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BRIEF REPORT

Non-albumin proteinuria as a parameter of tubulointerstitial inflammation in lupus nephritis

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Abstract

Tubulointerstitial inflammation (TI) has prognostic significance in the renal outcomes of lupus nephritis. Here, we aimed to determine whether non-albumin proteinuria is associated with TI severity and with the renal response in lupus nephritis. We included patients with biopsy-confirmed lupus nephritis at a tertiary medical center in Korea from January 2011 to April 2017. Patients in whom the urine protein/creatinine ratio (uPCR) and the urine albumin/creatinine ratio (uACR) were measured simultaneously were included. Laboratory data and renal pathology were reviewed. Non-albumin proteinuria was calculated by subtracting uACR from uPCR. The renal response was assessed by the amount of proteinuria present at 6 months after treatment with immunosuppressants. Logistic regression analyses were performed to identify factors associated with TI severity and renal response. Out of 45 patients, 36 (80%) had no-to-mild TI, whereas 9 (20%) had moderate-to-severe TI. Proliferative (class III ± V/IV ± V) and nonproliferative (class II/V) glomerulonephritis (GN) were present in 38 (84.4%) and 7 (15.6%) patients, respectively. In the logistic regression analyses, non-albumin proteinuria (uPCR − uACR) was associated with moderate-to-severe TI (odds ratio [OR] 3.166, 95% confidence interval [95% CI] 1.145–8.757, $p = 0.026$) and was inversely associated with complete renal response (adjusted OR 0.180, 95% CI 0.045–0.718, $p = 0.015$). In lupus nephritis, non-albumin proteinuria was associated with TI severity and with poor renal response after immunosuppressive treatment. Thus, the determination of non-albumin proteinuria can provide clinically valuable information on lupus nephritis.

Keywords Lupus nephritis · Non-albumin proteinuria · Systemic lupus erythematosus · Tubulointerstitial inflammation

Introduction

Lupus nephritis is a serious manifestation of systemic lupus erythematosus (SLE) and is associated with considerable morbidity and mortality. Lupus nephritis involvement patterns are currently defined according to the International Society of Nephrology/Renal Pathology Society's (ISN/RPS) 2003 classification, which is exclusively based on glomerular pathology [1]. However, pathologic changes in lupus nephritis are not confined to the glomerulus and can involve all kidney components [2]. Among these pathologic changes, tubulointerstitial inflammation (TI) is commonly observed in lupus nephritis [2]. Furthermore, several studies have suggested that TI severity rather than glomerular lesion type provides better prognostic information on long-term renal outcomes in lupus nephritis [3–5].

The mechanisms and types of urinary proteins are distinct between glomerular and tubulointerstitial pathologies. Glomerular proteinuria results from the disruption of the glomerular filtration barrier to the extent that plasma proteins, which are normally largely excluded from the glomerular filtrate, can readily pass through the disrupted barrier [6]. Thus, in glomerular pathologies, urinary proteins predominantly comprise high-molecular-weight proteins, mainly albumin [7]. Conversely, in tubulointerstitial pathologies, urinary protein excretion results

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from failure to reabsorb the filtered proteins owing to tubular damage [8]. Therefore, the predominant urinary proteins in tubulointerstitial pathologies are non-albumin proteins, such as α1-microglobulin, retinol-binding protein, and β2-microglobulin [7].

Accordingly, based on the difference in urinary protein types between glomerular and tubulointerstitial diseases, previous studies have suggested that non-albumin proteinuria, as measured by the urinary albumin to creatinine ratio (uACR)/urinary total protein to creatinine ratio (uPCR), is useful in determining the origin of proteinuria [9, 10]. However, the clinical significance of non-albumin proteinuria in lupus nephritis remains unclear.

Here, we aimed to assess whether non-albumin proteinuria is associated with TI severity in lupus nephritis and with the renal response after treatment with an immunosuppressive therapy.

