Ukrainian Journal of Nephrology and Dialysis
Scientific and Practical, Medical Journal

**Founders:**

- State Institution «Institute of Nephrology NAMS of Ukraine»
- National Kidney Foundation of Ukraine

**ISSN 2304-0238;**
**eISSN 2616-7352**

**Journal homepage: https://ukrjnd.com.ua**

**Research article**

**doi: 10.31450/ukrjnd.4(68).2020.04**

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# Reassessment of renal prognosis in patients with membranoproliferative glomerulonephritis according to the new pathologic classification

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Citation: Parmaksız E, Meşe M. Evaluation of patients with membranoproliferative glomerulonephritis according to the new histomorphological classification. Ukr J Nephr Dial. 2020;4(68):23-28. doi: 10.31450/ukrjnd.4(68).2020.04

**Abstract.** *Membranoproliferative glomerulonephritis (MPGN) is a heterogeneous disease characterized by a morphological injury pattern that can be seen under various disease conditions that share common pathogenic mechanisms. In this study, we analyzed clinical features, pathological findings, long-term kidney outcomes according to the new pathohistological classification of MPGN.*

*Methods. This retrospective study included 20 CKD patients with biopsy-proven MPGN that had been diagnosed between 2011 and 2019. We reclassified the patterns of MPGN as immune-complexes mediated (ICM) and complement-mediated (CM) according to the new classification.*

*Results. The level of daily proteinuria was lower in the ICM MPGN than the CM MPGN group but was not statistically significant at the end of the study. Histopathologically, the difference in C3 staining was found between the patients with ICM and CM MPGN. At the end of the follow-up period, no patients developed end-stage renal disease, and no death occurred in response to treatment in the ICM MPGN group. In the CM MPGN group, 2 patients evolved to end-stage renal disease and 1 of them had renal transplantation.*

*Conclusion. Larger sample size and longer follow-up may change the relationship between histological factors, treatment strategies, and kidney outcomes. We believe that the use of the new diagnostic approach that applies to the ICM MPGN and CM MPGN will help nephrologists to improve treatment options and renal outcomes for patients with MPGN.*

**Key words:** *membranoproliferative glomerulonephritis, classification, treatment, kidney outcomes.*

**Article history:**

*Received April 12, 2020*
*Received in revised form September 29, 2020*
*Accepted October 19, 2020*

**Conflict of interest statement.** The authors declare no competing interest.



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УДК: 616.611-002-052

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# Переоцінка ниркового прогнозу пацієнтів з мембранопроліферативним гломерулонефритом на основі нової патоморфологічної класифікації

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**Резюме.** *У цьому дослідженні ми проаналізували клінічні особливості, патоморфологічні дані та віддалені результати лікування хворих на мембранопроліферативний гломерулонефрит (МПГН) відповідно до нової класифікації.*

*Методи. Нами проведено ретроспективне, одноцентрове дослідження із залученням медичної документації 20 пацієнтів з морфологічно верифікованим діагнозом МПГН, який був встановлений у період між 2011 та 2019 рр. Ми перекласифікували патоморфологічні патерни як імунно-комплексний (ІК) МПГН та комплемент-асоційований (КА) МПГН відповідно до нової класифікації.*

*Результати. Рівень добової протеїнурії був нижчим у хворих на ІК МПГН у порівнянні з пацієнтами з КА МПГН, але не статистично значущо не відрізнявся на час закінчення дослідження. Гістопатологічно визначено статистично значущу різницю у С3 між пацієнтами обох груп. У групі ІК МПГН у жодного пацієнта не розвинулась термінальна стадія хронічної хвороби нирок, тоді як у групі КА МПГН 2 пацієнти еволюціонували до термінальної стадії хронічної хвороби нирок, одному з яких виконано трансплантацію нирки.*

*Висновок. Більша вибірка пацієнтів та триваліший період спостереження можуть змінити взаємозв'язок між патоморфологічними характеристиками МПГН, стратегіями лікування та нирковим прогнозом. Ми вважаємо, що використання нового діагностичного підходу, який застосовується до ІК та КА МПГН, допоможе нефрологам поліпшити можливості лікування та нирковий прогноз для пацієнтів з МПГН.*

