MORFOLOŠKE PROMENE U BUBREZIMA I KLINIČKA SLIKA PACIJENATA SA MEMBRANOZNIM GLOMERULONEFRITISOM PRIMARNE I SEKUNDARNE ETIOLOGIJE

ORIGINALNI RAD

ORIGINAL ARTICLE

MORPHOLOGICAL CHANGES IN KIDNEYS AND CLINICAL PRESENTATION IN PATIENTS WITH PRIMARY AND SECONDARY MEMBRANOUS NEPHROPATHY

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SAŽETAK

Uvod/Cilj: Membranozni glomerulonefritis (MGN) klinički se najčešće manifestuje nefrotskim sindromom, a etiološki može biti idiopatski – primarni MGN (pMGN), ili u sklopu drugih bolesti – sekundarni MGN (sMGN). Uzimajući u obzir različit terapijski pristup, cilj rada bio je uporediti kliničke i patohistološke parametre među pacijentima sa pMGN i sMGN.

Metode: Retrospektivnom analizom biopsijskih uzoraka tkiva bubrega dijagnostikovanih na Institutu za patologiju Medicinskog fakulteta u Beogradu u periodu 2011 - 2023. godine, izdvojeno je 99 pacijenata dijagnostikovanih kao MGN, podeljenih u odnosu na etiologiju u dve grupe: pacijente sa pMGN ($n = 44$) i pacijente sa sMGN ($n = 55$). Klinički, kao i patohistološki parametri (na optičkoj i imunofluorescentnoj mikroskopiji) upoređeni su u ispitivanim grupama.

Rezultati: Dok su muškarci češće obolevali od MGN, žene su češće imale sMGN ($p = 0,036$). Hematurija je češće uočena kod ispitanika sa sMGN ($p = 0,009$). Vrednosti proteinurije su bile značajno više među pacijentima sa pMGN ($p = 0,018$), što je u vezi sa znatno većim sniženjem koncentracije serumskih ukupnih proteina kod njih ($p = 0,011$). Endokapilarna proliferacija je znatno češće bila prisutna kod obolelih od sMGN ($p = 0,032$). Izrazita pozitivnost nekoliko imunoflourescentnih markera je bila statistički značajno češća kod ispitanika sa sMGN: IgA, IgM, C1q, κ-lanci i λ-lanci ($p < 0,05$).

Zaključak: Osobe ženskog pola češće boluju od sMGN. Karakteristike sMGN su prisustvo hematurije, endokapilarne hipercelularnosti i pozitivnosti imunofluorescence na markere koji se ne viđaju u pMGN (IgA, IgM, C1q), dok su karakteristike pMGN značajno više vrednosti proteinurije, praćene sniženjem koncentracije proteina u serumu.

Ključne reči: membranozni glomerulonefritis, primarni, sekundarni

ABSTRACT

Introduction/Aim: Membranous nephropathy (MN) typically presents as nephrotic syndrome and may be idiopathic (primary MN, pMN) or occur secondary to other diseases (secondary MN, sMN). Given the differing therapeutic approaches, this study aimed to compare clinical and pathohistological parameters between patients with pMN and sMN.

Methods: Through a retrospective analysis of kidney biopsy samples diagnosed at the Institute of Pathology, Faculty of Medicine, Belgrade, between 2011 and 2023, 99 patients with membranous nephropathy were identified. These patients were divided into two groups: patients with pMN ($n = 44$) and patients with sMN ($n = 55$). Clinical and pathohistological parameters (by optical and immunofluorescence microscopy) were compared among study participants.

Results: While males more frequently suffered from MN, females more frequently had sMN ($p = 0.036$). Haematuria was more common in subjects with sMN ($p = 0.009$). Proteinuria values were significantly higher among patients with pMN ($p = 0.018$), related to a significantly greater decrease in serum total protein values in them ($p = 0.011$). Endocapillary proliferation was significantly more frequent among those with sMN ($p = 0.032$). Marked positivity of several immunofluorescent markers was significantly more common in subjects with sMN: IgA, IgM, C1q, κ-chains, and λ-chains ($p < 0.05$).

Conclusion: Females are more commonly affected by sMN. Characteristics of sMN include presence of haematuria, endocapillary hypercellularity and immunofluorescence positivity for markers not seen in pMN (IgA, IgM, C1q), while characteristics of pMN include significantly higher levels of proteinuria, accompanied by significantly reduced serum protein values.

Keywords: membranous nephropathy, primary, secondary

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UVOD

Membranozni glomerulonefritis (MGN) predstavlja hronično bubrežno oboljenje koje karakteriše subepitelno taloženje depozita imunoglobulina i komponenata komplementa u glomerulima, te se najčešće klinički manifestuje nefrotskim sindromom [1]. Oboljenje se najčešće javlja u uzrastu 50 - 60 godina, i to oko dva puta češće kod muškaraca, dok deca retko obolevaju [2,3]. U odnosu na etiologiju deli se na primarni i sekundarni MGN [4]. Primarni MGN odlikuje autoimunski odgovor na podocitne antigene u odsustvu sekundarnog uzroka; neki od do sada detektovanih antigena su: *PLA_2R*, *THSD7A* [5,6]. U osnovi sekundarnog MGN mogu biti: autoimunske bolesti (sistemski eritemski lupus, Šegrenov sindrom, autoimunski tireoiditis), infekcije (hepatitis B i C virusne infekcije, HIV, sifilis, malarija), lekovi i toksini (nesteroidni antiinflamatorni lekovi, penicilamin, soli zlata, živa), kao i maligne bolesti (karcinomi pluća, prostate, kolona i uterusa, hematološka maligna oboljenja), kod kojih je detektovan *NELL-1* antigen [7,8].

