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Renal flare in class V lupus nephritis: increased risk in patients with tubulointerstitial lesions

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Abstract

The objective of this study is to investigate the risk factors of renal flare in patients with membranous lupus nephritis (class V lupus nephritis). Biopsy-proven pure membranous lupus nephritis patients diagnosed between January 1997 and September 2017 were studied. We assessed and compared the clinical and pathological parameters between patients who experienced renal flare and those who did not. To identify risk factors of renal flare, multivariable Cox proportional hazard regression analysis was performed. Out of the 53 patients with pure membranous lupus nephritis, 17 patients (32.1%) experienced renal flare during a median follow-up of 121.5 months (range 44.4–196.9). Patients who experienced renal flare had significantly higher proportion of tubulointerstitial inflammation (76.5% vs. 36.1%, $p=0.006$) and tubular atrophy/interstitial fibrosis (70.6% vs. 27.8%, $p=0.003$) at baseline. In multivariable Cox proportional hazard regression analysis, the presence of tubulointerstitial inflammation [adjusted hazard ratio (HR) 5.532, 95% confidence interval (CI) 1.722–17.776, $p=0.004$] and tubular atrophy/interstitial fibrosis (adjusted HR 4.328, 95% CI 1.450–12.916, $p=0.009$) at baseline was significantly associated with increased risk of renal flare. The presence of tubulointerstitial inflammation and tubular atrophy/interstitial fibrosis is associated with increased risk of renal flare in patients with membranous lupus nephritis.

Keywords Membranous lupus nephritis · Tubulointerstitial inflammation · Tubular atrophy · Interstitial fibrosis · Flare

Introduction

Lupus nephritis is a clinically important manifestation of systemic lupus erythematosus (SLE) that entails considerable morbidity and mortality [1]. Immune complexes and complements play an important role in pathogenesis of lupus nephritis [2]. According to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification, lupus nephritis is classified into six categories based on glomerular pathology [3]; as such, different ISN/RPS 2003 classes display different clinicopathologic characteristics, with class III and IV lupus nephritis (proliferative

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lupus nephritis) being characterized as highly inflammatory with immune complex deposition in the subendothelial space [3]. Conversely, class V lupus nephritis (membranous lupus nephritis) is characterized by immune complex deposition in the subepithelial space [3]. Thus, treatment strategies differ between proliferative lupus nephritis and membranous lupus nephritis [4]: proliferative lupus nephritis is generally treated with immunosuppressants, and membranous lupus nephritis is treated with anti-proteinuric agents and immunosuppressants for sub-nephrotic range and nephrotic range proteinuria, respectively [4, 5]. Renal prognosis, defined as the progression to chronic kidney disease and end-stage renal disease (ESRD), also differs between proliferative lupus nephritis and membranous lupus nephritis, with membranous lupus nephritis having a more favorable prognosis [4].

Although membranous lupus nephritis has a better renal prognosis than does proliferative lupus nephritis, renal flare [6] and progression to ESRD do occur [7], and, therefore, should not be considered a benign condition [8]. Considering that the occurrence of renal flares is an independent predictor of renal prognosis in membranous lupus nephritis [9], it is important to detect patients at a higher risk of renal flare in patients with membranous lupus nephritis. In this study, we aimed to identify the risk factors of renal flare in patients with pure class V lupus nephritis.

Materials and methods

Study population

The medical records of patients diagnosed with biopsy-proven pure membranous lupus nephritis at a tertiary referral hospital between January 1997 and September 2017 were retrospectively reviewed. For patients who underwent renal biopsy before the application of ISN/RPS 2003 classification, their biopsy results were reclassified according to ISN/RPS 2003 classification. All the patients met the 1997 American College of Rheumatology (ACR) classification criteria for SLE [10]. The institutional review board of the Asan Medical Center in Seoul, South Korea approved the protocol of this study (IRB No: 2018-0137). Due to the retrospective nature of this study, the requirement for informed consent was waived.

