M[3], Mukilan S[4]

[1]General Medicine, Indira Gandhi Medical College and Research Institute, Pondicherry, India.
[2]General Medicine, Indira Gandhi Medical College and Research Institute, Pondicherry, India.
[3]General Medicine, Indira Gandhi Medical College and Research Institute, Pondicherry, India.
[4]General Medicine, Indira Gandhi Medical College and Research Institute, Pondicherry, India.

Received : 21/05/2026
Received in revised form : 12/07/2026
Accepted : 27/07/2026

Keywords:
Membranous nephropathy, PLA2R; NELL1, Nephrotic syndrome, Renal biopsy, Antigen-based diagnosis, Case series.

Corresponding Author:
Dr. Seetharaman M,
Email: seetharamanmohan1996@gmail.com

DOI: 10.47009/jamp.2026.8.4.134

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2026; 8 (4); 786-795

ABSTRACT

Background: Membranous nephropathy (MN) is among the leading causes of nephrotic syndrome in adults and is characterized by subepithelial immune-complex deposition along the glomerular basement membrane. Traditionally classified as primary or secondary, the disease has undergone a paradigm shift following the identification of target podocyte antigens, including phospholipase A2 receptor (PLA2R), thrombospondin type-1 domain-containing 7A (THSD7A), neural epidermal growth factor-like 1 protein (NELL1), semaphorin-3B (SEMA3B), protocadherin-7 (PCDH7), exostosin 1/2 (EXT1/EXT2), neural cell adhesion molecule-1 (NCAM1), and other recently recognized antigens. This antigen-based classification has significantly improved diagnostic precision, prognostic assessment, and individualized therapeutic decision-making. **Case Series:** We describe three patients representing distinct manifestations of MN. The first patient, a middle-aged man with longstanding alcohol dependence, presented with generalized edema, ascites, and radiological features suggestive of decompensated chronic liver disease. However, preserved hepatic synthetic function and nephrotic-range proteinuria prompted renal evaluation, ultimately revealing biopsy-proven PLA2R-positive primary MN. The second patient, a young woman with nephrotic syndrome following antecedent consumption of an over-the-counter herbal weight-loss supplement, was diagnosed with NELL1-associated PLA2R-negative MN and achieved complete remission with optimized supportive therapy alone. The third patient presented with severe nephrotic syndrome, impaired renal function, and strongly positive PLA2R antibody titres. Renal biopsy confirmed primary MN, and treatment with the modified Ponticelli regimen resulted in marked clinical and biochemical improvement. **Conclusion:** MN should be considered in adults presenting with unexplained edema or nephrotic syndrome, even when alternative systemic disorders appear more likely. Antigen-specific serology, kidney biopsy, and risk-based management are fundamental to optimizing patient outcomes. This case series highlights the evolving role of antigen-based diagnosis and reinforces the need for individualized therapeutic approaches.

INTRODUCTION

Membranous nephropathy (MN) is an immune-mediated glomerular disease characterized by diffuse thickening of the glomerular basement membrane resulting from subepithelial deposition of immune complexes. It is one of the most common causes of nephrotic syndrome in adults, accounting for approximately one-third of biopsy-proven nephrotic syndrome in non-diabetic adults worldwide.[1,2] The estimated annual incidence ranges from 8 to 12 cases per million population, with a peak incidence between the fifth and sixth decades of life and a slight male predominance.[3,4] Although many patients present with classical nephrotic syndrome, the disease exhibits remarkable clinical heterogeneity, varying from asymptomatic proteinuria to severe nephrotic syndrome with

progressive renal dysfunction, thromboembolic complications, and atypical systemic manifestations.[5] This diversity often complicates diagnosis and delays appropriate management.

Historically, membranous nephropathy was classified as either primary (idiopathic) or secondary depending on the presence of an identifiable underlying cause. Secondary membranous nephropathy has been associated with autoimmune diseases such as systemic lupus erythematosus, chronic infections including hepatitis B, hepatitis C, syphilis, malaria, schistosomiasis, filariasis, and leprosy; malignancies (breast, colon, lung, stomach, kidney, prostate, ovary, esophagus and neuroblastoma); medications (NSAIDs, probenecid, penicillamine, gold, mercury), and environmental exposures.[5,6] Although this classification remains clinically useful, recent advances in molecular nephrology have fundamentally altered the understanding of the disease. The discovery of circulating autoantibodies directed against specific podocyte antigens has transformed membranous nephropathy into an antigen-defined autoimmune disease with distinct clinicopathological phenotypes.[7,8]

The landmark discovery of M-type phospholipase A2 receptor (PLA2R) by Beck and colleagues in 2009 revolutionized the field by identifying the principal target antigen in approximately 70–80% of patients with primary membranous nephropathy.[9] Subsequently, additional podocyte antigens have been identified, including THSD7A, NELL1, SEMA3B, PCDH7, EXT1/EXT2, NCAM1, HTRA1, and several others.[7,8] These discoveries have considerably enhanced diagnostic accuracy and improved the ability to distinguish primary disease from antigen-specific secondary forms. Importantly, antigen identification has also provided prognostic information and increasingly influences therapeutic decision-making. Patients with PLA2R-associated disease, for example, often demonstrate a correlation between antibody titres and disease activity, whereas NELL1-associated membranous nephropathy has been linked with malignancy, autoimmune diseases, medications, and environmental exposures.[8]

Current international guidelines advocate a comprehensive evaluation of every patient with membranous nephropathy.[10] Initial assessment includes confirmation of nephrotic syndrome, exclusion of secondary causes, measurement of circulating antigen-specific antibodies, and renal biopsy whenever clinically indicated. Histopathological examination remains the gold standard for diagnosis and provides invaluable information regarding chronicity, associated glomerular lesions, tubulointerstitial damage, and vascular changes.[11,12] Direct immunofluorescence demonstrating granular capillary wall deposition of immunoglobulins and complement remains the hallmark pathological finding.[12] Together with antigen-specific serology, biopsy findings enable accurate disease classification and facilitate individualized management.

