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THE IMPORTANCE OF GLOMERULAR C3 ACCUMULATION IN ELDERLY PATIENTS WITH PRIMARY MEMBRANOUS NEPHROPATHY

İLERİ YAŞLI PRİMER MEMBRANÖZ NEFROPATİLİ HASTALARDA GLOMERÜLER C3 BİRİKİMİNİN ÖNEMİ

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ABSTRACT

Objective: The purpose of this study was to investigate the impact of glomerular C3 accumulation density on clinical, histopathological parameters and outcomes in elderly (>60 years) individuals with primary membranous nephropathy (PMN).

Material and Methods: In this study, we examined the patients (n=105) in two groups according to the C3 staining density in kidney biopsy samples as low intensity (C3: 1+; LI group) and high intensity (C3: 2+ or C3: 3+; HI group). The primary endpoint of our study was the end-stage renal disease, and the secondary endpoints were the development of partial remission (PR) or complete remission (CR).

Results: At the end of the follow-up (mean 30.6 months), more patients achieved the primary endpoint, and fewer patients achieved the secondary endpoints in the HI group compared to the LI group. (p=0.015 and p=0.016, respectively). Moreover, the glomerular filtration rate (eGFR) was lower (p<0.001), and proteinuria was higher in the HI group (p=0.018). Kaplan-Meier survival analysis revealed that renal survival (p=0.031) was lower in the HI group compared to the LI group. In the multivariate logistic regression analyses, no predictive parameters could be detected for the endpoints.

ÖZET

Amaç: Bu çalışmada, primer membranöz nefropatili (PMN) yaşlı (>60 yaş) hastalarda glomerüler C3 birikim yoğunluğunun klinik, histopatolojik özellikler ve hastalığın seyri üzerindeki etkilerini araştırmayı amaçladık.

Gereç ve Yöntem: Bu retrospektif gözlemsel çalışmaya dahil ettiğimiz PMN'li 105 hastayı böbrek biyopsi örneklerinde C3 birikiminin yoğunluğuna göre düşük yoğunluklu (C3 1+; LI) ve yüksek yoğunluklu (C3 2+ veya C3 3+; HI) olmak üzere iki grupta inceledik. Birincil sonlanım noktası son evre böbrek hastalığı, ikincil sonlanım noktaları ise tam (CR) veya kısmi remisyon (PR) idi.

Bulgular: İzlem sonunda (ortanca 30,6 ay), HI grubunda LI grubuna kıyasla daha fazla hasta birincil noktaya ulaşırken daha az hasta ikincil son noktalara erişti (sırasıyla p=0,015 ve p=0,016). Ayrıca HI grubunda LI grubuna göre glomerüler filtrasyon hızı (eGFR) daha düşük (p<0,001), proteinüri ise daha fazlaydı (p=0,018). Kaplan-Meier analizlerinde böbrek sağ kalımının (p=0,031) HI grubunda LI grubundan daha düşük olduğu saptandı. Çok değişkenli lojistik regresyon analizlerinde, son noktalar öngördürücü bir parametre saptanamadı.

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Conclusion: Intense glomerular C3 deposition in elderly (>60 years) patients with PMN may be related to poor clinical outcomes.

Keywords: Complementary system, C3, older age, membranous nephropathy

Sonuç: Yoğun glomerüler C3 birikimi, PMN'li yaşlı hastalarda olumsuz klinik sonuçlarla ilişkilidir.

Anahtar Kelimeler: Kompleman sistemi, C3, ileri yaş, membranöz nefropati

INTRODUCTION

Primary membranous nephropathy (PMN) is one of the most important etiologies of nephrotic syndrome in the non-diabetic adult population. Although it was previously known as an idiopathic disease, this approach has changed in the last decade. Today, the dominant role of autoreactive antibodies in the pathogenesis of the disease has been proven (1). It occurs in 25% of patients due to infections, drugs, systemic diseases such as systemic lupus erythematosus, and malignancies (secondary membranous nephropathy-MN) (2-4). The most common autoantibodies in PMN are M-type phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain-containing 7A (THSD7A); the number of responsible autoantibodies is increasing day by day (5-7). Although various risk factors such as older age, decreased GFR at diagnosis, male gender, and persistent heavy proteinuria have been identified, the clinical course of PMN is still quite interesting (8-10). Spontaneous complete remission develops in approximately 33% of the patients, and in 33% of the patients, proteinuria persists, albeit at varying levels. The remaining develop end-stage renal disease within ten years despite all treatments (11).

