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Clinicopathological Features of Membranous Nephropathy in a Tertiary Center in Anathapur District

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Abstract
Membranous Nephropathy (MN) is a prevalent cause of nephrotic syndrome and proteinuria worldwide. It is characterized by diffuse thickening of the glomerular capillary wall due to immune complex deposition. The aim of this study is to elucidate the clinical and pathological features of MN and evaluate the response to treatment in a tertiary center located in Anathapur District. This study involved a prospective analysis of 46 patients diagnosed with MN at a tertiary care hospital. Data were collected regarding patient demographics, clinical presentation, pathological findings and response to various treatment modalities. The cohort comprised 20 female and 26 male patients, with a mean age of 40.65 years. Clinical parameters such as presence of nephrotic syndrome, hypertension, and microscopic hematuria were recorded. Pathological findings were correlated with serum creatinine levels and degree of proteinuria. Treatment responses were assessed based on clinical remission status. Among the 46 patients, 32 presented with nephrotic syndrome, 19% had concurrent hypertension, and 23.9% exhibited microscopic hematuria. The pathological stage of MN showed a significant correlation with serum creatinine levels, suggesting an association with renal function impairment. However, there was no significant correlation between pathological stage and the degree of proteinuria. Treatment led to complete remission in 48% of the patients. This study provides valuable insights into the clinical and pathological characteristics of MN in Anathapur District. It highlights the prevalence of nephrotic syndrome and the variability in clinical presentation. The correlation between pathological stage and serum creatinine underscores the importance of assessing renal function in MN patients. The finding that nearly half of the patients achieved complete remission underscores the effectiveness of current treatment modalities. These results are crucial for optimizing management strategies and improving patient outcomes based on individual clinical profiles.

INTRODUCTION

Membranous Nephropathy (MN) is a significant cause of nephrotic syndrome, particularly in tropical countries such as India. It is characterized by the thickening of the glomerular basement membrane due to immune complex deposition[1,2]. MN is classified into two categories: primary (idiopathic) and secondary. Primary Membranous Nephropathy occurs in the absence of identifiable causes such as autoimmune diseases, viral infections, or malignancies[3,4]. It accounts for the majority of MN cases and is associated with autoantibodies against podocyte antigens, such as the M-type phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain-containing 7A (THSD7A)[5].

Secondary MN, on the other hand, is associated with underlying conditions such as systemic lupus erythematosus, hepatitis B and C infections and malignancies[6,7]. The distinction between primary and secondary MN is crucial for determining appropriate management strategies and prognosis[8].

In recent years, there have been significant advances in the understanding, diagnosis and treatment of MN. The introduction of immunological markers and renal biopsy techniques has improved diagnostic accuracy[9]. Treatment options, including immunosuppressive therapies and supportive care, have evolved to improve patient outcomes. Despite these advances, the clinical presentation and prognosis of MN can vary widely among patients, depending on factors such as age, gender and underlying health conditions.

The present study aims to provide a comprehensive clinicopathological profile and assess the response to treatment in 46 cases of MN diagnosed at two centers in Ananthapur, a drought-prone region in the South Rayalaseema area of Andhra Pradesh, Southern India. The majority of the patients in this study belong to low and middle socioeconomic status, which may influence disease presentation and access to healthcare. Ananthapur's unique geographic and socioeconomic characteristics contribute to the complexity of healthcare delivery and patient management in this region.

MATERIALS AND METHODS

Study Population and Setting: This study included patients diagnosed with Membranous Nephropathy (MN) via kidney biopsy at the Kidney Clinic, Ananthapuram and the Department of Nephrology, Government General Hospital, Ananthapuram, from March 2018-June 2024. All patients provided informed consent for kidney biopsy, indicated for those presenting with edematous illness and proteinuria.

Biopsy Procedure: Kidney biopsies were performed using a Bard disposable core biopsy instrument (18G × 16mm) under ultrasound guidance, utilizing either a Mindray Z5 or GE Logic ultrasound machine. Patients were admitted and monitored for 24 hours post-procedure before being discharged.