Zlatni standard u dijagnostici MGN predstavlja patohistološka evaluacija biopsijskih uzoraka tkiva bubrega. Kod pacijenata sa nefrotskim sindromom u kliničkoj slici, serumskom pozitivnišću antitela na *PLA_2R* i očuvanom ekskretornom bubrežnom funkcijom, biopsija bubrega nije neophodna [9]. Na optičkoj mikroskopiji se uočava difuzno uniformno zadebljanje glomerularne bazalne membrane; vremenom njen matriks formira strukture nalik „šiljcima“ između deponovanih imunskih kompleksa [10]. Karakterističan nalaz imunofluorescentne mikroskopije predstavlja prisustvo sitnozrnastih, granularnih depozita IgG i C3 komponente komplementa duž glomerularne bazalne membrane [10].

Terapija za MGN zavisi od njegove etiologije. Pacijenti sa primarnom bolešću se leče imunosupresivnom terapijom (kortikosteroidima, ciklofosfamidom, inhibitorima kalcineurina), ali i rituksimabom, monoklonskim antitelom usmerenim ka CD20 antigenu B-limfocita [11,12]. Kod pacijenata sa sekundarnim MGN terapija je usmerena ka oboljenju koje je u njegovoj osnovi. Kod svih pacijenata se, kao suportivna terapija, primenjuju diuretici, ACE inhibitori, blokatori angiotenzinskih receptora i statini, a u cilju kontrole arterijskog pritiska, edema, proteinurije i lipidnog statusa [11].

Uzimajući u obzir značaj etiologije MGN u terapijskom pristupu, cilj ove studije je bio uporediti kliničke (distribucija prema polu, starosti, vrednosti proteinurije, prisustvo hematurije, koncentracije ukupnih proteina i albumina u serumu, pokazatelji ekskretorne bubrežne funkcije i prisustvo najčešćih komorbiditeta) i patohistološke parametre (promene na glomerulima, tubulointersticijumu i krvnim sudovima na optičkoj mikroskopiji, kao i intenzitet depozita imunoglobulina,

INTRODUCTION

Membranous glomerulonephritis (MGN) is a chronic kidney disease characterized by subepithelial deposition of immunoglobulins and complement components within the glomeruli, most commonly presenting clinically as nephrotic syndrome [1]. The disease most commonly occurs between 50 and 60 years of age and is approximately twice as prevalent in men, while it is rarely observed in children [2,3]. Based on etiology, it is classified into primary and secondary MGN [4]. Primary MGN is characterized by an autoimmune response against podocyte antigens in the absence of an identifiable secondary cause; antigens identified to date include *PLA2R* and *THSD7A* [5,6]. Secondary MGN may be associated with autoimmune diseases (systemic lupus erythematosus, Sjögren's syndrome, autoimmune thyroiditis), infections (hepatitis B and C, HIV, syphilis, malaria), drugs and toxins (non-steroidal anti-inflammatory drugs, penicillamine, gold salts, mercury), as well as malignant diseases (lung, prostate, colon, and uterine cancers, and hematological malignancies), in which the *NELL-1* antigen has been identified [7,8].

The gold standard for diagnosing MGN is the histopathological evaluation of kidney biopsy samples. In patients presenting with nephrotic syndrome who are serum-positive for *PLA2R* antibodies and have preserved renal excretory function, a kidney biopsy is not required [9]. On light microscopy, a diffuse and uniform thickening of the glomerular basement membrane is observed, with the matrix gradually forming "spike"-like projections between the deposited immune complexes [10]. A hallmark of immunofluorescence microscopy is the presence of fine, granular deposits of IgG and the complement component C3 along the glomerular basement membrane [10].

Treatment of MGN depends on its underlying etiology. Patients with primary MGN receive immunosuppressive therapy, including corticosteroids, cyclophosphamide, and calcineurin inhibitors, as well as rituximab, a monoclonal antibody targeting the CD20 antigen on B lymphocytes [11,12]. In patients with secondary MGN, treatment is focused on the underlying condition. Supportive therapy, including diuretics, ACE inhibitors, angiotensin receptor blockers, and statins, is used in all patients to manage blood pressure, edema, proteinuria, and lipid levels [11].

Considering the significance of MGN etiology for therapeutic strategy, this study aimed to compare clinical parameters, such as gender and age distribution, proteinuria levels, presence of hematuria, serum total protein and albumin concentrations, markers of renal excretory function, and the most common comorbidities, with pathohistological features, including

njihovih lakih lanaca i komponenata komplementa na imunofluorescentnoj mikroskopiji) među pacijentima sa primarnom i sekundarnom bolešću.

METODE RADA

U retrospektivnoj studiji obuhvaćeno je 99 biopsijskih uzoraka tkiva bubrega dijagnostikovanih kao MGN u periodu 2011 - 2023. godine na Institutu za patologiju „Dr Đorđe Joannović" Medicinskog fakulteta u Beogradu. Od pomenutih 99 uzoraka, 64 su pripadala pacijentima lečenim na Klinici za nefrologiju Univerzitetskog kliničkog centra Srbije, 27 pacijentima lečenim u Kliničko-bolničkom centru „Zvezdara", 4 pacijentima lečenim u Kliničko-bolničkom centru „Zemun", 2 pacijentima lečenim na Univerzitetskoj dečjoj klinici i 2 pacijentima lečenim u Institutu za zdravstvenu zaštitu majke i deteta Srbije „Dr Vukan Čupić". Pacijenti su podeljeni u dve grupe u odnosu na etiologiju bolesti: pacijente sa primarnim MGN ($n = 44$) i pacijente sa sekundarnim MGN ($n = 55$).

Klinički i laboratorijski podaci, zabeleženi u vreme biopsije, prikupljeni su pregledom medicinske dokumentacije pacijenata. Vrednosti proteinurije < 3,5 g/24 h označene su kao subnefrotske, dok su vrednosti ≥ 3,5 g/24 h označene kao nefrotske [11]. Fiziološke vrednosti ukupnih proteina u serumu iznose 62 - 82 g/L, a albumina 35-52 g/L [13]. Brzina glomerularne filtracije procenjena je primenom *CKD-EPI 2021* jednačine. Gradus hronične bubrežne bolesti određen je prema vrednostima procenjene brzine glomerularne filtracije [11]. Patohistološki podaci su prikupljeni iz izveštaja prethodno evaluiranih biopsijskih uzoraka tkiva bubrega.