Materials and methods

Study population

Electronic medical records of patients diagnosed with lupus nephritis at a tertiary referral hospital in Seoul, South Korea, between January 2011 and April 2017 were retrospectively reviewed. All patients fulfilling the 1997 American College of Rheumatology classification criteria for SLE were eligible [11]. In this cohort, patients with simultaneously measured uPCR and uACR levels were included in our analysis. The following data were collected from their records: age, sex, uACR, uPCR, creatinine (Cr), glomerular filtration rate (GFR) calculated using the MDRD equation, C3, C4, anti-double-stranded DNA (anti-dsDNA) antibodies, medication history [steroids, cyclophosphamide, and mycophenolate mofetil (MMF)], ISN/RPS class, and activity and chronicity indices of the National Institutes of Health system [12]. Urinary non-albumin protein levels were evaluated using the calculation uPCR − uACR. A pathologist without prior knowledge of the clinical outcome reviewed TI severity, which was semiquantitatively scored based on the extent of inflammatory cell infiltration in the tubulointerstitium. The score ranged from 0 to 4, which corresponded to no (0%), minimal (< 10%), mild (10–25%), moderate (26–50%), and severe (> 50%) inflammatory cell infiltration in the tubulointerstitium.

Response to immunosuppressants

Patients with class III ± V and IV ± V lupus nephritis were treated with immunosuppressive drugs (steroids with either cyclophosphamide or MMF) with corticosteroids. Patients with class II lupus nephritis did not receive immunosuppressive drugs, and those with class V lupus nephritis received steroids with/without MMF. A complete renal response was defined as a uPCR of < 500 mg/g and normal or near-normal GFR (≥ 60 mL/min/m^2) after 6 months of immunosuppressive therapy [13].

Statistical analysis

For comparisons among different groups, the Mann–Whitney *U* test and Fisher's exact test were used for continuous and categorical variables, respectively. A logistic regression analysis was performed to identify factors associated with moderate-to-severe TI and those associated with complete renal response after 6 months of immunosuppressive therapy. Factors with a p value of ≤ 0.15 in the univariable analysis were selected for multivariable analysis. uPCR and TI severity were not included in the multivariable analysis because of multicollinearity with uPCR − uACR. The chronicity index was not included in the multivariable analysis because of multicollinearity with glomerulosclerosis.

Results

Baseline characteristics

Patients included in the analysis were 32 (71.1%) females and 13 (28.9%) males with mean age 33.0 (± 16.7) years. According to the ISN/RPS classification, 1 (2.2%), 12 (26.7%), 16 (35.6%), 6 (13.3%), 5 (11.1%), and 5 (11.1%) patients were class II, class

Table 1 Histological features of patients

	Number of patients
ISN/RPS classification, n (%)	
II	1 (2.2)
III	12 (26.7)
IV	16 (35.6)
V	6 (13.3)
III + V	5 (11.1)
IV + V	5 (11.1)
Tubulointerstitial inflammation, n (%)	
No inflammation	6 (13.3)
Minimal inflammation	12 (26.7)
Mild inflammation	18 (40.0)
Moderate inflammation	6 (13.3)
Severe inflammation	3 (6.7)
Tubular atrophy, n (%)	
No-to-mild atrophy	41 (91.1)
Moderate-to-severe atrophy	4 (8.9)
Interstitial fibrosis, n (%)	
No-to-mild fibrosis	42 (93.3)
Moderate-to-severe fibrosis	3 (6.7)
Glomerulosclerosis (%), median (IQR)	7.1 (0.0–17.7)
Activity index (mean ± SD)	7.18 ± 4.10
Chronicity index (mean ± SD)	1.36 ± 1.50

ISN/RPS, the International Society of Nephrology/Renal Pathology Society; *SD*, standard deviation; *IQR*, interquartile range

