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ORIGINAL RESEARCH

Evaluation of Adult Patients Diagnosed with Idiopathic Membranous Glomerulonephritis: A Single-Center Retrospective Study

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ABSTRACT

Membranous glomerulonephritis (MGN), an immunocompetent nephropathy, is among the most prevalent causes of nephrotic syndrome. While spontaneous remission may occur, there is a risk of developing long-term end-stage renal failure. Treatment approaches for MGN lack full consensus; however, immunosuppressive therapies are critically important. This retrospective, cross-sectional study included 99 patients who visited our center between March 2007 and November 2015 and were diagnosed with MGN. Patient data were scanned and recorded retrospectively from the hospital information system. Of the 99 patients, 43 (43.4%) were female. The mean age of the patients was 46.7 years, with a mean follow-up duration of 18.5 months. A total of 71 patients (71.7%) presented with nephrotic proteinuria, while 57 patients (57.6%) had nephrotic syndrome. Immunosuppressive drugs were prescribed to 85 patients (85.9%). Among those receiving immunosuppressive therapy, 57 patients (79.9%) still exhibited proteinuria at the time of diagnosis. Remission was achieved in 63 patients (74.1%) who underwent immunosuppressive therapy, compared to 10 patients (71.3%) who received conservative treatment. Hypertension and IgG deposition may be associated with a poorer treatment response in patients diagnosed with idiopathic membranous glomerulonephritis (MGN). In summary, MGN is a common cause of nephrotic syndrome that can affect individuals of various ages and genders. Our study identified higher remission rates in patients treated with immunosuppressive therapy, which emphasizes the value of evaluating individual risk factors and selecting appropriate treatment strategies for effective disease management.

Keywords: Membranous glomerulonephritis. Immunosuppressive therapy. Remission.

İdiyopatik Membranöz Glomerülonefrit Tanısı Alan Yetişkin Hastaların Değerlendirilmesi: Tek Merkez Deneyimi

ÖZET

İmmünkompetan bir nefropati olan membranöz glomerülonefrit (MGN), nefrotik sendromun en yaygın nedenleri arasındadır. Spontan remisyon meydana gelebilse de, uzun vadeli son dönem böbrek yetmezliği gelişme riski vardır. MGN tedavi yaklaşımları konusunda tam bir fikir birliği yoktur; ancak immünosüpresif tedaviler kritik öneme sahiptir. Bu retrospektif, kesitsel çalışmaya, Mart 2007 ile Kasım 2015 tarihleri arasında merkezimizi ziyaret eden ve MGN tanısı alan 99 hasta dahil edilmiştir. Hasta verileri hastane bilgi sisteminden retrospektif olarak taranmış ve kaydedilmiştir. 99 hastanın 43'ü (%43,4) kadındı. Hastaların ortalama yaşı 46,7 yıl ve ortalama takip süresi 18,5 ay idi. Toplam 71 hasta (%71,7) nefrotik proteinüri ile başvururken, 57 hastada (%57,6) nefrotik sendrom vardı. 85 hastaya (%85,9) immünosupresif ilaç reçete edildi. İmmünosupresif tedavi görenler arasında 57 hastada (%79,9) tanı anında proteinüri devam ediyordu. İmmünosupresif tedavi uygulanan 63 hastada (%74,1) remisyon sağlanırken, konservatif tedavi uygulanan 10 hastada (%71,3) remisyon sağlandı. Hipertansiyon ve IgG birikimi, idiyopatik membranöz glomerülonefrit (MGN) tanısı alan hastalarda daha zayıf tedavi yanıtıyla ilişkili olabilir. Özetle, MGN, farklı yaş ve cinsiyetlerdeki bireyleri etkileyebilen nefrotik sendromun yaygın bir nedenidir. Çalışmamız, immünosüpresif tedavi gören hastalarda daha yüksek remisyon oranları tespit etmiş olup, bu durum, etkili hastalık yönetimi için bireysel risk faktörlerinin değerlendirilmesi ve uygun tedavi stratejilerinin seçilmesinin önemini vurgulamaktadır.

Anahtar Kelimeler: Membranöz glomerulonefrit. İmmunsupresif tedavi. Remisyon.

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Idiopathic membranous glomerulonephritis (MGN) is a chronic condition characterized by immune complex-mediated damage to the glomeruli and is one of the primary causes of nephrotic syndrome in adults. The hallmark of MGN is the deposition of subepithelial immune complexes along the glomerular basement membrane (GBM), which results in thickening that can be observed using light microscopy[1]. MGN can occur in all ethnic and age groups; however, it has the highest incidence in individuals during their fourth and fifth decades of life. It is rare in children and is the most common cause of nephrotic syndrome in adults[2-4].