**Ключові слова:** *мембранопроліферативний гломерулонефрит, класифікація, лікування, прогноз.*

**Introduction.** Membranoproliferative glomerulonephritis (MPGN) is a heterogeneous disease characterized by a morphological injury pattern that can be seen in a variety of disease conditions that share common pathogenic mechanisms [1]. MPGN has been reported in about 7–10% of renal biopsy cases [2]. MPGN refers to the histological model of glomerular disease, characterized by diffuse mesangial hypercellularity, endocapillary proliferation, lobulation of the glomerular pinch and division of the glomerular capillary wall [3]. A new classification by Sethi and Fervenza takes advantage of this improved knowledge by defining MPGN as immune complex (IC) disease and dominant complement (C) accumulation [4]. Immune complexes-mediated (ICM) MPGN shows immunoglobulin (Ig) and / or complement factors in immunofluorescent (IF) findings, while complement-mediated (CM) MPGN shows complement factors and Ig deficiency in IF findings [5]. The presence of both immunoglobulin and complement (especially the classical path component) accumulation by (IF) microscopy indicates an immune complex etiology and should direct the investigation into causes such as infection, autoimmune disease, paraproteinemia, carcinoma, or drug reaction [6, 7]. CM MPGN stained for C3 in the IF findings and Ig deficient was defined as C3 glomerulopathy in the new classification [8]. C3 glomerulopathy can also be classified into C3 glomerulonephritis and dens deposited disease [9].

The present study aimed to reevaluate all biopsies diagnosed with MPGN in our hospital and reclassified them to IC or CP. Moreover, in this study, we analyzed clinical features, pathological findings and long-term kidney outcomes according to the new classification of MPGN.

**Materials and Methods.** The study was carried out at the Kartal Dr Lütfi Kırdar City Hospital and approved by the local Ethical Committee (approval no: 2020.514.181.18 approval date: 07.07.2020). The patients diagnosed with MPGN between 2012-2019 were reevaluated retrospectively. All the diagnoses of MPGN were biopsy-proven. Renal biopsy was obtained in two vessels and at least 10 glomeruli for light microscopy and immunofluorescence. Each biopsy sample was evaluated with light microscopy (LM), IF (for IgG, IgM, IgA, C3, C1q, kappa and lambda) per standard techniques and had sufficient tissue for evaluation. IF semiquantitative intensity scoring at Stanford ranges from 0 to 4+. Using the Sethi criteria, the cohort was divided into two groups, "ICM MPGN" was identified by ≥ 2+ immunoglobulin staining, or CM MPGN was assigned when the Ig staining was ≤ 1+. Mesangial cell proliferation in each patient was semiquantitatively estimated as follows: grade 1, mild proliferation; grade 2, moderate proliferation; grade 3, severe proliferation. The extent of interstitial fibrosis was graded into four categories according to the percentage area of fibrotic lesions relative to the total cortical area: grade 0, none; grade 1, 1–25%; grade 2, 26–50%; grade 3, >50%.

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Arteriosclerotic changes were also evaluated using a similar grading scale: grade 0, no abnormality; grade 1, present. The recorded IF microscopy findings included staining force for IgG, IgA, IgM, C3, C1q, kappa, lambda. The intensity of glomerular mesangial proliferation was graded as follows: 1, mild; 2, moderate; 3, severe (graded 0–3 +).

Cases of MPGN clinically known to be related to systemic lupus erythematosus (or other connective tissue disorders), infections including hepatitis B, C, paraproteinemia or B cell lymphoma or plasma cell dyscrasia were excluded from the study cohort. The clinicopathological findings and prognosis of patients were compared between ICM- and CM MPGN.

Clinical and laboratory data during the initial kidney biopsy were obtained manually from the patient's medical records and included age, gender, blood pressure, hematuria, proteinuria, serum creatinine, serum albumin, serum C3, and treatment. The following laboratory tests were performed according to standard hospital procedures: measurement of 24-h urinary protein excretion (UP g/day); urinary red blood cell count per high power field (U-RBC/HPF); measurement of serum creatinine (sCr, mg/dl); estimated glomerular filtration rate (eGFR, ml/min); serum albumin (Alb, g/dl); C3 (mg/dl). Renal status was recorded at the last clinical follow-up. Microscopic hematuria was defined as > 5 red cells per HPF in microscopic examination. The patients with nephrotic syndrome (UP ≥ 3.5 g/day) were given immunosuppressive therapy.