Table 2 Comparisons between different histological groups

	ISN/RPS classification			TI severity		
	III ± V and IV ± V ($n = 38$)	II and V ($n = 7$)	p value	Moderate-to-severe ($n = 9$)	No-to-mild ($n = 36$)	p value
Age	28.0 (20.0–43.3)	34.0 (16.0–50.0)	0.915	44.0 (15.5–57.5)	27.5 (19.3–41.3)	0.293
Female	27 (71.1%)	5 (71.4%)	> 0.999	8 (88.9%)	24 (66.7%)	0.249
uACR (mg/g)	1302.9 (593.7–3291.3)	1563.9 (968.0–2608.4)	0.963	3163.1 (1186.8–4078.7)	1208.1 (682.9–2813.0)	0.071
uPCR (mg/g)	2281.7 (1010.0–4737.1)	2485.0 (1216.0–3716.9)	0.939	4644.5 (2835.0–5338.6)	1848.1 (880.4–3662.3)	*0.012*
uACR/uPCR	0.675 (0.522–0.776)	0.796 (0.565–0.912)	0.148	0.651 (0.487–0.732)	0.710 (0.536–0.796)	0.425
uPCR − uACR (mg/g)	652.9 (318.2–1470.8)	426.6 (248.0–2006.1)	0.549	1622.0 (869.4–1885.0)	499.4 (255.2–1022.1)	*0.008*
Cr (mg/dL)	0.82 (0.57–1.08)	0.54 (0.45–0.70)	0.157	1.12 (0.69–1.30)	0.70 (0.53–1.01)	*0.033*
GFR < 60 mL/min/1.73 m^2	7 (18.4%)	1 (14.3%)	> 0.999	4 (44.4%)	4 (11.1%)	*0.039*
C3 (mg/dL)	36.8 (24.7–50.3)	70.6 (56.8–93.7)	*0.002*	42.8 (34.5–55.4)	36.8 (24.4–60.3)	0.490
C4 (mg/dL)	5.4 (4.5–7.1)	13.8 (7.7–18.2)	*0.003*	5.4 (2.4–9.7)	6.2 (4.9–8.2)	0.320
Anti-dsDNA (IU/mL)	305.5 (88.4–1242.5)	22.2 (8.4–70.7)	*0.002*	192.6 (10.0–638.0)	230.0 (51.7–1160.0)	0.398
TI severity (moderate-to-severe/no-to-mild)	9 (23.7%)/29 (76.3%)	0 (0%)/7 (100%)	0.315	N/A	N/A	N/A
Tubular atrophy (moderate-to-severe/no-to-mild)	4 (10.5%)/34 (89.5%)	0 (0%)/7 (100%)	> 0.999	3 (33.3%)/6 (66.7%)	1 (2.8%)/35 (97.2%)	*0.021*
Interstitial fibrosis (moderate-to-severe/no-to-mild)	3 (7.9%)/35 (92.1%)	0 (0%)/7 (100%)	> 0.999	2 (22.2%)/7 (77.8%)	1 (2.8%)/35 (97.2%)	0.097
ISN/RPS class (proliferative/nonproliferative)	N/A	N/A	N/A	9 (100%)/0 (0%)	29 (80.6%)/7 (19.4%)	0.315
Glomerulosclerosis (%)	8.3 (0.0–16.5)	3.8 (0.0–20.0)	0.529	11.1 (0.0–39.6)	6.2 (0.0–14.5)	0.306
Activity index†	1.0 (1.0–2.0)	1.0 (0.0–1.0)	0.101	7.0 (4.5–11.0)	6.0 (3.0–8.8)	0.232
Chronicity index†	0.0 (0.0–2.0)	0.0 (0.0–0.0)	0.234	0.0 (0.0–1.0)	0.5 (0.0–1.0)	0.878

† Tubulointerstitial component of activity and chronicity indices for comparing ISN/RPS classification and glomerular component of activity and chronicity indices for comparing TI severity

ISN/RPS, the International Society of Nephrology/Renal Pathology Society; *uPCR*, urine protein/creatinine ratio; *uACR*, urine albumin/creatinine ratio; *dsDNA*, double-stranded DNA; *TI*, tubulointerstitial inflammation; *Cr*, creatinine; *GFR*, glomerular filtration rate

p value < 0.05 is indicated in italic

III, class IV, class V, class III + V, and class IV + V, respectively. The distribution of TI severity was as follows: no, minimal, mild, moderate, and severe inflammation in 6 (13.3%), 12 (26.7%), 18 (40.0%), 6 (13.3%), and 3 (6.7%) patients, respectively. The mean (± standard deviation) activity index and chronicity index scores were 7.18 ± 4.10 and 1.36 ± 1.50, respectively (Table 1). The mean follow-up time was 30.3 (± 19.8) months.