Pre-Biopsy Evaluation: Prior to the biopsy, baseline investigations, including a complete blood count, serum chemistry and coagulation profile, were conducted to ensure patient safety and suitability for the procedure.

Histopathological and Immunofluorescence Analysis: Biopsy samples were evaluated at the Department of Pathology and Laboratory Medicine, Manipal Hospitals, Bangalore. Immunofluorescence studies were conducted to detect the presence of IgG, C3, IgA and IgM deposits, as well as Kappa and Lambda light chain restrictions. PLA2R staining was performed on samples from six individuals, with all testing positive.

Treatment Protocols: Treatment regimens were determined based on the degree of proteinuria and the risk of progression to renal failure. Patients were followed up for six months post-diagnosis, with proteinuria quantified every 15 days to one month.

Modified Ponticelli Regimen: This six-month protocol involving corticosteroids and cyclophosphamide was initiated for patients with heavy proteinuria, edema resistant to diuretics, severe hypoalbuminemia and elevated serum creatinine[3].

Rituximab Therapy: For patients, particularly those PLA2R positive, Rituximab (500 mg) was administered in three doses alongside steroid therapy[4,5].

Tacrolimus with Steroids: In cases where the Modified Ponticelli regimen was unsuitable, a combination of Tacrolimus and steroids was administered[6].

Outcome Measures: Treatment outcomes were classified based on remission status.

Complete Remission: Defined as achieving a normal urinary protein excretion level of <0.3 g/day with stable glomerular filtration rate (GFR). A stable GFR was defined as one that remained unchanged or declined by <15%[7].

Partial Remission: Defined as attaining a protein excretion level of <3.5 g/day with a relative reduction of >50% from baseline and preserved GFR.

Statistical Analysis: Data were analyzed using SPSS version 25.0. Descriptive statistics summarized demographics and clinical characteristics, while comparative analyses, including Chi-square, Fisher's exact test and Student's t-test, evaluated differences between treatment groups. Kaplan-Meier survival analysis and Cox proportional hazards regression identified predictors of remission. A $p<0.05$ was considered significant.

Ethical Considerations: The study adhered to the Declaration of Helsinki and was approved by the Institutional Ethics Committees of the participating institutions. Informed consent was obtained from all patients, ensuring awareness of the study's purpose and procedures. Patient confidentiality was strictly maintained and participants could withdraw at any time without affecting their care.

RESULTS AND DISCUSSIONS

A total of 46 patients were included in the study. The demographic and clinical characteristics are summarized in Table 1. The cohort comprised 56.5% males (n=26) and 43.5% females (n=20). The majority of patients were aged 40 years or older (54.3%, n=25), while 45.7% (n=21) were younger than 40 years. Secondary Membranous Nephropathy (MN) was diagnosed in 8.7% of patients (n=4), with lupus membranous nephropathy accounting for 50% of these secondary cases. Notably, 75% of the secondary MN patients were under 40 years of age. Hypertension at diagnosis was present in 19.6% of the cohort (n=9). Microscopic hematuria was observed in 23.9% of patients (n=11) and nephrotic range proteinuria was identified in 69.5% (n=32). Abnormal renal function, characterized by elevated creatinine levels, was found in 6.5% of patients (n=3) and diabetes mellitus was also present in 6.5% (n=3). The mean time from onset to biopsy was 41.62±12.34 days.

Pathological findings are detailed in Table 2. Subepithelial spikes in the basement membrane were observed in 95.7% of patients (n=44). Mild interstitial fibrosis and tubular atrophy (IFTA) were present in 23.9% (n=11) and moderate IFTA was noted in 6.5% (n=3). Immunofluorescence findings revealed IgG and C3 deposition in 93.5% of patients (n=43), while IgA and IgM depositions were observed in 15.2% (n=7) and 10.9% (n=5) of patients, respectively.