Za statističku analizu korišćen je program *IBM SPSS Statistics 22* (*SPSS Inc.*, Čikago, Ilinois, SAD). Za proveru normalnosti podataka korišćene su računske metode: koeficijent varijacije, *skewness* i *kurtosis* vrednosti. Procena statističke značajnosti razlike u vrednostima numeričkih varijabli među pacijentima sa primarnim i sekundarnim MGN vršena je primenom Studentovog t-testa za dva nezavisna uzorka, za podatke koji su pratili normalnu raspodelu. Za podatke čija raspodela nije bila normalna ili su bili ordinalni primenjen je *Mann-Whitney U* test. Procena statističke značajnosti razlike u učestalostima nominalnih varijabli između dveju grupa pacijenata vršena je primenom χ^2 testa za rxk tabele i Fišerovog testa tačne verovatnoće. Hipoteze su testirane sa nivoom značajnosti od 0,05.

REZULTATI

Klinički parametri

Detaljan prikaz kliničkih parametara kod pacijenata sa primarnim i sekundarnim MGN prikazan je u Tabeli 1. Od ukupno 99 pacijenata, 63,6% ($n = 63$) bile su

glomerular, tubulointerstitial, and vascular changes on light microscopy, as well as the intensity of immunoglobulin, light chain, and complement component deposits on immunofluorescence microscopy, between patients with primary and secondary MGN.

METHODS

The retrospective study included 99 kidney biopsy samples diagnosed as MGN between 2011 and 2023 at the Institute of Pathology "Dr. Đorđe Joannović," Faculty of Medicine, Belgrade. Of these 99 samples, 64 were from patients treated at the Clinic for Nephrology, University Clinical Center of Serbia, 27 from the Clinical Hospital Center "Zvezdara", 4 from the Clinical Hospital Center "Zemun", 2 from the University Children's Clinic; and 2 from the Institute for Mother and Child Health Protection of Serbia "Dr. Vukan Čupić". Patients were divided into two groups based on disease etiology: those with primary MGN ($n = 44$) and those with secondary MGN ($n = 55$).

Clinical and laboratory data recorded at the time of biopsy were collected through review of patients' medical records. Proteinuria values < 3,5 g/24 h were classified as subnephrotic, while values of ≥ 3,5 g/24 h were classified as nephrotic [11]. Normal serum total protein levels range from 62 to 82 g/L, and albumin from 35 to 52 g/L [13]. Glomerular filtration rate was estimated using the CKD-EPI 2021 equation, and the stage of chronic kidney disease was determined based on the estimated glomerular filtration rate values [11]. Pathohistological data were obtained from the reports of previously analyzed kidney biopsy samples.

Statistical analysis was performed using IBM SPSS Statistics 22 (SPSS Inc., Chicago, Illinois, USA). Data normality was assessed using the coefficient of variation, skewness, and kurtosis. For numerical variables with a normal distribution, differences between patients with primary and secondary MGN were evaluated using the Student's t-test for two independent samples. For data with a non-normal distribution or ordinal scale, the Mann–Whitney U test was applied. Differences in the frequencies of nominal variables between the two patient groups were assessed using the χ^2 test for r×k tables and Fisher's exact test. Hypotheses were tested at a significance level of 0.05.

RESULTS

Clinical parameters

A detailed overview of the clinical parameters in patients with primary and secondary MGN is presented in Table 1. Among the 99 patients, 63.6% ($n = 63$) were male and 36.4% ($n = 36$) were female. The secondary

Tabela 1. Klinički parametri ispitanika sa membranoznim glomerulonefritisom

Table 1. Clinical parameters of subjects with membranous nephropathy

Klinički parametri / *Clinical parameters*		Primarni MGN / *Primary MN*	Sekundarni MGN / *Secondary MN*	*p*
Pol / *Sex [n (%)]*	Muški / *Male*	33 (75.0%)	30 (45.5%)	**0.036**
	Ženski / *Female*	11 (25.0%)	25 (54.5%)	
Starost (godine) / *Age (years)*		52.8 ± 14.74	51.7 ± 15.9	0.704
Rang proteinurije / *Proteinuria range [n (%)]*	Subnefrotska / *Subnephrotic*	2 (4.5%)	7 (12.7%)	0.159
	Nefrotska /*Nephrotic*	42 (95.5%)	48 (87.3%)	
Proteinurija / *Proteinuria (g/24 h)*		8.8 (2.9-55.0)	6.9 (1.9-45.1)	**0.018**
Hematurija / *Haematuria [n (%)]*	Odsutna / *Absent*	35 (79.5%)	30 (54.5%)	**0.009**
	Prisutna /*Present*	9 (20.5%)	25 (45.5%)	
Ukupni proteini u serumu / *Serum total protein (g/L)*		44.8 ± 7.87	50.1 ± 7.67	**0.011**
Albumin u serumu / *Serum albumin (g/L)*		22.6 ± 6.60	25.3 ± 6.40	0.085
Kreatinin u serumu / *Serum creatinine (μmol/L)*		88.5 (41–575)	87.5 (21-419)	0.938
Urea u serumu / *Serum urea (mmol/L)*		8.2 ± 4.2	8.0 ± 5.1	0.874
Procenjena brzina glomerularne filtracije / *eGFR (mL/min)*		89.1 ± 45.9	72.2 ± 43.3	0.125
Gradus hronične bubrežne bolesti / *Chronic kidney disease grade [n (%)]*	*G1*	14 (46.7%)	13 (35.1%)	0.110
	G2	9 (30.0%)	6 (16.2%)	
	G3	4 (13.3%)	12 (32.4%)	
	G4	3 (10.0%)	4 (10.8%)	
	G5	0 (0.0%)	2 (5.4%)	
Hipertenzija / *Hypertension [n (%)]*	Odsutna / *Absent*	12 (27.3%)	19 (34.5%)	0.438
	Prisutna /*Present*	32 (72.7%)	36 (65.5%)	
Dijabetes melitus / *Diabetes mellitus [n (%)]*	Odsutna / *Absent*	42 (95.5%)	49 (89.1%)	0.248
	Prisutna /*Present*	2 (4.5%)	6 (10.9%)	