Comparisons between different histological types

Comparisons between the different histological types according to the ISN/RPS classification and TI severity are presented in Table 2. Patients with proliferative glomerulonephritis (GN) (class III ± V/IV ± V) had lower levels of C3 [36.8 (24.7–50.3) versus 70.6 (56.8–93.7) mg/dL, $p = 0.002$] and C4 [5.4 (4.5–7.1) versus 13.8 (7.7–18.2) mg/dL, $p = 0.003$] and higher titers of anti-dsDNA antibodies [305.5 (88.4–1242.5) versus 22.2 (8.4–70.7) IU/mL, $p = 0.002$] than those with nonproliferative GN (class II/V). The extent of proteinuria, as determined by uACR or uPCR, did not differ between the two groups. Additionally, non-albumin proteinuria levels (uPCR − uACR) did not differ significantly between the proliferative and nonproliferative GN groups.

Comparisons among the patients with different TI severities revealed that the moderate-to-severe TI group had a higher uPCR value [4644.5 (2835.0–5338.6) versus 1848.1 (880.4–3662.3) mg/g, $p = 0.012$], higher non-albumin proteinuria (uPCR − uACR) [1622.0 (869.4–1885.0) versus 499.4 (255.2–1022.1) mg/g, $p = 0.008$], higher Cr level [1.12 (0.69–1.30) versus 0.70 (0.53–1.01) mg/dL, $p = 0.033$], and higher proportion of patients with GFR < 60 mL/min/1.73 m^2 [4 (44.4%) versus 4 (11.1%), $p = 0.039$] than the no-to-mild TI group. Further, a logistic regression analysis was performed to evaluate the factors associated with moderate-to-severe TI in lupus nephritis (Table 3). Notably, uPCR − uACR was significantly associated with moderate-to-severe TI (odds ratio [OR] 3.166, 95% confidence interval [95% CI] 1.145–8.757, $p = 0.026$).

Factors associated with renal response

Among the 38 patients with proliferative GN (classes III ± V and IV ± V), 21 patients received steroids with MMF and 17 patients received steroids with cyclophosphamide. Among the seven patients with nonproliferative GN (classes II and V), three patients received steroids with MMF, two patients received steroid monotherapy, and two patients did not receive an immunosuppressant. The renal response could be evaluated in 36 patients (32 patients with proliferative GN and 4 patients with nonproliferative GN) at 6 months. Among these 36 patients, 24 patients achieved a complete renal response. A logistic regression analysis was performed to evaluate the factors associated with complete renal response at 6 months after treatment with immunosuppressants (Table 4). In the univariable analysis, uPCR − uACR (unadjusted OR 0.184, 95% CI 0.053–0.638, $p = 0.008$) and TI severity (unadjusted OR 0.143, 95% CI 0.027–0.749, $p = 0.021$) were significantly associated with a lower complete renal response rate, whereas there was no significant association with uPCR alone (unadjusted OR 0.684, 95% CI 0.459–1.020, $p = 0.062$). Further, the multivariable analysis showed that uPCR − uACR was significantly associated with poor renal response in terms of complete renal response (adjusted OR 0.180, 95% CI 0.045–0.718, $p = 0.015$).