Management of membranous nephropathy has evolved substantially over the past decade. Rather than universal immunosuppression, current treatment emphasizes risk-stratified therapy based on proteinuria, renal function, serum albumin, antibody levels, and the likelihood of spontaneous remission.[10] Patients at low risk of progression may be managed successfully with optimized supportive care consisting of renin–angiotensin system blockade, blood pressure control, lipid-lowering therapy, dietary sodium restriction, and edema management. In contrast, patients with persistent nephrotic syndrome, declining renal function, or high immunological activity often require immunosuppressive therapy, including rituximab, cyclophosphamide-based regimens, calcineurin inhibitors, or other targeted therapies.[10] This individualized approach reflects the broader movement toward precision medicine in glomerular diseases.

Despite these advances, significant diagnostic challenges remain. Membranous nephropathy may masquerade as hepatic disease, cardiac failure, or other systemic disorders, particularly when generalized edema and serosal effusions dominate the clinical picture.[13] Similarly, emerging antigen-defined subtypes may not conform to classical clinical patterns, requiring clinicians to maintain a high index of suspicion and pursue systematic evaluation. Recognition of these diverse presentations is essential for timely diagnosis and appropriate treatment.

In this case series, we present three patients who collectively illustrate the evolving clinical spectrum of membranous nephropathy. The first patient demonstrates an unusual presentation initially mistaken for decompensated chronic liver disease. The second highlights the emerging entity of NELL1-associated membranous nephropathy following exposure to an herbal weight-loss supplement and successful conservative management. The third represents severe PLA2R-positive membranous nephropathy requiring immunosuppressive therapy with the modified Ponticelli regimen. Together, these cases underscore the importance of antigen-based diagnosis, kidney biopsy, and individualized therapeutic strategies in contemporary clinical practice while emphasizing the expanding heterogeneity of membranous nephropathy.

Case 1

Primary PLA2R-Associated Membranous Nephropathy Presenting as Decompensated Chronic Liver Disease

A 51-year-old gentleman from Puducherry presented with progressively increasing abdominal distension and bilateral scrotal swelling of three months duration, accompanied by bilateral lower limb edema and early morning facial puffiness for the preceding two months. He reported multiple

ISSN (O): 2687-5365; ISSN (P): 2753-6556

hospital visits over the previous three months because of persistent generalized swelling, without significant clinical improvement. During this period, he also noticed frothy urine, suggestive of significant proteinuria. There was no history of oliguria, gross hematuria, dysuria, fever, skin rash, arthralgia, photosensitivity, oral ulcers, weight loss, gastrointestinal bleeding, hematemesis, melena, altered bowel habits, dyspnea, chest pain, or previous renal disease. His past medical history was unremarkable, with no known diabetes mellitus or hypertension. However, he had a significant history of chronic alcohol consumption for nearly two decades, averaging approximately eight units of alcohol daily. This history strongly influenced the initial diagnostic impression toward chronic liver disease.

On examination, the patient was conscious, oriented, and hemodynamically stable. Blood pressure was 140/90 mmHg, pulse rate 96 beats/minute, respiratory rate 18 breaths/minute, and oxygen saturation 98% on room air. He was moderately built and nourished with a body mass index of 25 kg/m². General examination revealed marked generalized edema, including Grade III bilateral pitting pedal edema extending to the mid-thighs, bilateral scrotal edema, and mild facial puffiness. There was no pallor, icterus, cyanosis, clubbing, generalized lymphadenopathy, spider angiomas, palmar erythema, or other peripheral stigmata of chronic liver disease.

Abdominal examination demonstrated diffuse symmetrical distension with fullness of the flanks and an abdominal girth of 101 cm. The umbilicus was everted, and shifting dullness confirmed the presence of free intraperitoneal fluid. No hepatosplenomegaly or abdominal masses were palpable. Bowel sounds were normally audible, and there were no abdominal wall collaterals, scars, sinuses, fistulae, or visible peristalsis. Bilateral scrotal edema was present, although both testes remained palpable. Respiratory examination demonstrated reduced breath sounds over both infrascapular regions, consistent with bilateral pleural effusions. Cardiovascular and neurological examinations were entirely normal.

The combination of longstanding alcohol consumption, generalized edema, ascites, bilateral pleural effusions, and ultrasonographic evidence of chronic parenchymal liver disease initially suggested decompensated chronic liver disease with portal hypertension. Ultrasonography revealed coarse hepatic echotexture with surface nodularity, moderate ascites, and mild bilateral pleural effusions. Both kidneys were normal in size with preserved corticomedullary differentiation, and venous Doppler examination of the lower limbs excluded deep venous thrombosis. Ascitic fluid analysis demonstrated a serum-ascites albumin gradient (SAAG) of 1.4 g/dL, compatible with portal hypertension. At this stage, the clinical picture strongly favoured hepatic decompensation.

However, several biochemical findings were inconsistent with advanced liver failure. Liver synthetic function remained remarkably preserved, with normal serum bilirubin, alanine aminotransferase, alkaline phosphatase, coagulation profile, and international normalized ratio, while only minimal elevation of aspartate aminotransferase was noted. These findings, together with profound hypoalbuminemia disproportionate to hepatic dysfunction, prompted reconsideration of the diagnosis and evaluation for an alternative cause of generalized edema.