Clinical and pathological parameters

The following demographic and clinicopathologic data at the time of membranous lupus nephritis diagnosis were reviewed: age, sex, urine protein/creatinine ratio (uPCR), urinalysis results, serum albumin level, serum creatinine level, glomerular filtration rate (GFR), antibodies to extractable nuclear antigens, anti-double-stranded DNA (anti-dsDNA) antibodies, C3, C4, lupus anticoagulant, anticardiolipin antibodies, anti-beta2 glycoprotein antibodies, activity index, chronicity index, presence of tubulointerstitial inflammation, tubular atrophy/interstitial fibrosis, and severity of glomerulosclerosis. The severity of glomerulosclerosis was assessed according to the proportion of sclerotic glomeruli among the total glomeruli. The pathologic parameters were reviewed by a pathologist without prior knowledge of the clinical outcome. The SLE Disease Activity Index (SLEDAI), a validated index of lupus disease activity [11], and Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage index [12] were measured when membranous lupus nephritis was diagnosed.

We reviewed the medications prescribed during the follow-up period, including hydroxychloroquine, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB), tacrolimus, immunosuppressants (cyclophosphamide and mycophenolate mofetil as an induction therapy), and glucocorticoids. For glucocorticoids, the cumulative dose during the first year of use was assessed.

Definition of renal flare

Renal flare was defined as a decrease in estimated GFR of $\geq 10\%$ with the appearance of active urine sediment, or an increase of uPCR to more than 1000 mg/g after achieving complete renal response [13].

Statistical analysis

Mann–Whitney tests were used to compare continuous variables, and Fisher's exact tests were used to compare categorical variables. Multivariable Cox proportional hazard regression analysis with stepwise backward elimination was used to identify the risk factors of renal flare in membranous lupus nephritis. The proportional hazard assumption was confirmed by examining the log [− log (survival)] curves and by testing Schoenfeld partial residuals; no relevant violations were identified. Factors with a p value less than 0.1 in the univariable analysis were selected for inclusion in the multivariable analysis. Renal flare-free survival rates were analyzed using the Kaplan–Meier analysis and were compared using the log-rank test.

Results

Fifty-three biopsy-proven pure membranous lupus nephritis (class V lupus nephritis according to the 2003 ISN/RPS classification [3]) patients who met the 1997 ACR classification criteria [10] were identified. The median follow-up duration was 121.5 (range 44.4–196.9) months. Flare occurred

in 17 (32.1%) patients. The median time from diagnosis of membranous lupus nephritis to renal flare was 65.1 (range 41.1–78.8) months.

Comparison of patients according to the occurrence of renal flare

Table 1 shows the comparison of the characteristics between the two groups. Proportion of females ($p = 0.730$), age ($p = 0.901$), and time from SLE diagnosis to membranous lupus nephritis diagnosis ($p = 0.865$) did not significantly differ between the two groups. uPCR ($p = 0.291$), proportions of patients with pyuria ($p = 0.748$) and hematuria ($p = 0.246$), serum albumin levels ($p = 0.864$), serum creatinine levels ($p = 0.257$), and GFR ($p = 0.277$) were also not significantly different between the two groups. There were no significant differences in autoantibody profiles, SLEDAI ($p = 0.297$) and SLICC/ACR damage index ($p = 0.961$) between the two groups as well. When the histological parameters were compared, the two groups did not differ in activity index ($p = 0.091$), chronicity index ($p = 0.077$), and severity of