Table 3 Factors associated with moderate-to-severe TI

	OR	95% CI	*p* value
Age	1.033	0.989–1.078	0.147
Female	4.000	0.447–35.788	0.215
uACR	1.714	1.007–2.917	*0.047*
uPCR	1.677	1.085–2.593	*0.020*
uACR/uPCR	0.481	0.019–12.158	0.657
uPCR − uACR	3.166	1.145–8.757	*0.026*
Cr	7.724	0.970–61.480	0.053
GFR < 60 mL/min/1.73 m^2	6.400	1.198–34.203	*0.030*
C3	1.002	0.965–1.040	0.923
C4	0.899	0.708–1.141	0.381
Anti-dsDNA	0.954	0.867–1.050	0.334
Tubular atrophy	17.500	1.551–197.435	0.021
Interstitial fibrosis	10.000	0.793–126.027	0.075
Glomerulosclerosis	1.044	0.997–1.093	0.065
GN activity index	1.121	0.924–1.360	0.246
GN chronicity index	0.936	0.301–2.912	0.909
ISN/RPS class (proliferative GN)	N/A	N/A	0.894
Severity of proliferative lesions*	2.182	0.436–10.908	0.342

ISN/RPS, the International Society of Nephrology/Renal Pathology Society; *uPCR*, urine protein/creatinine ratio; *uACR*, urine albumin/creatinine ratio; *dsDNA*, double-stranded DNA; *GN*, glomerulonephritis; *TI*, tubulointerstitial inflammation; *Cr*, creatinine; *GFR*, glomerular filtration rate; *CI*, confidence interval

*Association between the severity of proliferative lesions and moderate-to-severe TI in classes III ± V and IV ± V

p value < 0.05 is indicated in italic

Discussion

Our results showed that non-albumin proteinuria (uPCR − uACR) was significantly higher in patients with moderate-to-severe TI than in patients with no-to-mild TI. Further, higher uPCR − uACR levels at baseline were associated with poor renal response after 6 months of treatment. To our knowledge, this is the first study evaluating the clinical significance of non-albumin proteinuria in lupus nephritis.

In our data, the values of uACR, uPCR, uPCR − uACR, and GFR < 60 (mL/min/1.73 m^2) were associated with moderate-to-severe TI (Table 3). In contrast to previous studies that

Table 4 Factors associated with complete renal response

	OR	95% CI	*p* value
Univariable analysis			
Age	0.932	0.844–1.030	0.169
Female	0.400	0.070–2.277	0.302
uACR	0.773	0.482–1.240	0.285
uPCR	0.684	0.459–1.020	0.062
uACR/uPCR	2.255	0.117–43.554	0.590
uPCR − uACR	0.184	0.053–0.638	*0.008*
Cr	0.317	0.042–2.376	0.264
GFR < 60 mL/min/1.73 m^2	0.286	0.052–1.570	0.150
C3	1.030	0.988–1.074	0.167
C4	1.175	0.917–1.505	0.202
Anti-dsDNA	0.968	0.923–1.015	0.176
Activity index	0.977	0.824–1.160	0.793
Chronicity index	0.685	0.427–1.098	0.116
ISN/RPS class (proliferative GN)	N/A	N/A	> 0.999
TI severity (moderate-to-severe)	0.143	0.027–0.749	*0.021*
Tubular atrophy	N/A	N/A	> 0.999
Interstitial fibrosis	N/A	N/A	> 0.999
Glomerulosclerosis	0.938	0.888–0.990	*0.021*
Cyclophosphamide	1.500	0.316–7.124	0.610
Mycophenolate mofetil	0.600	0.148–2.436	0.475
Steroid monotherapy	1.235	0.256–5.970	0.793
Cumulative steroid dose (grams of prednisolone or equivalent)	1.041	0.782–1.386	0.784
Multivariable analysis			
uPCR − uACR	0.180	0.045–0.718	*0.015*
GFR < 60 mL/min/1.73 m^2	1.552	0.142–17.012	0.719
Glomerulosclerosis	0.933	0.873–0.996	*0.037*