The first pathological finding in MGN is the accumulation of subepithelial IgG and complement along the outer surface of the glomerular capillary wall, which appears histologically normal, as typically demonstrated by immunofluorescent staining. MGN begins with the formation of immune complexes between podocytes and the glomerular basement membrane (GBM). This phase is followed by alterations in podocytes, the deposition of new extracellular matrix between and around the immune deposits, and thickening of the GBM, known as membranous change. In some cases, there may also be focal glomerulosclerosis, tubular atrophy, and interstitial fibrosis, depending on the extent of podocyte damage[5,6].

Most patients present with nephrotic-range proteinuria, hypoalbuminemia, and edema. However, a subset may show subnephrotic proteinuria and microscopic hematuria. Initially, renal function is often preserved. Despite intraglomerular complement activation, serum complement levels are normal. Serological markers (e.g., antinuclear antibodies, ANCA, and rheumatoid factor) are absent. At the time of diagnosis, only 10–20% of patients have hypertension[7,8]. The clinical course of MGN is variable. Spontaneous remissions in proteinuria have been reported in 30% of patients. As the severity of proteinuria at presentation increases, the frequency of spontaneous remission appears to decrease. Patients with proteinuria less than 3.5 g/day, no erythrocytes in the urine, no hypertension, normal renal function, and no features suggestive of secondary systemic disease have a positive prognosis. Despite the favorable prognosis data, end-stage renal failure remains a significant cause of glomerulonephritis due to its high prevalence. The KDIGO 2021 guidelines have updated risk stratification and treatment decisions. These guidelines now include serologic testing for PLA2R/THSD7A, proteinuria levels, and trends in renal function[9,10]. Treatment options available encompass supportive therapy, calcineurin inhibitors, cyclophosphamide, and, more recently, rituximab[11].

This study aimed to evaluate the demographic, clinical, histopathological, and treatment outcomes of patients diagnosed with idiopathic MGN in our center and to identify predictors of response to therapy.

Material and Method

This study is a retrospective, cross-sectional descriptive analysis that included patients diagnosed with MGN who were referred to our center between March 2007 and November 2015. Patients with evidence of secondary causes, such as malignancy, autoimmune diseases, or infections, were excluded through comprehensive clinical, laboratory, and radiological evaluations. We reviewed and recorded various patient demographics and clinical data, including age, gender, smoking status, initial examination findings (such as blood pressure and edema), kidney biopsy results, and both initial and follow-up laboratory findings (Table I). These laboratory findings included urinalysis, proteinuria levels, serum urea, creatinine, albumin, immunoglobulin levels (IgG, IgM, and IgA), and complement levels.

Table I. Demographic and clinical characteristics of patients diagnosed with membranous glomerulonephritis.

Characteristic	Value
Number of patients	99
Average age (years)	46
Gender (female)	43(%43)
Clinical findings at diagnosis	
Hematuria	63(%63,6)
Edema	76(%76,8)
Hypertension	35(%35,3)
Nephrotic Syndrome	57(%57,6)
Laboratory findings at diagnosis	
Renal dysfunction (GFR<60 ml/min)	31(%31,3)
Hypertriglyceridemia	60(%60,6)
Hypercholesterolemia	78(%78,8)
Hypoalbuminemia	72(%72,7)

Treatment protocols were documented, categorizing patients based on their treatment regimens: those receiving only steroids, those receiving steroids in combination with cyclophosphamide, those receiving steroids with cyclosporine, and those managed with conservative treatment. Kidney biopsy findings were evaluated using light microscopy and immunofluorescence. Light microscopy assessed various parameters, including glomerular count, sclerotic glomerular count, basement membrane thickening, interstitial inflammation, fibrosis, vascular changes, and tubular atrophy. Immunofluorescence staining was performed on all samples using markers such as IgG, IgM, IgA, C3q, C1q, and fibrinogen.

Patients were divided into three age groups: ≤30 years, 31-60 years, and >60 years. Treatment responses were evaluated based on 24-hour urine protein levels following treatment. Patients were classified as achieving complete remission, partial remission, or no response to treatment. Complete remission was defined as a reduction in 24-hour urine protein excretion to less than 0.5 g/24 hours, while partial remission was defined as a decrease of more than 50% from the initial proteinuria level.

Statistical analysis

Descriptive statistical methods, including mean, median, frequency, standard deviation, and ratios, were utilized to analyze categorical variables. For groups of variables that did not exhibit a normal distribution, Pearson's chi-square test was employed. Statistical analysis was conducted using SPSS (IBM Corp. Release 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.), with differences deemed significant at a p-value of less than 0.05.

The chi-square test was utilized for comparing categorical variables, while continuous variables were analyzed using ANOVA. To reduce the likelihood of false positives from multiple comparisons, the Bonferroni correction was applied when appropriate.