Laboratory investigations demonstrated severe hypoalbuminemia (1.5 g/dL) and total serum protein of 2.9 g/dL. Serum creatinine was mildly elevated at 1.5 mg/dL, whereas blood urea nitrogen remained within normal limits. Urinalysis revealed persistent albuminuria, and quantitative urine protein estimation confirmed nephrotic-range proteinuria, measuring 4.59 g/day initially and increasing to 8.64 g/day on repeat testing. Urine albumin-creatinine ratio exceeded 300 mg/g, confirming significant glomerular protein loss. Lipid profile demonstrated hypercholesterolemia, completing the classical biochemical triad of nephrotic syndrome. Complement levels (C3 and C4) were within normal limits, while serological evaluation for hepatitis B virus, hepatitis C virus, human immunodeficiency virus, antinuclear antibody, and antineutrophil cytoplasmic antibody were negative, effectively excluding common infectious and autoimmune secondary causes.

Because of persistent nephrotic syndrome without an identifiable secondary etiology, an ultrasound-guided percutaneous renal biopsy was performed. Light microscopy demonstrated diffuse uniform thickening of the glomerular capillary walls without significant endocapillary proliferation or crescent formation. Direct immunofluorescence microscopy revealed diffuse granular capillary wall deposition of IgG, C3, kappa, and lambda light chains, a characteristic immunopathological pattern of membranous nephropathy. [Figure 1] demonstrates the granular IgG deposits along the glomerular capillary wall on direct immunofluorescence. Subsequent serological testing revealed a positive anti-phospholipase A2 receptor (PLA2R) antibody, confirming the diagnosis of primary PLA2R-associated membranous nephropathy.

Considering the degree of proteinuria and persistent symptomatic nephrotic syndrome, the patient was initiated on immunosuppressive therapy. He received one cycle of intravenous cyclophosphamide (500 mg) followed by oral tacrolimus (5 mg twice daily). Supportive management included loop diuretics for edema control, dietary sodium restriction, optimization of nutritional status, and routine nephrology follow-up. At three months, therapeutic tacrolimus trough concentration was 8.91 ng/mL, indicating adequate immunosuppression. During six months of follow-up, the patient experienced progressive resolution of

ISSN (O): 2687-5365; ISSN (P): 2753-6556

pedal edema, ascites, and pleural effusions, accompanied by significant improvement in functional status and biochemical parameters, indicating an excellent clinical response to therapy.

Case 2

NELL1-Associated PLA2R-Negative Membranous Nephropathy Following Herbal Weight-Loss Supplement Exposure with Complete Remission on Conservative Therapy

A 32-year-old woman presented with progressively increasing generalized body swelling and frothy urine for two months. The edema initially involved the lower limbs and gradually progressed to generalized anasarca, significantly limiting her daily activities. She denied oliguria, gross hematuria, dysuria, fever, flank pain, skin rash, photosensitivity, oral ulcers, arthralgia, alopecia, recurrent infections, weight loss, or constitutional symptoms. There was no history suggestive of diabetes mellitus, hypertension, chronic kidney disease, autoimmune disorders, chronic liver disease, thyroid dysfunction, or malignancy. She had never received non-steroidal anti-inflammatory drugs, penicillamine, gold preparations, or other conventional nephrotoxic medications.

A meticulous drug history revealed the use of an over-the-counter herbal weight-loss supplement before the onset of symptoms. The supplement had been consumed for weight reduction purposes without medical supervision. Although the temporal relationship was noteworthy, no definitive causal association could be established, and the exposure was therefore interpreted cautiously as a possible trigger rather than confirmed etiology.

On physical examination, the patient was alert, cooperative, and hemodynamically stable. Blood pressure was 140/90 mmHg, pulse rate 84 beats/minute, respiratory rate 18 breaths/minute, and oxygen saturation 99% on room air. She measured 155 cm in height and weighed 76 kg, corresponding to a body mass index of 31.6 kg/m², consistent with obesity. General examination demonstrated diffuse pitting edema involving both lower limbs with generalized anasarca. There was no pallor, icterus, cyanosis, clubbing, lymphadenopathy, skin rash, or peripheral stigmata suggestive of systemic autoimmune disease. Cardiovascular, respiratory, abdominal, and neurological examinations were otherwise unremarkable.

Initial laboratory investigations confirmed nephrotic syndrome. Serum albumin was markedly reduced (2.4 g/dL) with a total serum protein concentration of 5.3 g/dL. Serum creatinine (0.83 mg/dL) and blood urea (30 mg/dL) indicated preserved renal function. Lipid profile demonstrated hypercholesterolemia (224 mg/dL) with triglycerides of 145 mg/dL. Urinalysis revealed 4+ albumin, and the 24-hour urinary protein was 4.5 g/day, confirming nephrotic-range proteinuria. These findings established the diagnosis of nephrotic syndrome while indicating a relatively preserved glomerular filtration rate.

A comprehensive evaluation for secondary causes of membranous nephropathy was subsequently undertaken. Antinuclear antibody testing, hepatitis B surface antigen, anti-hepatitis C antibody, and human immunodeficiency virus serology were all negative. Serum complement levels (C3 and C4) remained within normal limits, making lupus nephritis and complement-mediated glomerular diseases unlikely. There was no clinical or laboratory evidence of chronic infection or systemic autoimmune disease.

Given persistent nephrotic syndrome in a young adult with a negative secondary work-up, a percutaneous renal biopsy was performed. Light microscopy demonstrated Stage I membranous nephropathy, characterized by uniform thickening of the glomerular basement membrane without significant chronic glomerular injury. Direct immunofluorescence microscopy revealed diffuse granular capillary wall staining for IgG (3+) and C3 (2+), findings consistent with membranous nephropathy. Serum anti-PLA2R antibody testing was negative. Owing to the absence of PLA2R antibodies, additional antigen-specific evaluation was pursued and demonstrated positive NELL1 staining, establishing the diagnosis of NELL1-associated membranous nephropathy.