Legenda: MGN – membranozni glomerulonefritis

Legend: MN – membranous nephropathy; eGFR – estimated glomerular filtration rate

osobe muškog pola, dok su osobe ženskog pola činile preostalih 36,4% (n = 36). Sekundarnu formu bolesti imalo je 69,4% (n = 25) osoba ženskog pola naspram 47,6% (n = 30) osoba muškog pola, pri čemu je ova razlika u distribuciji prema polu bila statistički značajna (p = 0,036). Prosečna starost pacijenata sa primarnim MGN iznosila je 52,8 ± 14,7 godine, a kod onih sa sekundarnim MGN 51,7 ± 15,9 godina (p = 0,704).

Većina pacijenata je u vreme uzimanja biopsije imala proteinuriju nefrotskog ranga. Kod 9,1% (n = 9) ispitanika proteinurija je bila subnefrotska, a većina njih (n = 7) imala je MGN sekundarne etiologije. Medijana vrednosti proteina u 24-časovnom urinu kod pacijenata sa primarnim oblikom bolesti (medijana 8,8 g/24 h; opseg 2,9 - 55,0 g/24 h) bila je znatno viša nego kod onih sa sekundarnim MGN (medijana 6,9 g/24 h; opseg 1,9 - 45,1 g/24 h), p = 0,018. Hematuriju, najčešće mikroskopsku, imalo je 34,3% (n = 34) ispitanika, među kojima je 73,5% (n = 25) pacijenata bilo sa sekundarnom bolešću (p = 0,009).

form of the disease was observed in 69.4% (n = 25) of female patients compared to 47.6% (n = 30) of male patients, a difference that was statistically significant (p = 0.036). The mean age of patients with primary MGN was 52.8 ± 14.7 years, while that of patients with secondary MGN was 51.7 ± 15.9 years (p = 0.704).

Most patients exhibited nephrotic-range proteinuria at the time of biopsy. Proteinuria was subnephrotic in 9.1% (n = 9) of cases, the majority of whom (n = 7) had secondary MGN. The median 24-hour urine protein level in patients with primary MGN (median 8.8 g/24 h; range 2.9-55.0 g/24 h) was significantly higher than in those with secondary MGN (median 6.9 g/24 h; range 1.9-45.1 g/24 h; p = 0.018). Hematuria, mostly microscopic, was observed in 34.3% (n = 34) of patients, with 73.5% (n = 25) of these cases occurring in patients with secondary MGN (p = 0.009).

The mean total protein level in patients with primary MGN was 44.8 ± 7.9 g/L, representing a significantly greater reduction (p = 0.011) compared to patients

Izmerena vrednost ukupnih proteina kod pacijenata sa primarnim MGN bila je 44,8 ± 7,9 g/L, dakle sa znatno većim sniženjem vrednosti ($p = 0,011$) nego kod ispitanika sa sekundarnim MGN (50,1 ± 7,7 g/L). Koncentracije serumskog albumina, iako snižene, nisu se znatno razlikovale između dveju grupa ispitanika (Tabela 1).

Pokazatelji ekskretorne bubrežne funkcije (serumske koncentracije uree i kreatinina, procenjena brzina glomerularne filtracije i gradus hronične bubrežne bolesti) nisu pokazali statistički značajnu razliku kod pacijenata sa primarnim i sekundarnim MGN, iako su pacijenti sa gradusom G3, G4 i G5 hronične bubrežne bolesti češće imali sekundarnu formu bolesti (Tabela 1).

Najčešći komorbiditeti u ispitivanoj populaciji bili su hipertenzija i dijabetes melitus. Među pacijentima sa hipertenzijom raspodela je bila približno jednaka – 47,1% ($n = 32$) njih je imalo primarni MGN, a 52,9% ($n = 36$) sekundarni ($p = 0,438$). Sa druge strane, iako je dijabetes melitus zabeležen kod svega 8,1% ($n = 8$) ispitanika, njih 75,0% ($n = 6$) imalo je sekundarnu formu bolesti ($p = 0,248$).

Patohistološki parametri

Na optičkoj mikroskopiji kod svih pacijenata uočeno je jednolično zadebljanje glomerularne bazalne membrane, karakteristično za pacijente obolele od MGN, kako primarne, tako i sekundarne etiologije (Slika 1). Pokazatelji hroničnih lezija glomerula (udeo globalno