Table 1 Comparison of characteristics according to the occurrence of renal flare

	Flare occurred ($N = 17$)	Flare not occurred ($N = 36$)	p value
Female	14 (82.4%)	27 (75.0%)	0.730
Age (years)	32.0 (24.0–41.5)	29.5 (24.3–36.0)	0.901
Time from SLE to LN (months)	0.0 (0.0–43.7)	0.0 (0.0–27.7)	0.865
uPCR (mg/g)	2008.0 (1254.0–4141.5)	3286.0 (1910.3–4738.9)	0.291
Urine WBC ≥ 3–5/HPF	5 (29.4%)	9 (25.0%)	0.748
Urine RBC ≥ 3–5/HPF	8 (47.1%)	23 (63.9%)	0.246
Albumin (g/dl)	2.9 (2.3–3.5)	2.9 (2.5–3.3)	0.864
Creatinine (mg/dl)	0.70 (0.60–0.85)	0.62 (0.51–0.70)	0.257
GFR (ml/min/1.73 m^2)	119.0 (97.0–128.0)	122.0 (112.0–133.0)	0.277
C3 (mg/dl)	61.2 (36.1–82.8)	66.3 (50.2–88.5)	0.360
C4 (mg/dl)	12.6 (4.4–16.8)	12.3 (7.0–17.9)	0.696
Anti-dsDNA Ab (IU/ml)	14.3 (6.9–77.0)	10.47 (5.3–84.9)	0.413
Anti-Sm Ab ($N^a = 43$)	4 (28.6%)	8 (27.6%)	> 0.999
Anti-Ro Ab ($N^a = 45$)	7 (46.7%)	18 (60.0%)	0.396
Anti-La Ab ($N^a = 45$)	3 (20.0%)	4 (13.3%)	0.670
Anti-RNP Ab ($N^a = 43$)	6 (42.9%)	13 (44.8%)	0.903
Lupus anticoagulant ($N^a = 45$)	4 (25.0%)	4 (13.8%)	0.427
Anti-cardiolipin Ab ($N^a = 48$)	3 (20.0%)	11 (33.3%)	0.498
Anti-beta2 glycoprotein 1 Ab ($N^a = 39$)	2 (18.2%)	4 (14.3%)	> 0.999
SLEDAI	10.0 (8.5–12.5)	12.0 (8.0–13.8)	0.803
SLICC/ACR damage index	1.0 (1.0–3.0)	1.0 (1.0–3.0)	0.961
Activity index	2.0 (1.0–3.0)	0.0 (0.0–3.0)	0.091
Chronicity index	2.0 (0.0–4.0)	0.0 (0.0–3.0)	0.077
Tubulointerstitial inflammation	13 (76.5%)	13 (36.1%)	**0.006**
Tubular atrophy/interstitial fibrosis	12 (70.6%)	10 (27.8%)	**0.003**
Glomerulosclerosis (%)	0.0 (0.0–8.7)	0.0 (0.0–3.8)	0.346
Use of hydroxychloroquine	15 (88.2%)	31 (86.1%)	> 0.999
Use of ACEi or ARB	16 (94.1%)	27 (75.0%)	0.140
Use of tacrolimus	7 (41.2%)	8 (22.2%)	0.197
Use of cyclophosphamide	2 (11.8%)	7 (19.4%)	0.701
Use of mycophenolate mofetil	6 (35.3%)	11 (30.6%)	0.730
1-year cumulative dose (g)	4.09 (3.30–6.14)	4.08 (3.22–5.16)	0.666

SLE systemic lupus erythematosus, *LN* lupus nephritis, *uPCR* urine protein/creatinine ratio, *WBC* white blood cell, *RBC* red blood cell, *GFR* glomerular filtration rate, *anti-dsDNA Ab* anti-double-stranded DNA antibody, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index, *SLICC/ACR* Systemic Lupus International Collaborating Clinics/American College of Rheumatology, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker

[a]Patients with missing data excluded

p values <0.05 are indicated in bold

glomerulosclerosis ($p = 0.346$). However, patients who experienced renal flare during follow-up had significantly higher proportion of patients with tubulointerstitial inflammation [13 (76.5%) vs. 13 (36.1%), $p = 0.006$] and tubular atrophy/interstitial fibrosis [12 (70.6%) vs. 10 (27.8%), $p = 0.003$] at baseline. The proportion of patients using hydroxychloroquine ($p > 0.999$), ACEi or ARB ($p = 0.140$), tacrolimus ($p = 0.197$), cyclophosphamide ($p = 0.701$), mycophenolate mofetil ($p = 0.730$), and 1-year cumulative dose of glucocorticoids ($p = 0.666$) did not significantly differ between the two groups.