The immune deposits in PMN are rich in essential parts of the human complement system, such as C3 and C5b-9, indicating that the complement system has a vital role in PMN (12, 13). In PMN, immunofluorescent staining (IF) is characteristically detected for C3 and C4d, while C1q is negative (13). The process that begins with autoantibodies to cause glomerular damage results in building of a membrane attack complex (MAC) (13). It is accepted that the complement system activation in PMN is not via the classical pathway (CP). Anti-PLA2R IgG, which has an essential role in pathogenesis, predominantly activates mannose-binding lectin (MBL) or alternative complement (AP) pathways (14). On the other hand, glomerular MBL and C4b accumulation are also present in PMN (14). The accumulation of C1q, C3, C4, complement factor B (CFB), MBL, and C5b-9 accompanying the deposition of IgG in secondary MN supports the role of AP and MBL in the pathogenesis (14). Despite these data on the interaction between MN and the complement system, data on glomerular C3 accumulation, disease course, and prognosis are limited. However, in one study, the intensity of glomerular C3 accumulation was predictive of the development of kidney failure (15).

It is generally accepted that ageing activates the complement system (16). There is a strong relationship between the complement system activation and physiological ageing, as well as ageing diseases such as Alzheimer's and age-related macular degeneration. On the other hand, the complement system modulates many soluble and circulating factors responsible for renal ageing (17, 18).

Therefore, in this retrospective single-center study, our purpose was to examine the impact of C3 density on clinical, pathological parameters and endpoints in elderly (>60 years) patients with PMN.

MATERIAL AND METHODS

Study design

Patients over 60 years of age with biopsy-confirmed PMN, followed for at least six months between 1996 and 2019, were included after obtaining written informed consent. Patient information was gathered from hospital medical records. Patients with rheumatic diseases, hepatitis B or hepatitis C virus infections, cancers, or other secondary MN-related systemic diseases, and with an eGFR <15 ml/min/1.73 m^2 were excluded. In order to exclude malignancies in the elderly patient group, endoscopy, colonoscopy, thorax and abdominal tomography scans were performed and prostate-specific antigen levels were measured.

Standard laboratory methods were used for hemogram and biochemical parameters. The blood pressure (BP) measurements of the patients were measured twice with a manual sphygmomanometer and the higher value was recorded. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculation was used for eGFR (19). Proteinuria was detected by urine protein-creatinine ratio (uPCR, g/g) in the first urine in the morning.

We examined the patients in two groups according to the density of C3 accumulation glomerular C3 immunofluorescence staining: Low-intensity (C3: 1+; LI group) and high density (C3: 2+ or C3: 3+; HI group).

All patients with no contraindications received a renin-angiotensin aldosterone system blocker (angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs). The low/intermediate-risk patients received only supportive treatments for six months. Immunosuppressive therapies (cyclophosphamide or calcineurin inhibitors and corticosteroids) were given to patients un-

responsive to these treatments (19). Patients diagnosed after 2012 were treated based on the treatment recommendations in the Renal Disease Improvement Global Outcomes (KDIGO) Glomerulonephritis Clinical Practice Guidelines (20). The study was performed in accordance with the Declaration of Helsinki and approved by Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 04.01.2013, No: 2013/11).

Study outcomes

The primary endpoint of the study was end-stage kidney disease. The secondary endpoints were complete remission (CR) or partial remission (PR). Proteinuria <0.3 g/g with eGFR of ≥60 mL/min/1.73 m2 (or a recovery of ±15% in those patient with eGFR <60 mL/min/1.73 m2) was defined as CR. PR was described as follows. 1- Proteinuria drop of >50% with proteinuria level of <3.5 g/g in those patients with nephrotic proteinuria at diagnosis 2- Recovery or stabilization (±25%) in eGFR.

The period between the histological diagnosis and the last clinical visit or the development of end-stage renal disease was considered the follow-up period. Demographic characteristics, clinical and histopathological findings (interstitial fibrosis, tubular atrophy, and immunofluorescent staining intensity pattern for IgG and C3) were analyzed.

Histopathological evaluation

A semiquantitative scale was used to define the fluorescence intensity of IgM, IgA, IgG, C3, C1q, lambda and kappa from 0 to 3. According to this scale, 0 is negative; 1 is weak; 2 is medium; 3 is strong. These lesions were grouped into four grades according to the Ehrenreich and Churg's criteria (21). Similarly, tubular atrophy and interstitial fibrosis were classified using a semiquantitative scale as follows: 1- mild, <25% of interstitium, 2- moderate, 25–50%, 3- severe >50%.