NELL1-associated membranous nephropathy represents a recently recognized antigen-defined subtype of membranous nephropathy that differs from classical PLA2R-associated disease in both clinical associations and immunopathogenesis. Current evidence suggests possible relationships with malignancy, autoimmune disorders, medications, and environmental exposures. Consequently, the patient underwent careful evaluation to exclude underlying malignancy and systemic disease, which remained negative throughout follow-up.

Considering her preserved renal function, absence of progressive kidney injury, moderate degree of proteinuria, and relatively low predicted risk of progression, she was managed conservatively in accordance with current KDIGO risk-stratified recommendations. Treatment consisted of enalapril 5 mg twice daily, spironolactone-furosemide combination 20/50 mg once daily, atorvastatin 10 mg nightly, dietary sodium restriction, fluid restriction, and regular clinical follow-up. Immunosuppressive therapy was intentionally deferred because the anticipated benefits did not outweigh the potential risks in this low-risk clinical setting.

The patient demonstrated remarkable clinical improvement over subsequent follow-up. Generalized edema resolved completely, serum creatinine remained stable at 0.6 mg/dL, and 24-hour urinary protein excretion decreased to 120 mg/day after one year, fulfilling criteria for complete remission. She remained asymptomatic with preserved renal function and no evidence of disease relapse during continued surveillance. This

ISSN (O): 2687-5365; ISSN (P): 2753-6556

favourable outcome supports the principle that carefully selected patients with low-risk membranous nephropathy may achieve spontaneous or treatment-assisted remission with optimized supportive care alone, without the need for immunosuppressive therapy.

Case 3

High-Risk PLA2R-Associated Membranous Nephropathy with Severe Nephrotic Syndrome and Renal Dysfunction Successfully Treated with the Modified Ponticelli Regimen

A 50-year-old man presented to the Medicine Outpatient Department with progressively worsening bilateral lower limb swelling, facial puffiness, and frothy urine for one month. He was a known case of systemic hypertension diagnosed one year earlier and was receiving T. Amlodipine 10 mg once daily with satisfactory blood pressure control. He denied oliguria, gross hematuria, dysuria, fever, recent upper respiratory or skin infections, flank pain, breathlessness, chest pain, skin rash, arthralgia, photosensitivity, oral ulcers, or constitutional symptoms. There was no previous history of diabetes mellitus, chronic kidney disease, chronic liver disease, malignancy, or exposure to nephrotoxic medications. The relatively short duration of symptoms with rapidly progressive edema suggested an active glomerular disease requiring urgent evaluation.

On examination, the patient was conscious, oriented, and hemodynamically stable. Blood pressure was adequately controlled on antihypertensive therapy. General examination demonstrated mild pallor, diffuse facial puffiness, and bilateral pitting pedal edema extending up to the knees. There were no icterus, cyanosis, clubbing, generalized lymphadenopathy, or skin manifestations suggestive of connective tissue disease. Cardiovascular, respiratory, abdominal, and neurological examinations were unremarkable. Unlike the first case, there was no ascites or pleural effusion, and unlike the second case, renal dysfunction was evident at presentation, suggesting a higher-risk clinical phenotype.

Initial laboratory investigations confirmed severe nephrotic syndrome. Quantitative urine protein estimation demonstrated massive proteinuria of 20.1 g/day, one of the highest values encountered among the three patients. Serum albumin was profoundly reduced (1.8 g/dL), while total serum protein measured 3.7 g/dL. Serum creatinine was elevated to 2.7 mg/dL, indicating impaired renal function at diagnosis. Blood urea was 41 mg/dL, and arterial blood gas analysis demonstrated mild metabolic acidosis. Lipid profile showed marked dyslipidemia with total cholesterol of 429 mg/dL, elevated LDL cholesterol, and hypertriglyceridemia, consistent with severe nephrotic syndrome.

Urinalysis demonstrated persistent proteinuria with only minimal microscopic hematuria (2–4 red blood cells/high-power field). The urine albumin-creatinine ratio measured 645 mg/g creatinine, confirming significant glomerular albumin loss. Hematological evaluation revealed normocytic normochromic anemia without evidence of hemolysis or systemic inflammatory disease. Glycemic assessment showed a normal HbA1c of 5.4%, effectively excluding diabetic nephropathy as the underlying etiology.

A comprehensive investigation for secondary membranous nephropathy was undertaken. Serological testing for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus was negative. Antinuclear antibody testing was also negative, while complement levels (C3 and C4) remained within normal limits, reducing the likelihood of lupus nephritis or complement-mediated glomerular disease. Ultrasonography demonstrated bilateral mildly increased renal cortical echogenicity, suggesting underlying renal parenchymal involvement, together with a simple cortical cyst in the left kidney. No features suggestive of obstructive uropathy or chronic end-stage renal disease were identified.

Because of persistent nephrotic syndrome associated with declining renal function, a percutaneous renal biopsy was performed. Light microscopic examination demonstrated classical features of membranous nephropathy with associated acute tubular injury, 10–15% interstitial fibrosis and tubular atrophy (IFTA), and hypertensive vascular changes, indicating early chronic structural damage. Direct immunofluorescence microscopy showed diffuse granular capillary wall deposition of IgG, IgA, C3, kappa, and lambda light chains, consistent with immune complex-mediated membranous nephropathy [Figure 3]. Subsequent serological evaluation demonstrated a strongly positive anti-PLA2R antibody titre of 503.46 RU/mL, confirming the diagnosis of primary PLA2R-associated membranous nephropathy.

Compared with the previous two patients, this individual fulfilled several criteria associated with high-risk membranous nephropathy, including nephrotic-range proteinuria exceeding 20 g/day, impaired renal function at presentation, severe hypoalbuminemia, and markedly elevated PLA2R antibody levels. In accordance with contemporary risk-based therapeutic principles, immunosuppressive therapy was initiated without delay.