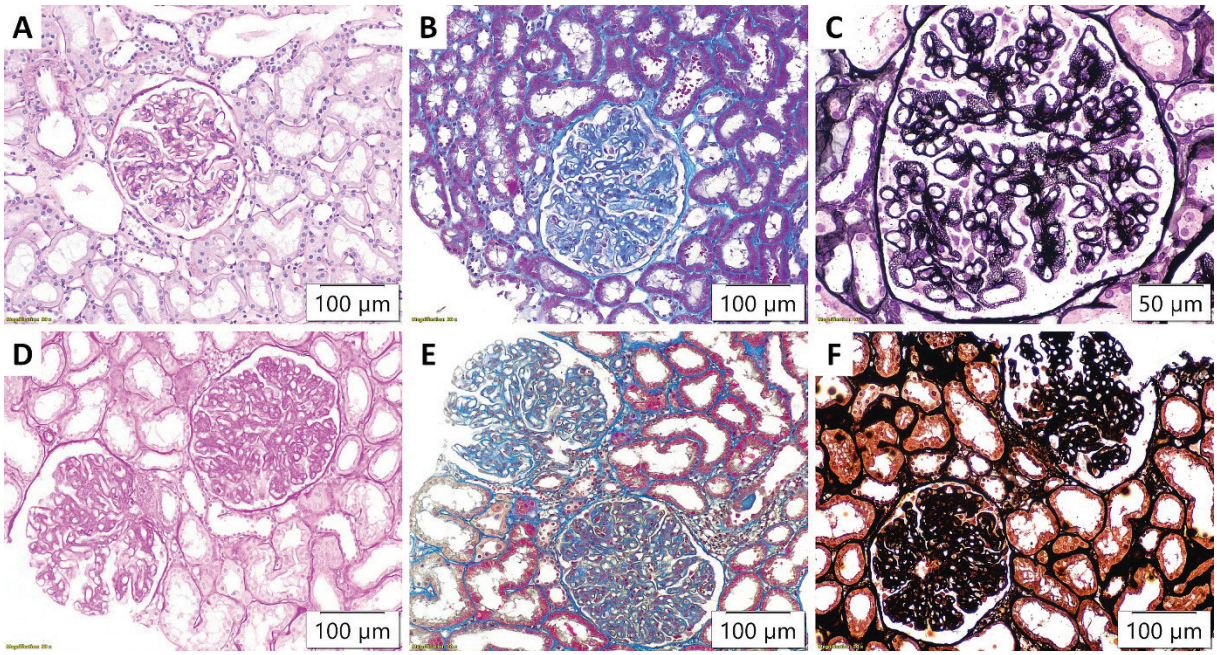
with secondary MGN (50.1 ± 7.7 g/L). Although serum albumin levels were also reduced, no significant difference was observed between the two groups (Table 1).

Indicators of excretory renal function, including serum urea and creatinine levels, estimated glomerular filtration rate, and chronic kidney disease stage, did not differ significantly between patients with primary and secondary MGN, although higher stages of chronic kidney disease (G3, G4, and G5) were more frequently observed in patients with secondary MGN (Table 1).

The most frequent comorbidities in the study population were hypertension and diabetes mellitus. Among patients with hypertension, the distribution was nearly even, with 47.1% ($n = 32$) having primary MGN and 52.9% ($n = 36$) having secondary MGN ($p = 0.438$). Diabetes mellitus was present in only 8.1% ($n = 8$) of patients, yet 75.0% ($n = 6$) of these cases were associated with secondary MGN ($p = 0.248$).

Histopathological parameters

On light microscopy, all patients exhibited uniform thickening of the glomerular basement membrane, a hallmark of MGN regardless of etiology (Figure 1). Indicators of chronic glomerular damage, such as the proportion of globally and segmentally sclerotic glomeruli, did not differ significantly between primary and secondary MGN (Table 2). Crescentic glomerular formations were more common in patients with secondary MGN, although this difference was not statistically



Slika 1. Promene u glomerulima na optičkoj mikroskopiji u primarnom (A) *Periodic acid-Schiff (PAS), x200,* (B) *Masson's trichrome stain (MTS), x200,* (C) *Jones methenamine silver* (JMS), x400; i sekundarnom membranoznom glomerulonefritisu, sa uočenom endokapilarnom hipercelularnošću (D) PAS, x200, (E) MTS, x200, (F) JMS, x200.

Figure 1. Changes in glomeruli on light microscopy in primary (A) Periodic acid-Schiff (PAS), x200, (B) Masson's trichrome (MTS), x200, (C) Jones methenamine silver (JMS), x400; and secondary membranous nephropathy, with evident endocapillary hypercellularity (D) PAS, x200, (E) MTS, x200, (F) JMS, x200

Tabela 2. Patohistološki parametri ispitanika s membranoznim glomerulonefritisom na optičkoj mikroskopiji

Table 2. Pathohistological parameters of patients with membranous nephropathy by light microscopy

Patohistološki parametri / *Pathohistological parameters*		Primarni MGN / *Primary MN*	Sekundarni MGN / *Secondary MN*	*p*
Udeo globalno sklerotičnih glomerula / *Global sclerotic glomeruli percentage (%)*		0.0 (0.0-66.7)	0.0 (0.0-61.5)	0.412
Udeo glomerula sa segmentnom glomerulosklerozom / *Segmental sclerotic glomeruli percentage (%)*		0.0 (0.0-20.0)	0.0 (0.0-42.9)	0.814
Udeo glomerula sa polumesecima / *Percentage of glomeruli with crescents (%)*		0.0 (0.0-14.3)	0.0 (0.0-40.0)	0.091
Endokapilarna proliferacija / *Endocapillary hypercellularity [n (%)]*	Odsutna / *Absent*	43 (97.7%)	46 (85.2%)	**0.032**
	Prisutna / *Present*	1 (2.3%)	8 (14.8%)	
Karioreksa / *Karyorrhexis [n (%)]*	Odsutna / *Absent*	44 (100.0%)	52 (96.3%)	0.500
	Prisutna / *Present*	0 (0.0%)	2 (3.7%)	
Intersticijska fibroza / *Interstitial fibrosis [n (%)]*	Odsutna / *Absent*	15 (34.1%)	8 (14.8%)	**0.008**
	Blaga / *Mild*	24 (54.5%)	31 (57.4%)	
	Umerena / *Moderate*	4 (9.1%)	11 (20.4%)	
	Teška / *Severe*	1 (2.3%)	4 (7.4%)	
Tubulska atrofija / *Tubular atrophy [n (%)]*	Odsutna / *Absent*	22 (50.0%)	14 (25.9%)	**0.031**
	Blaga / *Mild*	16 (36.4%)	30 (55.6%)	
	Umerena / *Moderate*	5 (11.4%)	8 (14.8%)	
	Teška / *Severe*	1 (2.3%)	2 (3.7%)	
Hijalinizacija krvnih sudova / *Blood vessels hyalinosis [n (%)]*	Odsutna / *Absent*	30 (68.2%)	43 (78.2%)	0.261
	Prisutna / *Present*	14 (31.8%)	12 (21.8%)	
Fibrointimalna hiperplazija / *Fibrointimal hyperplasia [n (%)]*	Odsutna / *Absent*	20 (45.5%)	25 (45.5%)	1.000
	Prisutna / *Present*	24 (54.5%)	30 (54.5%)	