Statistical analyses

Quantitative parameters were depicted using standard deviations or medians with interquartile range (IQR, 25-75). Categorical parameters were expressed by percentages and numbers. Chi-square test was used for qualitative parameters. The Mann-Whitney U test was used for quantitative variables that did not show parametric distribution. Renal survival was evaluated by Kaplan-Meier analysis. Logistic regression analyzes were used to figure out risks associated with study endpoints. SPSS statistical software (SPSS version 26.0, IBM Corp., USA) and MedCalc were used for statistical analysis. A $p<0.05$ was accepted as a statistically significant value.

RESULTS

In total, 105 patients with PMN (36.1% female, median age 57.0 (IQR 45.0-66.0) were followed for a median of 30.6 (IQR 13.8-63.8) months. There were 49 patients in the LI group and 56 patients in the HI group. The mean age was higher in the HI group (71.0±6.1) than in the LI group (67.8±5.0 years) (p=0.003). Systolic and diastolic BPs and follow-up time were similar between groups. Higher serum albumin levels (2.9±0.8 versus 2.5±0.7 g/dL, p<0.001) and hemoglobin (13.1±1.9 versus 12.1±1.8, p=0.001) levels were determined in the LI group. Other demographic, clinical, and laboratory parameters of the study groups are shown in Table 1.

Therapeutic and histopathological features

There was no difference between the groups according to histopathological (Ehrenreich and Churg's) stage (p=0.751) and tubular atrophy/interstitial fibrosis density (p=0.414). However, the IgG density was greater in

Table 1: Demographic, clinical and laboratory characteristics of patients according to C3 accumulation

	LI group (n=49)	HI group (n=56)	p
Age mean±SD, years	67.8±5.0	71.0±6.1	0.003
Gender n (%)			
Male	30 (61.2)	37 (66.1)	0.606
Female	19 (38.8)	19 (33.9)	
Blood pressure mean±SD, mmHg			
Systolic	129.6±19.0	129.8±17.6	0.938
Diastolic	81.1±11.6	81.4±11.2	
Baseline proteinuria level mean±SD, g/g	5613.0±3395.6	6848.6±4099.2	0.199
Baseline serum albumin level mean±SD, g/dL	2.9±0.8	2.5±0.7	0.004
Baseline hemoglobin mean±SD, g/dL	13.1±1.9	12.1±1.8	0.001
Baseline eGFR mean±SD, mL/min/1.73 m^2	78.9±23.8	68.7±28.4	0.052

eGFR: estimated glomerular filtration rate, HI: high intensity, IQR: interquartile range, LI: low intensity, SD: standard deviation
Note: p-values compared low intensity and high intensity, obtained from the Chi-Square test, Fisher's exact test, or Mann–Whitney U test

Table 2: Histopathological characteristics of patients according to C3 accumulation density

	LI group (n=49)	HI group (n=56)	p
Histological stage n (%)			
Stage I			
Stage II	12 (24.5)	11 (19.6)	0.751
Stage III	28 (57.1)	32 (57.7)	
	9 (18.4)	13 (23.2)	
IgG intensity n (%)			
II +	20 (40.8)	7 (12.5)	0.001
III +	29 (59.2)	49 (87.5)	
IFTA intensity n (%)			
Mild	19 (38.8)	15 (26.8)	0.414
Moderate	1 (38.8)	1 (1.8)	

HI: high intensity, IFTA: interstitial fibrosis tubular atrophy, LI: low intensity
Note: p-values compared low intensity and high intensity, obtained from the Chi-Square test, Fisher's exact test, or Mann–Whitney U test

the HI group compared to the LI group (p<0.001). The histopathological features of the patients are shown in Table 2. There was no difference between therapeutic regimens (antiproliferative drugs, CNIs, and rituximab) (Table 3).

Study outcomes

After a follow-up of 30.6 (IQR 13.8-63.8) months, the primary endpoint developed in nine (16.1%) patients in the HI group, and in one patient (2.0%) in the LI group (p=0.015). The Kaplan-Meier survival analysis revealed that renal survival (p=0.031) was lower in the HI group than in the LI group (Figure 1). The number of patients who achieved the composite secondary endpoint was lower in the HI group (p= 0.016). However, CR [12 (24.5%) vs. 7 (12.5%)] and PR [23 (46.9%) vs. 20 (35.7%)] rates did not achieve statistical significance (p=0.111 and p=0.243, respectively).