Treatment regimens and their outcomes are summarized in Table 3. The Modified Ponticelli Regimen was administered to 22 patients, with 14 achieving complete remission and 7 achieving partial remission. A regimen of steroids combined with tacrolimus was used in 19 patients, resulting in 8 patients achieving complete remission and 10 achieving partial remission. Steroids plus rituximab were given to 5 patients, none of whom achieved complete remission, though 5 attained partial remission.

Renal outcomes are presented in Table 4. Chronic Kidney Disease (CKD) was reported in 7 patients, while 3 patients progressed to End-Stage Renal Disease (ESRD). Complete remission of proteinuria was achieved in 22 patients, and partial remission was observed in another 22 patients.

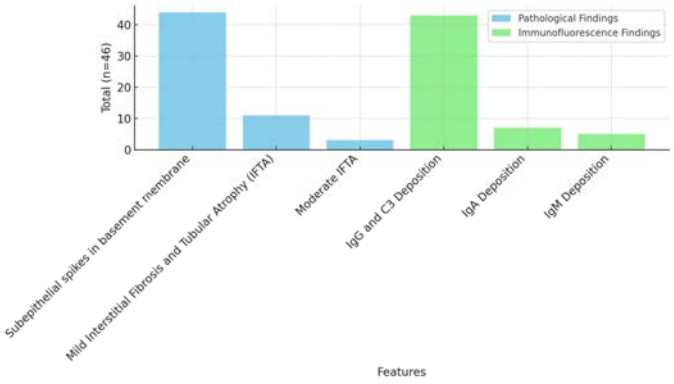

Fig. 1: Pathological and Immunofluorescence Findings in Patients with Membranous Nephropathy

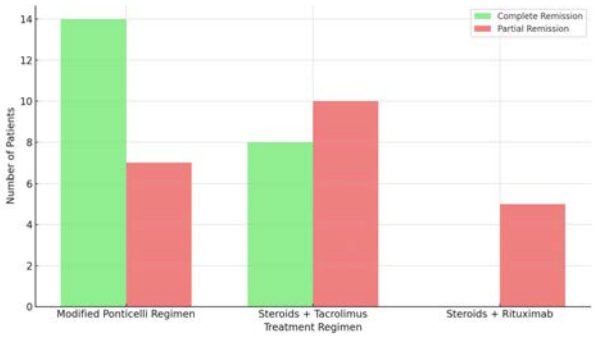

Fig. 2: Treatment Regimens and Outcomes in Membranous Nephropathy

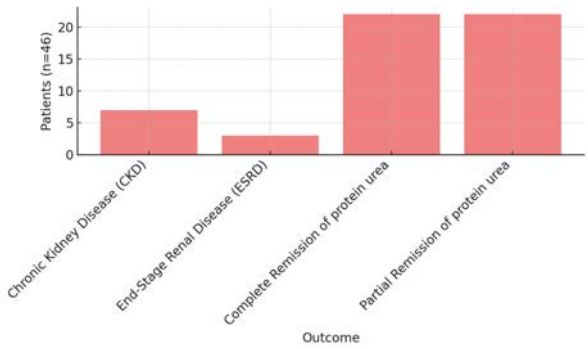

Fig. 3: Renal Outcomes in Patients with Membranous Nephropathy Membranous Nephropathy

Table 1: Demographic and Clinical Characteristics of Patients

Characteristic	Total (n=46)
Gender	
Male	26 (56.5%)
Female	20 (43.5%)
Age	
> 40 years	25 (54.3%)
< 40 years	21 (45.7%)
Secondary Membranous Nephropathy	4 (8.7%)
Lupus Membranous Nephropathy	2 (50% of secondary)
Secondary MN patients < 40 years	3 (75%)
Hypertension at Diagnosis	9 (19.6%)
Microscopic Hematuria	11 (23.9%)
Nephrotic Range Proteinuria	32 (69.5%)
Abnormal Renal Function (Elevated Creatinine)	3 (6.5%)
Diabetes Mellitus	3 (6.5%)
Mean Time from Onset to Biopsy (days)	41.62 ±12.34