ISN/RPS, the International Society of Nephrology/Renal Pathology Society; *uPCR*, urine protein/creatinine ratio; *uACR*, urine albumin/creatinine ratio; *dsDNA*, double-stranded DNA; *GN*, glomerulonephritis; *TI*, tubulointerstitial inflammation; *Cr*, creatinine; *GFR*, glomerular filtration rate; *OR*, odds ratio; *CI*, confidence interval

p value < 0.05 is indicated in italic

suggested using uACR/uPCR to determine the origin of proteinuria [9, 10], TI severity was not significantly associated with uACR/uPCR (OR 0.481, 95% CI 0.019–12.158, $p = 0.657$; Table 3) in the current study. Pathologic changes in lupus nephritis can involve both the glomeruli and tubulointerstitium; this differs from other renal disorders that predominantly or exclusively involve either compartment, such as membranous nephropathy. Thus, in lupus nephritis, where concomitant GN and TI exist, uPCR − uACR appears to be superior to uACR/uPCR in assessing TI severity. In other words, the coexistence of a glomerular pathology increases the variability in the amount of urinary albumin excreted, which may underlie the inaccuracy of using uACR/uPCR for TI severity assessment compared with uPCR − uACR.

Here, TI severity in patients with proliferative GN did not differ from that in patients with nonproliferative GN (Table 2). The lack of association between the ISN/RPS class and TI severity suggests that glomerular and tubulointerstitial pathologies are mediated by different processes. Previous studies have indicated that severe TI could be mediated by local in situ immunologic processes, whereas GN is associated with systemic autoimmunity [14, 15]. Indeed, we observed significant differences in the levels of serum C3, C4, and anti-dsDNA antibodies—markers of systemic autoimmunity—between the proliferative GN and nonproliferative GN groups. Conversely, these values did not differ significantly according to the extent of TI severity (Table 2). Thus, these findings suggest that TI assessment captures an important pathologic process that may be confined to the renal tissue and is independent of glomerular and/or systemic autoimmunity.

A previous study noted that low C4 level, low GFR, and time from lupus nephritis diagnosis are predictors of a renal response in lupus nephritis [16]. However, C4 level and low GFR were not associated with a renal response in our data (Table 4). All patients with proliferative GN (Table 2) had low C4 levels (lower than the reference level), and none of these patients had a GFR of < 30

mL/min/1.73 m^2. In the previous study, the C4 level was lower than the reference in only 63% of the patients, and GFR was < 30 mL/min/1.73 m^2 in 9% of the patients. Thus, we can speculate that these differences in clinical characteristics may account for the conflicting results. In our data, non-albumin proteinuria (uPCR − uACR), as a parameter reflecting TI severity, was significantly associated with poor renal response at 6 months after immunosuppressive treatment. Because early response to induction therapy is important for long-term renal outcomes in lupus nephritis [17, 18], uPCR − uACR can be valuable in assessing long-term renal outcomes in lupus nephritis.

Serial measurements of uPCR during follow-up in patients with lupus nephritis are recommended by current guidelines including the European League Against Rheumatism [13]. However, there are currently no guidelines that recommend uACR measurement in lupus nephritis. In the present study, non-albumin proteinuria, which was defined as uPCR − uACR, was significantly associated with both the TI severity and renal response. Thus, the simultaneous measurements of urinary albumin and urinary total protein at baseline may be beneficial in predicting renal response to immunosuppressive therapy.

Our study has several limitations. TI severity was reviewed by a pathologist as a five-tier variable. However, the statistical analysis was only possible using a two-tier variable (no-to-mild and moderate-to-severe) because of the small sample size. Similarly, the ISN/RPS classification required a two-tier variable for the analysis (proliferative/nonproliferative) because of the small sample size. The follow-up time was relatively short, and we were unable to evaluate long-term renal outcomes including the rate of renal flare and end-stage renal disease. Therefore, future studies are necessary to confirm the present results and long-term renal outcomes in larger sample sizes.

In conclusion, we found that non-albumin proteinuria (uPCR − uACR) is associated with severe TI in lupus nephritis and inversely associated with complete renal response after immunosuppressive treatment. Thus, the assessment of non-albumin proteinuria by simultaneous measurements of urinary protein and albumin seems to be clinically significant and can provide valuable information for patients with lupus nephritis.

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Compliance with ethical standards

This study was approved by the Institutional Review Board of the Asan Medical Center in Seoul, South Korea (IRB no. 2016-1258). Requirement for informed consent was waived because of the retrospective nature of the study.

Disclosures None.

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