The last eGFR was lower [52 (IQR 40-88) vs. 71 (IQR 69-117) mL/min/1.73 m^2, p<0.001)], and the last proteinuria

Table 3: Outcomes and treatment modalities according the groups

	LI group (n=49)	HI group (n=56)	p
Follow-up time months, median, (IQR 25-75)	49.7 (15-72)	47 (19-69)	0.716
Last eGFR level mL/min/1.73 m^2, median, (IQR 25-75)	71 (69-117)	52 (40-88)	<0.001
Last proteinuria level g/g, median (IQR 25-75)	2.1 (0.6-3.5)	3.8 (1.3-4.7)	0.018
Medication n (%)			
Calcineurin inhibitors	17 (34.7)	18 (32.1)	0.782
Cyclophosphamide	3 (6.1)	1 (1.8)	0.247
Antiproliferative agent	8 (16.3)	10 (17.9)	0.836
Rituximab	2 (4.1)	4 (7.1)	0.500
No immunosuppression	29 (59.2)	31 (55.4)	0.693
Primary endpoint n (%)	1 (2.0)	9 (16.1)	0.015
Secondary endpoint n (%)	35 (71.4)	27 (48.2)	0.016
Complete remission	12 (24.5)	7 (12.5)	0.111
Partial remission	23 (46.9)	20 (35.7)	0.243

eGFR: estimated glomerular filtration rate, HI: high intensity, IQR: interquartile range, LI: low intensity, SD: standard deviation
Note: P-values compared low intensity and high intensity, obtained from the Chi-Square test, Fisher's exact test, or Mann–Whitney U test

Table 4: The logistic regression analyses with factors that may predict primary outcome

	Univariate analysis		Multivariate analysis	
	OR (%95 CI)	P value	OR %95 CI	P value
Patient age	0.147 (0.977- 1.173)	0.147		
Initial eGFR	0.968 (0.941- 0.996	0.024	0.981 (0.952- 1.011)	0.219
Initial proteinuria	1.000 (1.000- 1.001)	0.833		
HI group	9.191 (1.120- 75.418)	0.039	5.856 (0.666- 51.459)	0.111
Serum albumin level	0.454 (0.169- 1.218)	0.117		
Histological stage	1.025 (0.379- 2.773)	0.961		
Baseline hemoglobin level	0.631 (0.423- 0.941)	0.024	0.800 (0.517- 1.239)	0.318

eGFR: estimated glomerular filtration rate, HI: high intensity, CI: Confidence interval

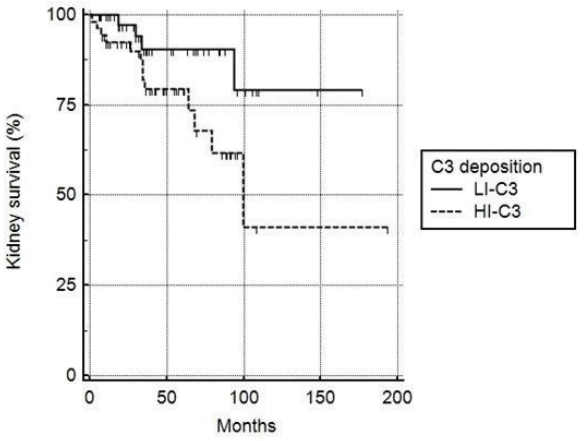

Figure 1: Kaplan-Meier survival analysis revealed that renal survival was lower in the HI group compared to in the LI group. (p= 0.031 with log-rank test)

DISCUSSION

In this single-center retrospective study examining the effect of glomerular C3 staining on disease outcomes in elderly (>60 years) patients with PMN, patients with strong C3 accumulation had lower final eGFR and higher last proteinuria. We also found that patients with strong C3 deposition were found to have lower baseline hemoglobin and serum albumin levels compared to patients with mild C3 deposition. Moreover, patients in this group (extensive C3 accumulation) had a high incidence of end-stage renal disease.