The patient received the modified Ponticelli regimen over six months in combination with comprehensive supportive management, including optimization of antihypertensive therapy, dietary sodium restriction, lipid-lowering therapy, diuretics for edema control, and regular nephrology follow-up. Treatment was well tolerated, and no significant adverse effects necessitating discontinuation of therapy were encountered.

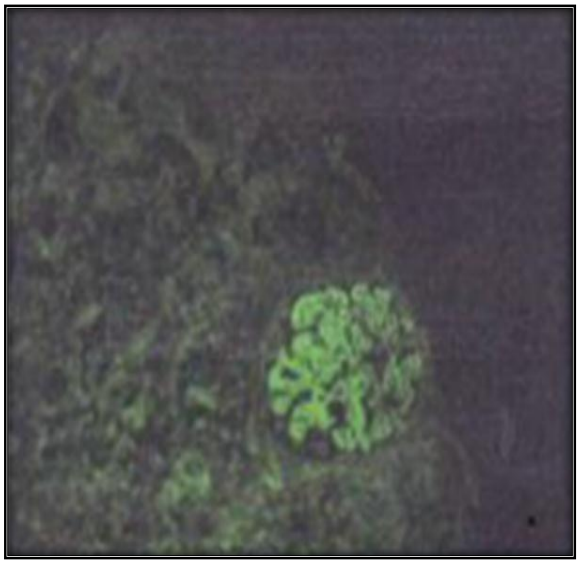
Clinical improvement became evident during follow-up. Peripheral edema resolved completely that serum albumin gradually improved, and renal function stabilized. Most importantly, 24-hour

ISSN (O): 2687-5365; ISSN (P): 2753-6556

urinary protein excretion decreased dramatically from 20.1 g/day to 700 mg/day, representing near-complete remission. The excellent therapeutic response reinforced the effectiveness of timely immunosuppressive therapy in carefully selected high-risk patients and highlighted the prognostic importance of early recognition and intervention before irreversible chronic kidney damage develops. The baseline demographic and clinical characteristics of the three patients are summarized in [Table 1].

[Figure 1] Renal biopsy findings of case 1.

Direct immunofluorescence microscopy demonstrating diffuse granular IgG deposition along the glomerular capillary wall, consistent with membranous nephropathy (Case 1).

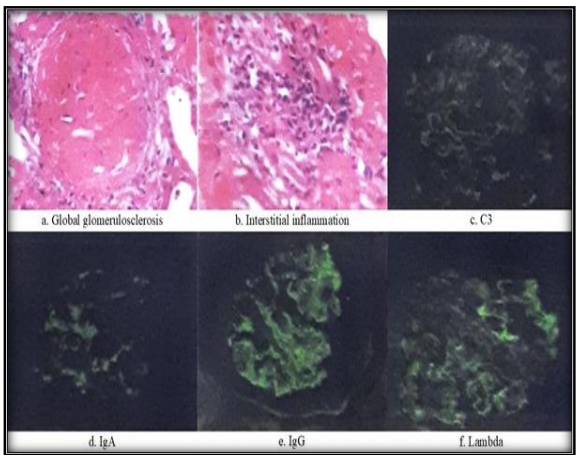


[Figure 2] Renal biopsy findings in Case 3.

(a) Light microscopy showing global glomerulosclerosis involving the glomerulus.

(b) Interstitium demonstrating patchy mixed inflammatory cell infiltrate with associated tubular injury.

(c–f) Direct immunofluorescence microscopy showing granular deposits along the glomerular capillary walls and mesangium: (c) C3, (d) IgA, (e) IgG, and (f) Lambda light chain.



[Figure 3] Proposed diagnostic algorithm for adults presenting with nephrotic syndrome, highlighting the role of antigen-specific serology (PLA2R, NELL1, and other podocyte antigens), kidney biopsy, exclusion of secondary causes, and risk-based treatment selection.

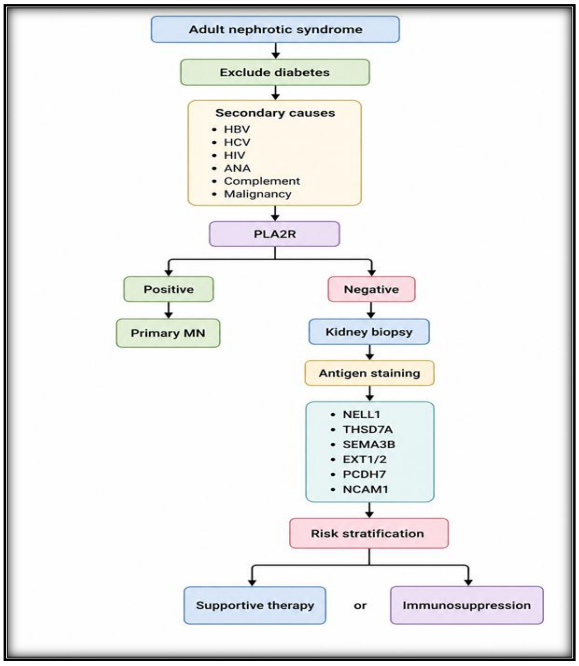


Table 1: Baseline Clinical Characteristics of the Three Patients

Characteristic	Case 1	Case 2	Case 3
Age (years)	51	32	50
Sex	Male	Female	Male
Major comorbidity	Alcohol use disorder	-	Hypertension
Duration of symptoms	3 months	2 months	1 month
Chief presenting complaints	Ascites, bilateral scrotal swelling, pedal edema, facial puffiness	Generalized edema, frothy urine	Pedal edema, facial puffiness, frothy urine
Initial clinical diagnosis	Decompensated chronic liver disease	Nephrotic syndrome	Nephrotic syndrome
Blood pressure	140/90 mmHg	140/90 mmHg	120/80 mmHg on antihypertensive therapy
Generalized edema	Present	Present	Present
Ascites	Present	Absent	Absent
Pleural effusion	Bilateral	Absent	Absent
Facial puffiness	Present	Mild	Present
Frothy urine	Present	Present	Present
Renal dysfunction at	Mild	No	Significant