Legenda: MGN – membranozni glomerulonefritis

Legend: MN – membranous nephropathy

i segmentno sklerotičnih glomerula) nisu pokazali značajne razlike među ispitanicima sa primarnim i sekundarnim MGN (Tabela 2). Glomeruli sa polumesečastim formacijama su bili češći kod obolelih od sekundarnog MGN, ali bez statističke značajnosti ($p = 0,091$). Endokapilarna proliferacija uočena je kod 9,1% ($n = 9$) ispitanih uzoraka tkiva, među kojima je 88,9% ($n = 8$) odgovaralo pacijentima sa sekundarnom bolešću ($p = 0,032$), (Tabela 2, Slika 1D). Karioreksa je uočena kod svega dva pacijenta sa sekundarnim MGN ($p = 0,500$).

Za razliku od hroničnih lezija krvnih sudova (hipertrofija medije, fibroelastoza intime i hijalinizacija krvnih sudova), pokazatelji hroničnih lezija tubulointersticijuma (intersticijska fibroza i tubulska atrofija) pokazali su statistički značajnu razliku između ispitivanih grupa, pri čemu su češće bile udružene sa sekundarnim MGN (Tabela 2).

Na imunofluorescentnoj mikroskopiji, pored IgG i C3 komponente komplementa, čiji sitnozrnasti depoziti duž glomerularne bazalne membrane predstavljaju tipičan nalaz u MGN (Slika 2), izrazita pozitivnost ostalih markera (IgA, IgM, C1q, κ-lanci i λ-lanci) znatno češće je bila udružena sa sekundarnim MGN (Tabela 3).

significant ($p = 0.091$). Endocapillary proliferation was noted in 9.1% ($n = 9$) of the examined tissue samples, of which 88.9% ($n = 8$) were from patients with secondary MGN ($p = 0.032$) (Table 2, Figure 1D). Karyorrhexis was observed in only two patients with secondary MGN ($p = 0.500$).

Unlike chronic vascular lesions (including medial hypertrophy, intimal fibroelastosis, and vascular hyalinization), indicators of chronic tubulointerstitial damage, such as interstitial fibrosis and tubular atrophy, differed significantly between the groups, occurring more frequently in patients with secondary MGN (Table 2).

On immunofluorescence microscopy, in addition to IgG and the complement component C3, whose fine granular deposits along the glomerular basement membrane represent a characteristic finding in MGN (Figure 2), pronounced positivity for other markers (IgA, IgM, C1q, κ chains, and λ chains) was significantly more frequently observed in secondary MGN (Table 3).

DISCUSSION

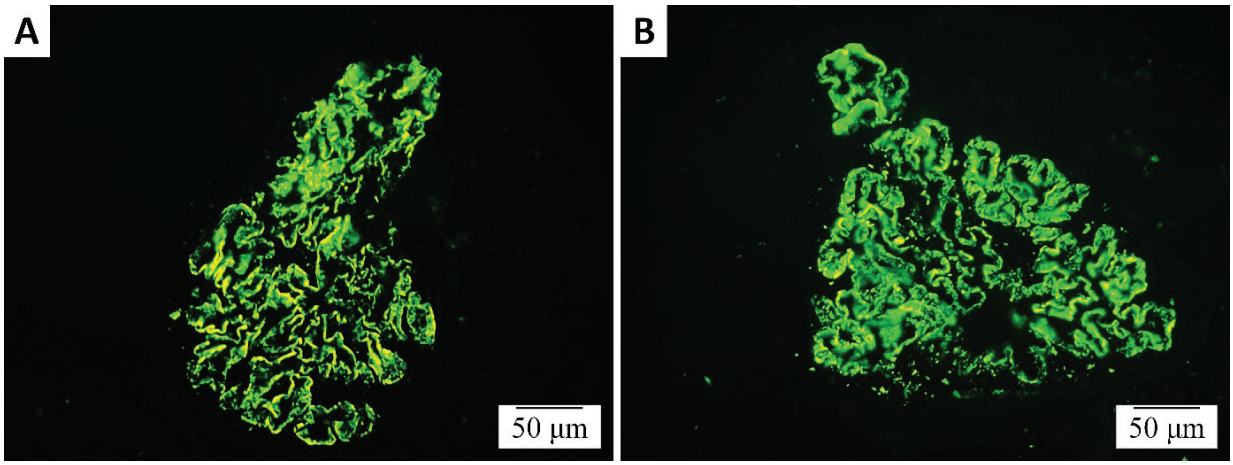
Tabela 3. Patohistološki parametri pacijenata s membranoznim glomerulonefritisom na imunofluorescentnoj mikroskopiji

Table 3. Pathohistological parameters of patients with membranous nephropathy by immunofluorescence