Risk factors of renal flare in membranous lupus nephritis

To evaluate the risk factors of renal flare in membranous lupus nephritis patients, we performed Cox proportional hazard regression analysis (Table 2). In the univariable

Table 2 Risk factors of renal flare in pure membranous lupus nephritis

	Univariable analysis			Multivariable analysis		
	Unadjusted HR	95% CI	*p* value	Adjusted HR	95% CI	*p* value
Female	0.748	0.204–2.737	0.661			
Age	0.997	0.955–1.041	0.888			
uPCR	1.083	0.962–1.220	0.188			
Urine WBC ≥ 3–5/HPF	2.689	0.908–7.963	0.074	0.854	0.193–3.774	0.835
Urine RBC ≥ 3–5/HPF	0.534	0.197–1.448	0.218			
Albumin	0.710	0.330–1.527	0.381			
Creatinine	0.430	0.042–4.388	0.477			
GFR	1.008	0.986–1.030	0.472			
C3	0.991	0.971–1.011	0.376			
C4	0.980	0.919–1.045	0.533			
Anti-dsDNA Ab	1.001	0.999–1.002	0.371			
Anti-Sm Ab	1.805	0.549–5.934	0.331			
Anti-Ro Ab	0.734	0.254–2.119	0.568			
Anti-La Ab	1.141	0.234–5.566	0.870			
Anti-RNP Ab	1.278	0.422–3.870	0.664			
Lupus anticoagulant	2.871	0.898–9.179	0.075	1.118	0.039–4.040	0.865
Anti-cardiolipin Ab	0.658	0.180–2.404	0.527			
Anti-beta2 glycoprotein 1 Ab	1.321	0.277–6.288	0.727			
SLEDAI	1.137	0.973–1.330	0.107			
SLICC/ACR damage index	1.080	0.771–1.512	0.654			
Activity index (glomerular component)[a]	1.619	1.033–2.539	**0.036**	1.218	0.621–2.387	0.567
Chronicity index (glomerular component)[b]	1.364	0.968–1.924	0.076	1.135	0.752–1.712	0.547
Tubulointerstitial inflammation	4.841	1.541–15.209	**0.007**	5.532	1.722–17.776	**0.004**
Tubular atrophy/interstitial fibrosis	3.309	1.139–9.616	**0.028**	4.328	1.450–12.916	**0.009**
Glomerulosclerosis	1.007	0.965–1.051	0.742			
Use of hydroxychloroquine	0.876	0.183–4.187	0.868			
Use of ACEi or ARB	3.079	0.404–23.442	0.278			
Use of tacrolimus	0.872	0.294–2.588	0.805			
Use of cyclophosphamide	0.788	0.579–1.072	0.130			
Use of mycophenolate mofetil	1.512	0.544–4.207	0.428			
1-year cumulative dose of glucocorticoid	1.066	0.849–1.338	0.583			

HR hazard ratio, *CI* confidence interval, *uPCR* urine protein/creatinine ratio, *WBC* white blood cell, *RBC* red blood cell, *GFR* glomerular filtration rate, *anti-dsDNA Ab* anti-double-stranded DNA antibody, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index, *SLICC/ACR* Systemic Lupus International Collaborating Clinics/American College of Rheumatology, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker

[a]Glomerular component of activity index, rather than total activity index, to avoid multicollinearity with tubulointerstitial inflammation

[b]Glomerular component of chronicity index, rather than total chronicity index, to avoid multicollinearity with tubular atrophy/interstitial fibrosis