ISSN (O): 2687-5365; ISSN (P): 2753-6556

presentation			
Final diagnosis	Primary PLA2R-associated membranous nephropathy	NELL1-associated membranous nephropathy	Primary PLA2R-associated membranous nephropathy

Table 2: Laboratory, Histopathological and Immunological Characteristics

Parameter	Case 1	Case 2	Case 3
Serum creatinine	1.5 mg/dL	0.83 mg/dL	2.7 mg/dL
Serum albumin	1.5 g/dL	2.4 g/dL	1.8 g/dL
Total protein	2.9 g/dL	5.3 g/dL	3.7 g/dL
Maximum proteinuria	8.64 g/day	4.5 g/day	20.1 g/day
Total cholesterol	322 mg/dL	224 mg/dL	429 mg/dL
Complement levels	Normal	Normal	Normal
ANA	Negative	Negative	Negative
Viral markers	Negative	Negative	Negative
Renal biopsy	Membranous nephropathy	Stage I membranous nephropathy	Membranous nephropathy with acute tubular injury and mild IFTA
Direct immunofluorescence	IgG, C3, κ, λ	IgG (3+), C3 (2+)	IgG, IgA, C3, κ, λ
PLA2R antibody	Positive	Negative	Strongly positive (503.46 RU/mL)
NELL1	Not tested	Positive	Not detected
Secondary causes	Excluded	Excluded	Excluded

Table 3: Treatment, Risk Stratification and Clinical Outcome

Variable	Case 1	Case 2	Case 3
KDIGO risk category	Moderate risk	Low risk	High risk
Initial therapy	Intravenous cyclophosphamide	ACE inhibitor + diuretics + statin	Modified Ponticelli regimen
Maintenance therapy	Tacrolimus with supportive care	ACE inhibitor + diuretics + statin	Supportive care
Immunosuppressive therapy	Yes	No	Yes
RAAS blockade	Yes	Yes	Yes
Lipid-lowering therapy	Yes	Yes	Yes
Diuretics	Yes	Yes	Yes
Follow-up duration	6 months	12 months	6 months
Outcome	Marked clinical improvement	Complete remission	Near-complete remission
Proteinuria at follow-up	245 mg/day	120 mg/day	700 mg/day
Renal function	Stable	Preserved	Improved/stabilized

DISCUSSION

Membranous nephropathy (MN) remains one of the leading causes of nephrotic syndrome in adults and is responsible for approximately one-third of biopsy-proven nephrotic syndrome in non-diabetic individuals.[1,2] Although traditionally regarded as a relatively homogeneous glomerular disease characterized by diffuse thickening of the glomerular basement membrane, contemporary research has demonstrated that membranous nephropathy represents a heterogeneous group of autoimmune disorders defined by distinct target podocyte antigens, variable immunopathogenesis, differing clinical phenotypes, and diverse therapeutic responses.[7,8] The present three-case series exemplifies this heterogeneity by illustrating three markedly different clinical presentations, two antigenic profiles, and three individualized therapeutic strategies within the same disease spectrum.

Evolution of Disease Classification

For several decades, membranous nephropathy was simply categorized into primary (idiopathic) and secondary disease.[3,6] Primary membranous nephropathy was diagnosed only after excluding infections, autoimmune diseases, malignancies, and drugs. Secondary disease was considered a consequence of an identifiable systemic disorder. This traditional classification has undergone a major transformation following the discovery of PLA2R by Beck et al. in 2009,[9] followed by the identification of THSD7A, NELL1, EXT1/EXT2, SEMA3B, PCDH7, NCAM1, HTRA1, and several other podocyte antigens.[7,8] Consequently, membranous nephropathy is increasingly classified by the responsible target antigen rather than simply labelled as primary or secondary. This antigen-based approach provides several advantages, such as greater diagnostic precision, better understanding of disease pathogenesis, improved prediction of disease activity, ability to monitor immunological remission, and more individualized therapeutic decision-making.[8] Our case series reflects this evolution. Two patients demonstrated PLA2R-associated disease, whereas one patient represented the increasingly recognized NELL1-associated subtype, illustrating how antigen identification complements conventional histopathology. The key laboratory, histopathological, and immunological characteristics of the three patients are summarized in [Table 2].

Case 1 – A Diagnostic Mimic

The first patient illustrates perhaps the greatest clinical lesson. Generalized edema, bilateral pleural effusion, ascites, chronic alcoholism, coarse hepatic echotexture, and elevated SAAG collectively suggested decompensated chronic liver disease. In routine clinical practice, such patients are frequently admitted under hepatology services. However, several findings were inconsistent, such as preserved bilirubin, near-normal liver enzymes, normal

ISSN (O): 2687-5365; ISSN (P): 2753-6556

coagulation profile, profound hypoalbuminemia, and massive proteinuria. Recognition of these inconsistencies prompted nephrological evaluation, ultimately leading to the diagnosis of PLA2R-positive primary membranous nephropathy.[9] Diagnostic overlap between chronic liver disease and coexisting or mimicking glomerular disease has been described previously and reinforces the need for careful biochemical scrutiny in patients with generalized edema.[13] This case highlights an important clinical principle: Generalized edema with ascites should never automatically be attributed to liver disease. Nephrotic syndrome remains an important differential diagnosis whenever hypoalbuminemia is disproportionate to hepatic dysfunction.