Table 2: Pathological Findings

Pathological Feature	Total (n=46)
Subepithelial spikes in basement membrane	44 (95.7%)
Mild Interstitial Fibrosis and Tubular Atrophy (IFTA)	11 (23.9%)
Moderate IFTA	3 (6.5%)
Immunofluorescence Findings	
IgG and C3 Deposition	43 (93.5%)
IgA Deposition	7 (15.2%)
IgM Deposition	5 (10.9%)

Table 3: Treatment Regimens and Outcomes

Treatment Regimen	Patients (n)	Complete Remission (n)	Partial Remission (n)
Modified Ponticelli Regimen	22	14	7
Steroids + Tacrolimus	19	8	10
Steroids + Rituximab	5	0	5

Table 4: Renal Outcomes

Outcome	Patients (n=46)
Chronic Kidney Disease (CKD)	7
End-Stage Renal Disease (ESRD)	3
Complete Remission of protein urea	22
Partial Remission of protein urea	22

(MN) is a prevalent histopathological type in patients biopsied for proteinuria in the Indian subcontinent. Consistent with previous studies, MN was found to be more common in middle-aged and elderly individuals[8,9]. In our study, secondary forms of MN were more frequent in younger patients. The gender distribution showed a higher prevalence in males than females, aligning with earlier reports[8,9].

Approximately 70% of the patients presented with nephrotic syndrome, while the remainder exhibited subnephrotic proteinuria. This distribution is consistent with previous findings, where 80% of patients presented with nephrotic syndrome and 20% with non-nephrotic proteinuria[12]. Pathological features such as tubular atrophy and interstitial fibrosis were strongly associated with disease progression and response to treatment. Higher levels of fibrosis correlated with prolonged control of proteinuria and faster progression to chronic kidney disease (CKD)[11]. Notably, calcineurin inhibitor (CNI)-based regimens were avoided in patients with moderate interstitial fibrosis and tubular atrophy (IFTA), consistent with recommendations by Zhang[10]. The presence of glomerulosclerosis on biopsy also correlated with a faster progression to end-stage renal disease (ESRD)[11].

The Modified Ponticelli regimen was administered to older and middle-aged adults with moderate to severe proteinuria. Our study found that 63.6% of patients treated with steroid and cyclophosphamide achieved complete remission, while 31% attained partial remission. In contrast, younger patients were treated with alternative therapies, such as steroid with Tacrolimus or Rituximab. Complete remission was achieved earlier in patients on the Modified Ponticelli regimen[13]. The combination of Tacrolimus and steroids resulted in complete remission in 42.1% of patients and partial remission in 52%. However, Rituximab and steroid therapy only led to partial remission. The absence of complete remission with Rituximab may be attributed to factors such as Rituximab resistance, inadequate dosing and loss of the drug in the urine in nephrotic patients[14,16].

Interestingly, a combination of Rituximab followed by Tacrolimus maintenance demonstrated better outcomes for proteinuria compared to Rituximab and steroid alone[15,18]. Among our cohort, three patients progressed to ESRD, with a higher likelihood observed in those presenting with heavy proteinuria and renal failure at the time of biopsy. Serum albumin levels at partial remission were also predictive of progression to

ESRD[19]. The treatment responses observed in our study align with findings from previous studies[17-20].

CONCLUSION

This study demonstrates that Membranous Nephropathy (MN) presents with a broad spectrum of clinical manifestations, ranging from subnephrotic proteinuria to overt nephrotic syndrome. While the condition is more commonly diagnosed in older adults, there is a growing number of younger patients identified with primary MN. Despite advancements in treatment options, the Modified Ponticelli regimen remains the standard therapy in resource-limited regions due to its effectiveness. However, it is important to note that this regimen carries risks, including potential sterility and infections. The study underscores the need for accessible and safe treatment alternatives in economically constrained settings.

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