p values <0.05 are indicated in bold

analysis, the following factors had p values less than 0.1: pyuria [unadjusted hazard ratio (HR) 2.689, 95% confidence interval (CI) 0.908–7.963, $p=0.074$], positivity of lupus anticoagulant (unadjusted HR 2.871, 95% CI 0.898–9.179, $p=0.075$), activity index (glomerular component) (unadjusted HR 1.619, 95% CI 1.033–2.539, $p=0.036$), chronicity index (glomerular component) (unadjusted HR 1.364, 95% CI 0.968–1.924, $p=0.076$), tubulointerstitial inflammation (unadjusted HR 4.841, 95% CI 1.541–15.209, $p=0.007$), and tubular atrophy/interstitial fibrosis (unadjusted HR 3.309, 95% CI 1.139–9.616, $p=0.028$). In the multivariable analysis, tubulointerstitial inflammation (adjusted HR 5.532, 95% CI 1.722–17.776, $p=0.004$) and tubular atrophy/interstitial fibrosis (adjusted HR 4.328, 95% CI 1.450–12.916, $p=0.009$) remained statistically significant. Kaplan–Meier analysis showed a significantly higher rate of renal flare in the group with tubulointerstitial inflammation ($p=0.003$) (Fig. 1a) and in the group with tubular atrophy/interstitial fibrosis ($p=0.020$) (Fig. 1b).

Repeat renal biopsies in patients who experienced renal flare

In our study population, 11 of the 17 patients who experienced renal flare underwent repeat renal biopsy. Of the 11 patients who underwent repeat renal biopsy, class transformation to proliferative lupus nephritis occurred in 7 patients (63.6%). Among the 7 patients who transformed to proliferative lupus nephritis, 3 patients (42.9%) eventually progressed to ESRD (Table 3).

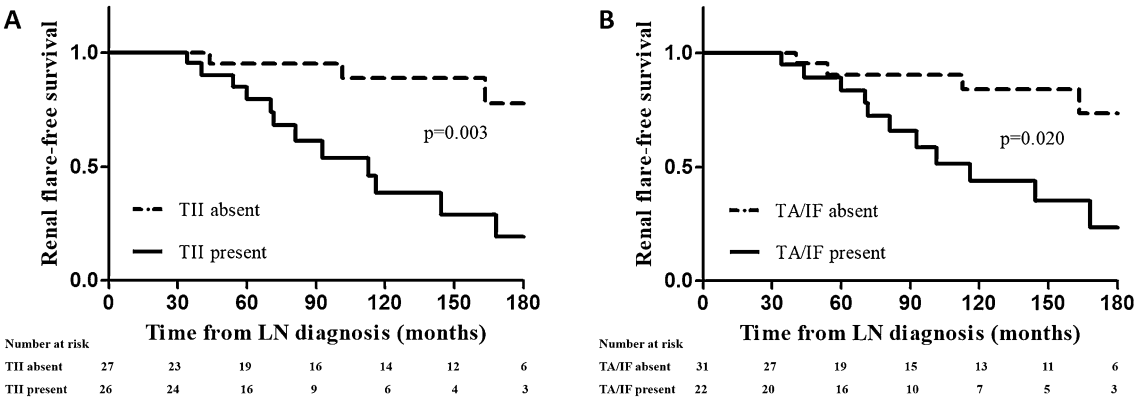

Fig. 1 Kaplan–Meier survival curve for occurrence of renal flare according to the presence of **a** tubulointerstitial inflammation, **b** tubular atrophy/interstitial fibrosis. *TII* tubulointerstitial inflammation, *TA/IF* tubular atrophy/interstitial fibrosis, *LN* lupus nephritis

Table 3 Characteristics of the 11 patients who underwent repeat renal biopsy

	At index biopsy									At second biopsy	Progression to
	Age (years)	Sex	Cr (mg/dl)	uPCR (mg/g)	ISN/RPS class	AI	CI	TII	TA/IF	ISN/RPS class	ESRD
Patient 1	25	Female	0.70	845.0	V	3	0	Present	Absent	IV + V	Yes
Patient 2	40	Female	0.60	6309.7	V	2	6	Present	Present	V	No
Patient 3	65	Male	0.60	581.0	V	0	3	Absent	Present	III	Yes
Patient 4	36	Female	0.80	1795.0	V	2	3	Present	Present	IV + V	No
Patient 5	24	Male	0.90	23783.0	V	2	2	Present	Present	III + V	No
Patient 6	33	Female	0.80	1332.0	V	2	4	Present	Present	III + V	No
Patient 7	27	Female	0.50	1494.0	V	0	0	Absent	Absent	V	No
Patient 8	24	Female	0.70	2221.0	V	3	2	Present	Present	IV	Yes
Patient 9	28	Female	0.70	3840.0	V	0	4	Absent	Present	V	No
Patient 10	39	Female	1.20	4242.0	V	3	2	Present	Present	V	No
Patient 11	56	Female	0.70	1452.0	V	3	2	Present	Present	III + V	No