Patohistološki parametri / *Pathohistological parameters*		Primarni MGN / *Primary MN*	Sekundarni MGN / *Secondary MN*	*p*
IgA [n (%)]	-	32 (74.4%)	28 (50.9%)	**0.002**
	+	10 (23.3%)	7 (12.7%)	
	++	1 (2.3%)	13 (23.6%)	
	+++	0 (0.0%)	7 (12.7%)	
IgG [n (%)]	-	0 (0.0%)	0 (0.0%)	**0.045**
	+	1 (2.3%)	0 (0.0%)	
	++	4 (9.3%)	1 (1.8%)	
	+++	38 (88.4%)	54 (98.2%)	
IgM [n (%)]	-	22 (51.2%)	14 (25.5%)	**0.001**
	+	19 (44.2%)	25 (45.5%)	
	++	2 (4.7%)	15 (27.3%)	
	+++	0 (0.0%)	1 (1.8%)	
C1q [n (%)]	-	22 (51.2%)	9 (16.4%)	**<0.001**
	+	19 (44.2%)	21 (38.2%)	
	++	2 (4.7%)	19 (34.5%)	
	+++	0 (0.0%)	6 (10.9%)	
C3 [n (%)]	-	6 (14.0%)	6 (10.9%)	**0.046**
	+	13 (30.2%)	12 (21.8%)	
	++	17 (39.5%)	15 (27.3%)	
	+++	7 (16.3%)	22 (40.0%)	
κ-lanci [n (%)]	-	41 (95.3%)	38 (69.1%)	**0.001**
	+	1 (2.3%)	7 (12.7%)	
	++	0 (0.0%)	7 (12.7%)	
	+++	1 (2.3%)	3 (5.5%)	
λ-lanci [n (%)]	-	33 (76.7%)	32 (58.2%)	**0.023**
	+	3 (7.0%)	4 (7.3%)	
	++	6 (14.0%)	7 (12.7%)	
	+++	1 (2.3%)	12 (21.8%)	

Legenda: MGN – membranozni glomerulonefritis

Legend: MN – membranous nephropathy



Slika 2. Nalaz na imunofluorescentnoj mikroskopiji: sitnozrnasti depoziti (A) IgG i (B) C3 duž glomerularne bazalne membrane, x400

Figure 2. Immunofluorescence microscopy findings: fine granular deposits of (A) IgG and (B) C3 along the glomerular basement membrane, x400

DISKUSIJA

U ovoj retrospektivnoj studiji poređeni su klinički i patohistološki parametri između pacijenata sa primarnim i sekundarnim MGN. Osobe muškog pola su činile 63,6% ispitanika, što je u skladu sa podacima iz literature, koji navode da je odnos muškog prema ženskom polu u obolevanju od MGN 1,5 -2 : 1 [14,15]. Takođe, čak 69,4% ispitanika ženskog pola imalo je sekundarni oblik bolesti. Ovakva distribucija prema polu se može objasniti značajnim udelom autoimunskih bolesti u etiologiji sekundarnog MGN. Naime, osobe ženskog pola znatno češće obolevaju od autoimunskih bolesti, koje mogu biti u osnovi sekundarnog oblika MGN [7,16]. Takva bolest sa najvećom učestalošću jeste sistemski eritemski lupus, kod kojeg bubreg može pokazivati promene po tipu membranoznog glomerulonefritisa, lupus nefritis klase V [17]. Osobe ženskog pola obolevaju 2 – 15 puta češće od sistemskog eritemskog lupusa [18,19].

Membranozni glomerulonefritis se najčešće prezentuje nefrotskim sindromom: izraženom proteinurijom, hipoalbuminemijom, perifernim edemima ili anasarkom, hiperlipidemijom i lipidurijom [20]. Jedna trećina pacijenata sa primarnim MGN ulazi u spontanu remisiju nakon više meseci ili godina [21]. Vrednosti proteinurije su važan faktor progresije bolesti – vrednosti < 4 g/24 h su udružene sa niskim rizikom, a vrednosti > 8 g/24 h sa visokim rizikom od progresije [22]. Naši rezultati su pokazali statistički značajno više vrednosti proteina u 24-časovnom urinu kod ispitanika sa primarnim MGN. Posledično, zbog većeg gubitka proteina urinom, ispitanici sa primarnim oblikom bolesti su imali znatno niže vrednosti ukupnih proteina u serumu od fizioloških.

Podaci iz literature ukazuju na to da prisustvo mikroskopske hematurije, arterijske hipertenzije i promena u bubrežnoj funkciji povećavaju verovatnoću sekundarne etiologije MGN [23,24]. Rezultati naše studije ukazali su na statistički značajno češće javljanje mikroskopske hematurije kod obolelih od sekundarnog MGN (73,5%) u poređenju sa obolelima od primarnog. Takođe, pacijenti sa sekundarnom formom bolesti su imali niže vrednosti procenjene brzine glomerularne filtracije nego ispitanci sa primarnim MGN, kao i češće javljanje viših gradusa (G3, G4 i G5) hronične bubrežne bolesti, ali ove razlike nisu dostigle statističku značajnost. Nasuprot ovome, raspodela u prisustvu arterijske hipertenzije nije pokazala razlike.

Pored toga što predstavlja zlatni standard u postavljanju dijagnoze MGN, patohistološka evaluacija biopsijskih uzoraka tkiva bubrega može ukazati i na moguću etiologiju, primarnu odnosno sekundarnu. Tako prisustvo mezangijalne i endokapilarne hipercelular-

In this retrospective study, clinical and pathohistological parameters were compared between patients with primary and secondary MGN. Male patients accounted for 63.6% of the study population, which is consistent with published data indicating a male-to-female ratio of approximately 1.5-2:1 in the incidence of MGN [14, 15]. Moreover, as many as 69.4% of female patients had a secondary form of the disease. This gender-based distribution may be explained by the substantial contribution of autoimmune diseases to the etiology of secondary MGN, as women are considerably more likely to develop autoimmune disorders, which can underlie the secondary form of MGN [7,16]. The autoimmune disease most frequently associated with this pattern is systemic lupus erythematosus, in which renal involvement may manifest as membranous glomerulonephritis, corresponding to class V lupus nephritis [17]. Systemic lupus erythematosus occurs 2 to 15 times more frequently in females [18,19].