Results

The study included 99 patients who were diagnosed with kidney biopsies between March 2007 and November 2015. All patients underwent the necessary examinations for their initial evaluation. Their ages ranged from 18 to 74 years, with a mean age of 46.7 ± 13.6 years. Specifically, 14 cases (14.1%) were in the 18–30 age group, 67 cases (67.7%) were aged 31–60 years, and 18 cases (18.2%) were over 60 years of age. Among the patients, 43 (43.4%) were female and 56 (56.6%) were male. Regarding smoking history, 32 patients (32.3%) reported having smoked, which included 26 males and 6 females. The average follow-up period for the patients was 18.5 months, with a minimum of 3 months and a maximum of 190 months.

The histopathological analysis of 93 patients who underwent kidney biopsy and pathology results at our center is shown in Table II. The immunofluorescence findings of the kidney biopsy are shown in Table III.

The histopathological analysis of 93 patients who underwent kidney biopsy, the immunosuppressive treatment protocols implemented for these patients, and the evaluation of treatment responses are detailed in Table IV. Among the patients, 85 (85.9%) received immunosuppressive treatment, with an average treatment duration of 12 months (3,100). Treatment responses were assessed based on 24-hour urine protein levels following the treatment. Complete remission was defined as a reduction in 24-hour urine protein excretion to less than 0.5 g/24 hours, while partial remission was characterized by a decrease of more than 50% from the baseline proteinuria level.

Table II. Histopatholological findings in renal biopsies (n=93)

Finding	n(%)
Basement membrane thickening	92 (98,9)
Interstitial inflammation	87 (%93,5)
Interstitial fibrosis	49(%52,6)
Mesangial proliferation	3 (%3,22)
Tubular atrophy	64(%68,8)
Vascular changes	40(%43)

Table III. Immunofluorescence staining results.

Markers	Positive n(%)
IgG	86(%92,4)
IgM	19(%20,4)
IgA	14(%15)
C3c	43(%46,2)
C1q	3(%3,2)
Fibrin	12(%12,9)

Table IV. Treatment modalities and treamtment outcomes.

Treatment Group	n	Complete remission	Partial remission	No response	p-value
Steroid Only	37(%37,4)	14(%37,4)	13(%35,1)	10(%27,5)	0,441
Steroid+Cyclophosphamide	36(%36,4)	15(%41,6)	14(%38,8)	7(%19,6)	0,429
Steroid+Cyclosporine	12(%12,1)	4(%33,3)	3(%25)	5(%41,7)	0,426
Conservative	14(%14,1)	2(%14,2)	8(%57,1)	4(%28,7)	0,264

Note: p-values reflect overall chi-square comparisons; Bonferroni correction was applied to account for multiple testing.

The effect of demographic and clinical data at the time of application on treatment outcomes is summarized in Table V. An analysis of the demographic data showed no statistically significant impact of age, gender, or smoking status on treatment responses. Likewise, the clinical data evaluated at the time of presentation revealed no statistically significant effects of hematuria, edema, or nephrotic syndrome on treatment response. However, the presence of hypertension at the time of application was found to have a statistically significant effect on treatment response (p=0.046) (Table V). A post-hoc chi-square analysis indicated that the difference was specifically between the group that experienced a partial response to treatment and the group that exhibited no response (p=0.031).

Table V. The effect of demographic data and clinical and laboratory data at the time of admission on treatment outcome.

	Complete remission	Partial remission	No response	p-value
Average age	48,34	44,34	48,03	0,395
Female	18(%41,8)	16(%37,2)	9(%21)	0,415
Male	17(%30,4)	22(%39,2)	17(%30,4)	0,415
Smoking	13(%40,6)	11(%34,4)	8(%25)	0,741
Hematuria	21(%33,3)	26(%41,3)	16(%25,4)	0,731
Edema	20(%30,7)	23(%35,4)	22(%33,9)	0,302
Hypertension	14(%40)	8(%22,8)	13(%37,1)	0,046*
Nephrotic syndrome	20(%35,1)	23(%40,3)	14(%24,6)	0,957
Renal dysfunction	11(%35,4)	14(%45,2)	6(%19,4)	0,620
Hypertriglyceridemia	23(%38,4)	21(%35)	16(%26,6)	0,561
Hypercholesterolemia	30(%38,5)	30(%38,5)	18(%23)	0,570
Hypoalbuminemia	27(%37,5)	28(%39)	17(%23,5)	0,858

Note: p-values reflect overall chi-square comparisons; Bonferroni correction was applied to account for multiple testing. *Statistically significant ($p<0.05$)

The effects of biopsy data on treatment outcomes are shown in Table VI. A statistically significant effect of IgG accumulation in immunofluorescence on response to treatment was detected ($p=0.027$). When examining which groups this difference originated from, it was seen to be between the group that responded partially to treatment and the group that did not respond ($p=0.007$).