Cr creatinine, *uPCR* urine protein/creatinine ratio, *ISN/RPS* International Society of Nephrology/Renal Pathology Society, *AI* activity index, *CI* chronicity index, *TII* tubulointerstitial inflammation, *TA/IF* tubular atrophy/interstitial fibrosis, *ESRD* end-stage renal disease

Discussion

In this study, we showed that the presence of tubulointerstitial inflammation and tubular atrophy/interstitial fibrosis in pure membranous lupus nephritis patients is associated with a significantly higher risk of renal flare during the course of disease. Renal flare is an important event that occurs during the natural course of lupus nephritis and provides opportunity for additional preventive strategies [14]. Previous studies have reported younger age, higher serum creatinine level, and higher chronicity index as factors associated with risk of renal flare [14–16]. In those studies, the majority of patients had proliferative lupus nephritis, which limits generalizability to patients with membranous lupus nephritis. Our study is meaningful in that it provides risk factors of renal flare particularly in patients with membranous lupus nephritis.

An increasing body of evidence shows that tubulointerstitial pathologies, rather than glomerular pathologies, are better at predicting renal prognosis in lupus nephritis patients [5, 17]. Tubulointerstitial lesions and glomerular lesions do not always coexist, and tubulointerstitial inflammation, tubular atrophy, and interstitial fibrosis are independent risk factors for poor renal outcomes [18]. Although several studies have reported the importance of tubulointerstitial damage in renal outcome of lupus nephritis, little is known about its association with renal flare in lupus nephritis. Our study adds to the existing knowledge by showing that tubulointerstitial lesions are independent risk factors of renal flare, as well.

In membranous lupus nephritis, repeat renal biopsy is recommended in renal flare cases, because class transformation to proliferative lupus nephritis occurs frequently [4, 19]. Since treatment strategy and renal prognosis differ between proliferative lupus nephritis and membranous lupus nephritis [4, 5], class transformation should be taken into consideration, especially for patients with membranous lupus nephritis at index biopsy. In our study, class transformation from membranous lupus nephritis to proliferative lupus nephritis was observed in the majority of patients (63.6%, 7 of 11 patients). This finding supports performing repeat renal biopsy in patients with membranous lupus nephritis when renal flare occurs.

Our study has several limitations. First, although we showed that the presence of tubulointerstitial inflammation and tubular atrophy/interstitial fibrosis was associated with a higher risk of renal flare, we were unable to analyze the association between the severity of the tubulointerstitial lesions and renal flare due to the relatively small sample size. Further studies with a larger sample size would be helpful in this regard. Second, our study had a retrospective design. Although we evaluated a wide variety of parameters in all patients, there may have been other confounding factors that we could not identify. Third, repeated biopsies were performed in small number of patients and we were unable to evaluate risk factors of class transformation. Fourth, we lack data on anti-C1q antibodies, which are associated with renal disease activity in lupus nephritis [20].

In conclusion, our results showed that the presence of tubulointerstitial inflammation and tubular atrophy/interstitial fibrosis is a risk factor for renal flare in membranous lupus nephritis. This result may help clinicians to identify membranous lupus nephritis patients who are at a higher risk of poor renal outcome. Closer monitoring of such patients may lead to earlier treatments and better outcomes.

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Author contributions OCK and Y-GK contributed to the conception and design of the study, data collection and analysis, manuscript writing, and final approval of the manuscript. YMC, JSO, SH, C-KL, and BY contributed to data collection and analysis, and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval All procedures were performed in accordance with the ethical standards of the Institutional Review Board of Asan Medical Center (IRB No: 2018-0137) and with the 1964 Helsinki declaration.

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