Membranous glomerulonephritis most commonly presents with nephrotic syndrome, characterized by marked proteinuria, hypoalbuminemia, peripheral edema or anasarca, hyperlipidemia, and lipiduria [20]. Approximately one third of patients with primary MGN achieve spontaneous remission after several months or years. [21]. Proteinuria levels are an important factor in disease progression – values < 4 g/24 h are associated with a low risk, whereas values > 8 g/24 h are associated with a high risk of progression [22]. Our results demonstrated significantly higher 24-hour urinary protein levels in patients with primary MGN. Consequently, owing to greater urinary protein loss, patients with the primary form of the disease exhibited significantly reduced serum total protein levels compared with physiological values.

Literature data indicate that the presence of microscopic hematuria, arterial hypertension, and impaired renal function increases the likelihood of a secondary etiology of MGN [23,24]. The results of our study showed that microscopic hematuria was significantly more common in patients with secondary MGN (73.5%) compared to those with primary MGN. Additionally, patients with secondary MGN had lower estimated glomerular filtration rates and a higher frequency of advanced chronic kidney disease stages (G3, G4, and G5) than those with primary MGN, although these differences were not statistically significant. In contrast, the prevalence of arterial hypertension did not differ between the groups.

In addition to serving as the gold standard for diagnosing MGN, histopathological evaluation of kidney biopsy samples can also suggest a possible etiology, whether primary or secondary. Specifically, the pres-

nosti na optičkoj mikroskopiji sa većom verovatnoćom ukazuje na sekundarnu etiologiju MGN [23]. Rezultati naše studije upućuju na isti zaključak – od 9 uzoraka tkiva sa uočenom endokapilarnom proliferacijom, 88,9% njih je odgovaralo pacijentima sa sekundarnim MGN. Pozitivnost na *PLA$_2$R* i *THSD7A* antigene upućuje na primarnu etiologiju bolesti [25,26]. Sa druge strane, pozitivnost na *EXT1* i *EXT2* antigene udružena je sa autoimunskim bolestima kao etiološkim činiocem sekundarnog MGN (pre svega sistemskim eritemskim lupusom), dok je *NELL-1* u trećini slučajeva udružen sa malignim oboljenjem [27,28].

„*Full house*" nalaz imunofluorescentne mikroskopije predstavlja izrazitu pozitivnost na svih 5 markera, IgG, C3, ali i IgA, IgM i C1q, i odlika je pre svega sekundarnog MGN u okviru sistemskog eritemskog lupusa [29]. Depoziti IgG i C3 komponente komplementa duž glomerularne bazalne membrane predstavljaju karakterističan nalaz u membranoznom glomerulonefritisu, bez obzira na etiologiju bolesti, ali je ipak primećeno da je njihova izrazita pozitivnost bila češće udružena sa sekundarnom bolešću. Markeri IgA, IgM i C1q pokazali su statistički značajnu razliku u distribuciji u odnosu na etiologiju MGN i znatno češće su bile prisutne umerena i izražena pozitivnost na ove markere kod obolelih od sekundarnog MGN. Razlike u distribuciji pozitivnosti na κ-lance i λ-lance ne mogu se adekvatno tumačiti iz razloga što se ova dva markera do 2018. godine nisu rutinski određivala na Institutu za patologiju Medicinskog fakulteta u Beogradu.

ZAKLJUČAK

Osobe ženskog pola češće boluju od sekundarnog MGN. Karakteristike MGN sekundarne etiologije su prisustvo hematurije, endokapilarne hipercelularnosti i pozitivnosti imunofluorescence na markere koji se ne viđaju u primarnom MGN (IgA, IgM, C1q), dok su karakteristike MGN primarne etiologije značajno više vrednosti proteinurije, praćene značajno sniženom koncentracijom proteina u serumu.

SPISAK SKRAĆENICA

MGN – membranozni glomerulonefritis
pMGN – primarni membranozni glomerulonefritis
sMGN – sekundarni membranozni glomerulonefritis

Sukob interesa: Nije prijavljen.

ence of mesangial and endocapillary hypercellularity on light microscopy is more indicative of a secondary etiology [23]. The results of our study support this conclusion–of the nine tissue samples exhibiting endocapillary proliferation, 88.9% were from patients with secondary MGN. Conversely, positivity for *PLA2R* and *THSD7A* antigens indicates a primary etiology [25,26]. On the other hand, positivity for EXT1 and *EXT2* antigens is linked to autoimmune diseases as the underlying cause of secondary MGN, primarily systemic lupus erythematosus, whereas *NELL-1* positivity is associated with malignancy in approximately one-third of cases [27,28].

The "full house" pattern on immunofluorescence microscopy, characterized by positivity for all five markers, i.e., IgG, C3, as well as IgA, IgM, and C1q, is primarily indicative of secondary MGN in the context of systemic lupus erythematosus [29]. Deposits of IgG and the complement component C3 along the glomerular basement membrane are a characteristic feature of membranous glomerulonephritis, regardless of disease etiology; however, marked positivity for these markers was more frequently observed in secondary MGN. The distribution of IgA, IgM, and C1q positivity differed significantly according to MGN etiology, with moderate to strong positivity for these markers being significantly more common in secondary MGN. Differences in κ-chain and λ-chain positivity could not be adequately interpreted, as these markers were not routinely assessed at the Institute of Pathology, Faculty of Medicine in Belgrade, until 2018.

CONCLUSION

Females are more likely to develop secondary MGN. Features of secondary MGN include hematuria, endocapillary hypercellularity, and immunofluorescence positivity for markers not typically seen in primary MGN (IgA, IgM, C1q). In contrast, primary MGN is characterized by significantly higher levels of proteinuria, accompanied by markedly reduced serum protein concentrations.

ABBREVIATION LIST

MGN – membranous glomerulonephritis
pMGN – primary membranous glomerulonephritis
sMGN – secondary membranous glomerulonephritis

Conflict of interest: None declared.

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