Statistical analysis was performed using the SPSS package program. For the statistical analysis, we used the Student's t-test and the data expressed as mean and standard deviation (M ± SD). Categorical variables were expressed as proportions. The Chi-square tests ($\chi 2$) were used to compare 2 groups.

**Results.** The clinical and laboratory characteristics of the included patients are summarized in Table 1.

*Table 1*

**The patients' clinical and laboratory findings**

| | ICM MPGN (n = 14) | CM MPGN (n = 6) | P-value |
|---|---|---|---|
| Age | 46.93±14.31 | 36.50±8.45 | 0.09 |
| Gender (F/M) | 6/8 | 3/3 | 0.77 |
| Creatinine (first) (mg/dl) | 2.00±2.70 | 1.21±0.76 | 0.68 |
| Creatinine (end) (mg/dl) | 1.09±0.44 | 1.99±2.39 | 0.90 |
| Proteinuria (first) (g/day) | 5.30±3.4 | 4.1±2.9 | 0.93 |
| Proteinuria (end) (g/day) | 2.2±1.4 | 2.7±1.7 | 0.13 |
| Hematuria (present/not) | 13/1 | 6/0 | 0.51 |
| Serum albumin (first) (g/dl) | 3.11±0.54 | 2.90±0.48 | 0.47 |
| Serum albumin (end) (g/dl) | 3.96±0.52 | 3.66±0.41 | 0.21 |
| C3 (first) | 1.40±0.30 | 1.40±0.30 | 0.91 |
| C3 (end) | 1.46±0.26 | 1.61±0.16 | 0.15 |
| Hypertension (present/not) | 13/1 | 5/1 | 0.52 |
| Follow-up period (month) | 66.42±33.32 | 55.0±24.71 | 0.54 |

Although there was no statistically significant difference in clinical and laboratory data between the patients of ICM and CM groups, the creatinine value decreased in the ICM MPGN group, while the creatinine value increased in the CM MPGN group at the end of the study period. The PU level was also lower in the patients of ICM MPGN compared with the patients of the CM MPGN group, but it was not statistically significant at the end of the study.

As presented in Table 2, a statistically significant difference in C3 staining was found between the groups.

*Table 2*

**Histopathological findings of the patients with MPGN**

| | ICM MPGN (n = 14) | | CM MPGN (n = 6) | | P-value |
|---|---|---|---|---|---|
| Global sclerosis | | | | | 0.06 |
| Absent | 11 | 78.6% | 2 | 33.3% | |
| Present | 3 | 21.4% | 4 | 66.7% | |
| Crescent | | | | | 0.52 |
| Absent | 13 | 92.9% | 5 | 83.3% | |
| Present | 1 | 7.1% | 1 | 16.7% | |
| Mesengial proliferation(%) | | | | | |
| Mild | 3 | 21.4% | 0 | | |
| Moderate | 8 | 57.1% | 5 | 83.3% | 0.21 |
| Severe | 3 | 21.4% | 1 | 16.7% | 0.81 |
| Interstitial fibrosis(%) | | | | | |
| None | 12 | 85.7% | 3 | 50.0% | 0.09 |
| 1-25 | 2 | 14.3% | 3 | 50.0% | |
| 26-50 | 0 | | 0 | | |
| >50 | 0 | | 0 | | |
| Arteriolar sclerosis | | | | | 0.09 |
| Absent | 12 | 85.7% | 3 | 50.0% | |
| Present | 2 | 14.3% | 3 | 50.0% | |
| IgG | 14 | 100% | 0 | | |
| IgA | 8 | 57.1% | 0 | | |
| IgM | 8 | 57.1% | 0 | | |
| C3 | 6 | 42.9% | 6 | 100% | 0.02 |
| C1q | 4 | 28.6% | 0 | | |
| Kappa | 2 | 14.3% | 0 | | |
| Lambda | 3 | 21.4% | 0 | | |

RAA as a treatment option was used in 13 (92.9%) patients in ICM MPGN, while RAA was prescribed for all patients in the CM MPGN group. Methylprednisolone in a dose 1 g per 3 days was used in both groups. 13 (92.9%) patients of the CM MPGN group used methylprednisone and all the patients of the CM MPGN group. Methylprednisone treatment was started in dose 0.8 mg/ kg/day and decreased at the end of 2 months and discontinued in 6 months. Cyclophosphamide was applied to 10 (71.4%) patients in the ICM MPGN group and 5 (83.3%) patients of the CM MPGN group.