Table VI. Effect of biopsy data on treatment outcome.

	Complete remission	Partial remission	No response	p-value
Mesangial proliferation	1(%33,3)	1(%33,3)	1(%33,3)	0,253
Basement membrane thickening	33(%35,8)	35(%38)	24(%26,2)	0,526
Interstitial inflammation	29(%33,3)	34(%39)	24(%27,7)	0,191
Interstitial fibrosis	18(%36,8)	19(%38,7)	12(%24,5)	0,944
Vascular changes	14(%35)	13(%32,5)	13(%32,5)	0,382
IgG	31(%36,1)	32(%37,2)	23(%26,7)	0,027*
IgM	5(%26,4)	8(%42,1)	6(%31,5)	0,406
IgA	6(%42,9)	6(%42,9)	2(%14,2)	0,752
C3c	13(%30,3)	16(%37,2)	14(%32,5)	0,438
C1q	2(%66,6)	1(%33,3)	0(%0)	0,893
Fibrin	4(%33,3)	4(%33,3)	4(%33,3)	0,851

Note: p-values reflect overall chi-square comparisons; Bonferroni correction was applied to account for multiple testing. *Statistically significant ($p<0.05$)

Additionally, age was categorized into three groups (≤30, 31–60, and >60 years) to assess treatment response. However, no statistically significant difference was observed among age categories.

Although hypertension and IgG deposition initially appeared to be associated with poor treatment response, these associations did not remain statistically significant after Bonferroni correction, underscoring the need for cautious interpretation of subgroup analyses.

Discussion and Conclusion

Despite advancements in diagnosis and treatment, idiopathic membranous glomerulonephritis (MGN) remains a major cause of end-stage renal disease. In our cohort, the average baseline creatinine level was within the normal range, consistent with the indolent progression of MGN. The majority of patients (57%) presented with nephrotic syndrome, in line with previous literature.

Although smoking is considered a risk factor for glomerular injury, our study did not observe a significant association between smoking status and treatment response[12,13]. This limitation may be attributed to the lack of data on smoking intensity and duration. Given the increased risk of malignancy in smokers with MGN, closer monitoring is warranted.

Histopathological findings were generally consistent with previous reports[14-19]. While IgG deposition appeared to correlate with reduced treatment response, no other biopsy features including interstitial fibrosis, tubular atrophy, or vascular changes showed significant predictive value. Subtyping of IgG or the inclusion of modern biomarkers like anti-PLA2R and THSD7A antibodies could have strengthened the pathological correlations[9,10]. Unfortunately, these tests were not routinely available during the study period.

Although hypertension and IgG deposition initially showed associations with poorer treatment response, these did not remain statistically significant after Bonferroni correction. This highlights the importance of cautious interpretation, particularly when multiple subgroup analyses are conducted.

Most patients (85.9%) received immunosuppressive therapy, with an overall response rate (complete or partial remission) of 74.1%. However, 26% failed to respond. New biomarker-focused approaches offer higher success rates with fewer side effects than immunosuppressive treatments by optimizing the treatment of high-risk patients. According to findings in the current literature, the widespread use of treatment options such as rituximab in MGN patients has improved treatment compliance and patient comfort[20,21].

The lack of significant differences between treatment groups may reflect the relatively small subgroup sizes. However, the overall remission rate is consistent with previous reports.

This study has several limitations. It was retrospective and single-centered, with missing data for some patients. The relatively short follow-up period (average 18.5 months) limited the ability to assess

long-term renal outcomes. In addition, treatment side effects were not systematically documented, preventing an evaluation of risk-benefit balance. This created a gap in analyzing the balance between treatment efficacy and side effects. Recent KDIGO 2021 guidelines emphasize individualized risk-based therapy, including the use of rituximab, which was not available during our study period but holds promise in refractory or high-risk cases.

Limitations include retrospective design, absence of biomarker data (PLA2R, THSD7A), and single-center setting. Nonetheless, the identification of hypertension and IgG positivity as adverse prognostic factors may aid clinical risk stratification.

In conclusion, while our study reinforces some established clinical and pathological features of idiopathic MGN, the absence of significant predictors after correction for multiple comparisons suggests a need for larger, biomarker-integrated studies. Incorporating modern diagnostics and risk stratification tools may help guide more individualized treatment approaches in the future.

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Idea and design: C.P, A.Y., A.E.; Data collection and processing: C.P, A.Y., A.E.; Analysis and interpretation of data: C.P, A.Y., A.E.; Writing of significant parts of the article: C.P, A.Y., A.E.
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