Studies show that ageing is associated with an increased immunoreactivity associated with alternative and classical pathway dysregulation of the complement system (22). This chronic inflammatory environment appears to be a contributing factor to many essential diseases of ageing (23-25). The kidney is susceptible to complement-mediated injury, mainly due to its high ultrafiltration capacity, the local increase in the production of complement compounds, and partially low renal expression of complement regulatory factors (26). This explains why the complement system is an essential pathogenic mediator in developing various kidney diseases such as lupus nephritis, antineutrophil cytoplasmic antibody-associated vasculitis, IgA nephropathy, C3 glomerulopathy, and atypical hemolytic uremic syndrome (aHUS) (27-29). There is evidence to support the idea that the complement system activation is one of the initiating factors that lead to tissue damage and subsequent proteinuria resulting from these immune reactions (30-32). Although it is unclear which pathway is more active in PMN, previous studies show that C4b, Bb, and MBL residues are related to the lectin pathway activation. In addition, accumulation of MAC, C3b, and renal excretion of C3dg suggest that the AP pathway is also effective in the pathogenesis of PMN (33-35).

Table 5: Logistic regression analysis with factors that may predict secondary outcomes

	Univariate analysis		Multivariate analysis	
	OR (%95 CI)	P value	OR %95 CI	p value
Patient age	0.947 (0.892-1.007)	0.082		
Initial eGFR	0.991 (0.976-1.006)	0.224		
Initial proteinuria	1.000 (1.000-1.000)	0.848		
HI group	2.685 (1.192-6.046)	0.017	2.196 (0.946-5.101)	0.067
Serum albumin level	2.179 (1.166-4.071)	0.015	1.911 (1.000-3.653)	0.050
Histological stage	0.729 (0.400-1.330)	0.303		
Baseline hemoglobin level	1.138 (0.919-1.408)	0.235		

eGFR: estimated glomerular filtration rate, HI: high intensity, CI: Confidence interval

levels were significantly higher (3.8 IQR 1.3-4.7) g7g vs. 2.1 (IQR 0.6-3.5) g/g, p=0.018) in the HI group compared to the LI group. Further details are shown in Table 3.

In univariate logistic regression analyses, baseline eGFR (OR 0.968, 95%CI 0.941-0.996, p=0.024), baseline hemoglobin (OR 0.631, 95%CI 0.423-0.941, p=0.024), and the presence of HI (OR 9.191, 95%CI 1.120-75.418, p=0.039) were associated with the primary endpoint. However, none of these parameters predicted the primary endpoint development in multivariate logistic regression analyses.

In univariate logistic regression analysis, the presence of HI (OR 2.685, 95%CI 1.192-6.046, p=0.017) and baseline serum albumin (OR 2.179, 95%CI 1.166-4.071, p=0.015) predicted the secondary outcome. However, none of these predicted secondary endpoint development in multivariate logistic regression analyses (Table 5).

Results of the studies investigating the prognostic importance of pathological parameters in PMN show significant differences (36, 37). Moreover, there are conflicting data about the intensity of complement deposition and clinicopathological findings. Zhang et al. reported higher serum anti-PLA2R antibody levels, more severe proteinuria, higher serum creatinine, and lower serum albumin levels in patients with strong complement accumulation. On the other hand, they found that C3 density was not predictive of adverse outcomes (38). Similarly, Horvatic et al. did not find any relationship between C3 density and negative results. Although a study reports that quantitative complement accumulation and disease progression are strongly associated, it is challenging to reach decisive conclusions due to the semiquantitative and unconfirmed grading system and differences in the specificity of the reagents used to predict complement accumulation (37). Our previous studies found that intense C3 accumulation was predictive of renal survival in patients with PMN (15). In this study, we showed that patients with extensive C3 deposition had worse kidney outcomes than patients with mild C3 accumulation. However, the C3 deposition amount was not predictive of end-stage renal disease development and complete or partial remission. The fact that the HI group was older than the LI group might have affected the results of the logistic regression analyses. Other reasons for the differences between these two outcomes may be related to the number of patients, the duration of the follow-up, differences in the scaling of C3 accumulation, variability in treatment regimens, and changes in the disease course in different populations.

Our study suffers from some limitations because of its retrospective nature. Serum anti-PLA2R was not detected in all patients at the time of diagnosis, and changes in the disease course could not be recorded. Hence, we were not able to obtain information about the relationship between C3 accumulation and autoantibody levels. In addition, due to technical limitations, electron microscopic evaluation, distribution of C3 residues, and an IgG subgroup determination could not be performed.

In conclusion, elderly patients with PMN with extensive glomerular C3 deposition have worse clinical outcomes than those with mild C3 deposition; therefore, it would be beneficial to determine and apply individualized treatment protocols for this patient group.

Ethics Committee Approval: This study was approved by Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 04.01.2013, No: 2013/11).

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