Case 2 – Emerging Antigen-Specific Disease

The second patient illustrates another contemporary challenge. Unlike classical PLA2R-positive disease, this patient demonstrated negative PLA2R antibodies, positive NELL1 staining, preserved renal function, and complete remission without immunosuppression. NELL1-associated membranous nephropathy has emerged as an important subtype during the past few years.[7,8] Current literature suggests associations with malignancy, autoimmune diseases, medications, environmental exposures, and herbal preparations.[8] Although our patient's exposure to the herbal weight-loss supplement cannot be considered causative, it raises an important clinical question regarding the role of environmental triggers in genetically susceptible individuals. Importantly, we deliberately interpret this relationship as a temporal association rather than proof of causation, avoiding conclusions that are not supported by the available evidence.

Case 3 – Classical High-Risk Disease

The third patient represents the opposite end of the disease spectrum. Features included are massive proteinuria (>20 g/day), impaired renal function, very high PLA2R antibody titre, acute tubular injury, and mild chronic tubulointerstitial damage.[9,11] Unlike Case 2, spontaneous remission was unlikely. This patient fulfilled multiple KDIGO high-risk criteria and therefore required prompt immunosuppressive therapy using the modified Ponticelli regimen.10 The dramatic fall in proteinuria to 700 mg/day demonstrates the benefit of timely intervention before irreversible chronic kidney injury develops.

Importance of Kidney Biopsy

Although circulating PLA2R antibodies have greatly improved non-invasive diagnosis, renal biopsy remains indispensable in many patients.[11,12] Across our three cases, biopsy served several important purposes: First, it confirmed membranous nephropathy. Second, it excluded alternative glomerular diseases. Third, it assessed chronicity. Fourth, it identified associated lesions, including acute tubular injury, interstitial fibrosis, tubular atrophy, and hypertensive vascular disease. These findings directly influenced therapeutic decisions. Case 3 is particularly illustrative because the biopsy demonstrated early chronic structural injury, supporting the decision for aggressive immunosuppressive treatment.

Direct Immunofluorescence Remains Central

All three patients demonstrated classical granular capillary wall immune deposits. Despite differences in antigenic subtype, direct immunofluorescence consistently showed deposition of IgG, complement C3, and light chains.[12] These findings remain the pathological hallmark of membranous nephropathy and continue to complement antigen-specific serology. Importantly, antigen identification does not replace renal biopsy. Rather, the two investigations are complementary. Biopsy provides structural information, whereas antigen testing provides immunological classification. The integration of these two modalities represents the current diagnostic standard.[11,12]

Lessons from Our Three Cases

Taken together, these patients demonstrate that membranous nephropathy should no longer be viewed as a single clinicopathological entity. Instead, clinicians should recognize it as a spectrum characterized by diverse clinical presentations, multiple antigenic phenotypes, variable immunological activity, different risks of progression, and individualized therapeutic requirements. Recognition of this diversity is essential for early diagnosis, appropriate treatment selection, and improved long-term renal outcomes.

Individualized Risk-Based Management

The management of membranous nephropathy has evolved considerably over the past decade. Earlier therapeutic strategies often relied on uniform immunosuppressive treatment once nephrotic syndrome was diagnosed. However, recognition of the variable natural history of the disease has shifted the focus toward individualized risk stratification, as recommended by the KDIGO 2021 Clinical Practice Guideline for Glomerular Diseases.[10]

Contemporary

Management incorporates clinical severity, degree and persistence of proteinuria, renal function, serum albumin, anti-PLA2R antibody titres, and histopathological findings to identify patients at low, moderate, or high risk of progression.[10] Our three cases exemplify this risk-based approach. The risk stratification, treatment strategies, and clinical outcomes of the three patients are summarized in [Table 3].

Case 1 represented an intermediate-risk phenotype. Although renal function was relatively preserved, the patient had persistent nephrotic-range proteinuria, severe edema, and biopsy-confirmed PLA2R-associated disease. These findings justified immunosuppressive therapy using cyclophosphamide followed by tacrolimus, resulting in marked clinical improvement. Case 2 represented a low-risk phenotype. Preserved renal function, moderate proteinuria, absence of progressive kidney

ISSN (O): 2687-5365; ISSN (P): 2753-6556

injury, and NELL1-associated disease favoured conservative management. Complete remission following renin–angiotensin system blockade, control of oedema, lipid-lowering therapy, and dietary modification illustrates that carefully selected patients can achieve excellent outcomes without immunosuppression. In contrast, Case 3 fulfilled several high-risk criteria, including nephrotic-range proteinuria exceeding 20 g/day, declining renal function, severe hypoalbuminemia, and strongly positive PLA2R antibody titres. Prompt initiation of the modified Ponticelli regimen resulted in a substantial reduction in proteinuria and stabilization of renal function. Together, these cases reinforce that therapeutic decisions should be guided by overall disease risk rather than histopathological diagnosis alone.[10]

Role of Antigen-Specific Diagnosis

Perhaps the greatest advance in membranous nephropathy over the last decade has been the transition from morphology-based diagnosis to antigen-specific classification. Approximately 70–80% of patients with primary membranous nephropathy demonstrate circulating anti-PLA2R antibodies, making PLA2R the predominant target antigen.[9] These antibodies correlate with disease activity, treatment response, and the likelihood of relapse, allowing clinicians to monitor immunological remission in addition to clinical remission. However, the remaining PLA2R-negative patients should not simply be classified as idiopathic. Increasing evidence supports evaluation for other podocyte antigens, particularly NELL1, THSD7A, SEMA3B, PCDH7, EXT1/EXT2, and NCAM1, when clinically appropriate.[7,8] Recognition of these antigen-defined subtypes has enhanced diagnostic precision and may identify patients requiring evaluation for associated malignancies, autoimmune diseases, medications, or environmental exposures.[8] Our second patient illustrates the practical value of this approach. Identification of NELL1 transformed a diagnostically challenging PLA2R-negative case into a clearly defined antigen-specific subtype, facilitating appropriate counselling, investigation, and follow-up. [Figure 3] outlines a proposed stepwise diagnostic approach for the evaluation of adults presenting with nephrotic syndrome.