Finally, in the ICM MPGN group, none of the patients neither developed end-stage renal failure nor died in response to the treatment. In the CM MPGN group, 2 patients evolved to end-stage renal disease and 1 of them underwent kidney transplantation.

**Discussion.** Several recent studies have greatly improved our understanding of MPGN's pathophysiology and emphasized frequent association with complement activation or lymphoproliferative disease disorders [10]. Due to these findings, a new classification divides MPGN into cases that are CM or ICM MPGN. This study provides a detailed explanation of the differences in clinical and histopathological features observed in ICM and CM MPGN patients. Viswanathan et al calculated the CM MPGN incidence in all renal biopsies of 0.7% [11]. Indian study conducted by Himamani showed an incidence of 14% among all MPGN cases [12]. In our study, the percentage of CM MPGN covers 30% of all MPGN patients. Servais et al. reported that 71% of CP-mediated glomerulonephritis patients had genetic disorders and/or autoantibodies. Genetic abnormalities such as variants of complement factor H (CFH), complement factor I (CFI), membrane cofactor protein (MCP), and autoantibodies, such as anti-C3-Nef (C3 nephritic factor) and anti-factor H antibodies, stabilize C3 convertase (C3bBb) and amplify conversion from C3 to the active molecule C3b in

the fluid phase of complement activation [13]. Genetic studies of complement factors could not be performed due to the technical inadequacy of CM MPGN.

Serum C3 was significantly lower in the CM MPGN group than in the ICM MPGN group. This fact is evidence of a more active alternative complement pathway in the fluid phase [14]. In our study, there was no difference in serum C3 levels between IC MPGN and CM MPGN at the time of diagnosis and after the treatment. The small sample size might result in this conclusion.

In addition, there were no differences in sclerosis or necrotic glomeruli, crescent presence, degree of mesangial proliferation, interstitial fibrosis percentage, and other pathological findings in terms of arteriolar sclerosis. These results suggest that there is no significant difference in complement activation of the solid phase in local tissue, and therefore no equivalence in other pathological findings and kidney prognosis [15]. In our study, light microscopy findings had similar characteristics in both groups.

In patients with ICM MPGN, targeting the treatment of the underlying disease (hepatitis, lupus, dysproteinemia) is effective. Otherwise, immunosuppressive agents are widely used in the treatment of MPGN [16, 17]. The secondary MPGN cases were not included in our study population.

Steroids are the cornerstone therapy for MPGN even when other immunosuppressive agents are used together. In terms of immunosuppressive agents, only a few reports are showing that cyclophosphamide (CYC) is effective for patients with MPGN other than steroids [18, 19]. The mechanism of conventional therapy for solid-phase complement activation remains unclear. AP irregularity also occurs in CM MPGN, and the establishment of treatment for complement activation in the solid phase is expected in recent years [20]. Complement-mediated type is important because complement-targeting therapies can be developed as potential disease-modifying agents. Eculizumab is one of the available anti-complement treatments. Bomback et al found promising results using eculizumab in c3 glomerulopathies in natural and allograft biopsies [21, 22]. In our study, most of the patients in both groups received steroid and cyclophosphamide therapy as immunosuppressive therapy. Although there was no statistical difference in response to treatment, at the end of the study, ICM MPGN cases were found to have lower creatinine and proteinuria values compared to CM MPGN, Considering this difference, it may be thought that giving specific agents effective to the alternative complement pathway to the CM MPGN group may affect the treatment results. Eculizumab treatment was given to a patient who developed posttransplant CM MPGN, and improvement in proteinuria and kidney function tests of the patient was observed during the following treatment. Nephrologists should consider checking alternative complementary pathway defects in patients with CM MPGN in IF.

**Limitations.** It was a small sample size retrospective study performed in a single-center, and, thus, our results will need to be confirmed in full-scale studies. There was no study on the evaluation of alternative path abnormalities. We also believe that the choice of alternative pathway-specific agents can select the treatment selection and outcomes of CM MPGN relationships. Larger sample size and longer follow-up may change the relationship between histological factors, treatment strategies, and kidney outcomes.

**Conclusions.** In conclusion, we believe that the use of the new diagnostic approach that applies to the ICM MPGN and CM MPGN will help nephrologists to improve treatment options and renal outcomes for patients with MPGN.

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