Future Directions

Rapid advances in renal proteomics continue to identify novel target antigens involved in membranous nephropathy.8 Future research should focus on validating antigen-specific biomarkers, refining risk prediction models, developing personalized immunological monitoring, and evaluating targeted therapies that minimize treatment-related toxicity while maximizing renal preservation. Larger multicentre studies are also needed to clarify the clinical significance of emerging antigen-defined subtypes and their relationship with environmental exposures, autoimmune disease, and malignancy.

CONCLUSION

This three-case series highlights the remarkable clinical, immunological, and therapeutic heterogeneity of membranous nephropathy in the era of antigen-based diagnosis. Although all three patients had biopsy-proven membranous nephropathy, they differed substantially in their initial presentation, antigenic profile, disease severity, and management. One patient presented with features closely resembling decompensated chronic liver disease, another represented NELL1-associated PLA2R-negative membranous nephropathy with complete remission on conservative therapy, while the third demonstrated high-risk PLA2R-positive disease requiring immunosuppressive therapy with the modified Ponticelli regimen.

These cases reinforce several important clinical principles. First, nephrotic syndrome should remain an important differential diagnosis in adults presenting with generalized edema, particularly when clinical or biochemical findings are discordant with an apparent systemic diagnosis. Second, antigen-specific serological testing has transformed the diagnostic approach to membranous nephropathy and should be integrated into routine evaluation whenever feasible. Third, renal biopsy remains indispensable for confirmation of diagnosis, assessment of chronicity, and exclusion of competing glomerular diseases. Finally, treatment should be individualized according to overall disease risk rather than histopathological diagnosis alone.

As our understanding of antigen-specific membranous nephropathy continues to evolve, future classification systems and therapeutic strategies will increasingly emphasize precision medicine. This case series contributes to the growing evidence supporting antigen-guided diagnosis and risk-stratified management while illustrating the diverse clinical spectrum encountered in everyday nephrology practice.

REFERENCES

1. Hull RP, Goldsmith DJA. Nephrotic syndrome in adults. BMJ. 2008 May 24;336(7654):1185–9. doi:10.1136/bmj.39576.709711.80 PubMed PMID: 18497417; PubMed Central PMCID: PMC2394708.
2. Verma PR, Patil P, Verma PR, Patil P. Nephrotic Syndrome: A Review. Cureus. 2024 Feb 9;16. doi:10.7759/cureus.53923
3. Mathieson PW. Membranous nephropathy. Clin Med (Lond). 2012 Oct;12(5):461–6. doi:10.7861/clinmedicine.12-5-461 PubMed PMID: 23101149; PubMed Central PMCID: PMC4953771.
4. Couser WG. Primary Membranous Nephropathy. Clin J Am Soc Nephrol. 2017 Jun 7;12(6):983–97. doi:10.2215/CJN.11761116 PubMed PMID: 28550082; PubMed Central PMCID: PMC5460716.
5. Orth SR, Ritz E. The Nephrotic Syndrome. New England Journal of Medicine. 1998 Apr 23;338(17):1202–11. doi:10.1056/NEJM199804233381707
6. Dantas M, Silva LBB, Pontes BTM, dos Reis MA, de Lima PSN, Moysés Neto M. Membranous nephropathy. Braz J

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Nephrol. 2023;45:229–43. doi:https://doi.org/10.1590/2175-8239-JBN-2023-0046en
7. Gu Y, Xu H, Tang D. Mechanisms of Primary Membranous Nephropathy. Biomolecules. 2021 Mar 30;11(4):513. doi:10.3390/biom11040513 PubMed PMID: 33808418; PubMed Central PMCID: PMC8065962.
8. Francis JM, Beck LH, Salant DJ. Membranous Nephropathy: A Journey From Bench to Bedside. Am J Kidney Dis. 2016 Jul;68(1):138–47. doi:10.1053/j.ajkd.2016.01.030 PubMed PMID: 27085376; PubMed Central PMCID: PMC4921260.
9. Beck LH, Bonegio RGB, Lambeau G, Beck DM, Powell DW, Cummins TD, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009 Jul 2;361(1):11–21. doi:10.1056/NEJMoa0810457 PubMed PMID: 19571279; PubMed Central PMCID: PMC2762083.
10. Rovin BH, Adler SG, Barratt J, Bridoux F, Burdge KA, Chan TM, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney International. 2021 Oct 1;100(4):S1–276. doi:10.1016/j.kint.2021.05.021 PubMed PMID: 34556256.
11. Zhang XD, Cui Z, Zhang MF, Wang J, Zhang YM, Qu Z, et al. Clinical implications of pathological features of primary membranous nephropathy. BMC Nephrol. 2018 Aug 28;19(1):215. doi:10.1186/s12882-018-1011-5 PubMed PMID: 30153817; PubMed Central PMCID: PMC6114049.
12. Smith CC, Conran RM. Educational Case: Membranous Nephropathy. Acad Pathol. 2018 Dec 16;5:2374289518813673. doi:10.1177/2374289518813673 PubMed PMID: 30574541; PubMed Central PMCID: PMC6295683.
13. Onwuzo SS, Hitawala AA, Boustany A, Kumar P, Almomani A, Onwuzo C, et al. Prevalence of non-alcoholic fatty liver disease in patients with nephrotic syndrome: A population-based study. World J Hepatol. 2023 Feb 27;15(2):265–73. doi:10.4254/wjh.v15.i2.265 PubMed PMID: 36926242; PubMed Central PMCID: PMC10011912.