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Original Article

Glomerular necrotic lesions and long-term outcomes among patients with proliferative lupus nephritis

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Abstract: Objectives: Although necrotic lesions are common in proliferative lupus nephritis (LN), little is known about the impact of these lesions on outcomes. This study was undertaken to investigate the impact of glomerular necrotic lesions on renal outcomes of doubling serum creatinine in patients with class III and IV LN and necrotic lesions. Methods: 52 patients with ISN/RPS class III or IV LN were enrolled in this retrospective study, with mean follow-up of 7.4 years. All patients underwent a repeat biopsy at 12-18 months after a baseline biopsy. Results: The prevalence of necrotizing lesions was observed in 24% of those with class III versus 70.4% with class IV ($P = 0.001$). The rate of no remission was 44% and 22.2% in those with and without necrosis ($P = 0.007$), respectively. The doubling of serum creatinine was observed in 32% of those with necrosis and in 14.8% with no necrosis ($P = 0.01$). The chronicity index in the repeat biopsy was significantly worse among those with necrosis. Conclusions: Glomerular necrosis identifies lupus nephritis patients at the greatest risk for progression to renal failure. Proactive intervention and possibly more aggressive induction therapies in patients with necrotizing lesions may protect the kidneys from developing chronic renal impairment.

Keywords: ISN/RPS, Lupus nephritis, necrosis, renal function

Introduction

The prognosis of systemic lupus erythematosus (SLE) has improved over the last few decades [1]. However, as a significant proportion of patients still develop varying degrees of chronic kidney disease [2, 3], patients with lupus nephritis require early aggressive treatment to protect their kidneys from developing chronic damage [4]. The International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification stresses the importance of reporting of the proportion of glomeruli affected by fibrinoid necrosis and crescents [5]. However, the consequences of reporting these lesions in terms of their prognostic value and the implications in choosing the type and level of immunosuppressive medication have not yet been clarified. A recent study has shown that crescentic lesions are associated with a poor treatment response and a worse renal outcome [6]. However, the clinical significance of necrotic lesions in proliferative lupus nephritis remains unclear.

Materials and methods

The clinicopathological characteristics of 52 biopsy-proven proliferative lupus nephritis (PLN) patients with necrosis diagnosed between 2000 and 2012 at King Khaled University Hospital were reviewed. The inclusion criteria were (1) diagnosed with SLE, as defined by the American College of Rheumatology criteria [7] and (2) renal biopsy-confirmed PLN according to the 2003 ISN/RPS classification [5]. The PLN patients were divided into two subgroups according to their histological necrosis. The determination of disease activity and chronicity indices was performed according to the scoring system of Pollak et al., as modified by Austin et al. [8, 9].

It has been a policy at King Khaled University Hospital for over 15 years to encourage all

Table 1. Demographics, clinical characteristics, and laboratory analysis of the participants at baseline

Age-Mean ± SD (Year)	25.7 ± 2.7
Male-no. (%)	5 (9.6%)
Clinical Presentation	N (%)
Malar rash	14 (26.9%)
Photosensitivity	7 (13.5%)
Arthritis	20 (38.5%)
Serositis	3 (5.8%)
Hematological	10 (19.2%)
Oral ulcers	12 (23.1%)
Cerebral	4 (7.7%)
Creatinine (μmol/L)	
Mean ± SD	125.0 ± 112.5
24-hr urine protein (g/day)	
Mean ± SD	2.57 ± 3.0
ISN/RPS Classification	n (%)
III	25 (48.1%)
IV	27 (51.9%)

ISN/RPS, International Society of Nephrology and Renal Pathology Society.

patients to undergo a second biopsy to assess disease activity at the end of the maintenance phase, 12-18 months from the initiation of induction, regardless of their remission status [10, 11]. Repeat biopsies were also performed in most subsequent renal flares. Similarly, many patients with persisting abnormal laboratory parameters were encouraged to undergo a second biopsy. The patients gave informed consent before undergoing kidney biopsy. Necrosis was defined as the fragmentation of nuclei or disruption of the glomerular basement membrane with fibrin-rich material [12].

All patients with class III to IV lupus nephritis initially received induction therapy consisting of a maximum of six monthly boluses of intravenous cyclophosphamide (0.5 to 1.0 g per square meter of body-surface area to induce a nadir leukocyte count that was no lower than 2000 cells per cubic millimeter) and corticosteroids. After induction, the patients were either given 0.5 to 1.0 g of intravenous cyclophosphamide per square meter every three months or 1 to 3 mg of oral azathioprine per kilogram of body weight per day. Since its introduction in 2004, mycophenolate mofetil has been used for both the induction and maintenance phases of therapy, in addition to the above protocol. All therapeutic options were left to the discretion of the physician and patient, and the study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Board of King Saud University.

Outcome variables

We examined the impact of necrosis on the probability of doubling the initial serum creatinine or ESRD at the final follow-up in patients with PLN. Complete remission was defined as a serum creatinine level ≤ 1.4 mg/dl and proteinuria ≤ 0.33 g/d at the time of the second biopsy. Partial remission was defined as a ≤ 25% increase in baseline creatinine and a ≥ 50% reduction in baseline proteinuria to ≤ 1.5 g/d (but > 0.33 g/d) [13].

Statistical analysis

For the normally distributed data, values are expressed as the means and standard deviations. To compare categorical data of clinical, laboratory, and pathological relevance, we used the chi-square test and Fisher's exact test; for continuous variables, the Kruskal-Wallis test was utilized. A significant difference was accepted if $P < 0.05$. Outcome analyses were performed to test the association between the main outcome of the worsening of renal function and the existence of necrosis. Renal function was compared from the first clinical assessment to the last follow-up visit for each patient. The end point for renal survival was defined as the doubling of serum creatinine or ESRD.

Results

A total of 52 participants were included in the study, and the mean SLE duration was 3.8 ± 2.7 years. The mean age (standard deviation) of the participants was 25.7 (9.6) years, with a median of 8.8 years of follow-up. Of the participants, 9.6% were males (n = 5). Other baseline characteristics are shown in **Table 1**. Nineteen patients (36.5%) received mycophenolate mofetil for induction therapy, and the rest received cyclophosphamide. Among those who were given cyclophosphamide, 19% (10 patients) received azathioprine, 9% (3 patients) received MMF, and the remainder continued on

Table 2. Comparison of baseline characteristics between those with and without necrosis among patients with lupus nephritis

	Necrosis	No Necrosis	*P*
Number of patients-n (%)	25 (48.1%)	27 (51.9%)	
Urinalysis-Red cells-per HPF*	188 ± 400	156 ± 343	0.06
Urinalysis-White Blood cells-per HPF*	151 ± 267	44 ± 66	0.02
24-h urine protein-g/d*	3.4 ± 3.1	1.7 ± 2.8	0.03
Serum Creatinine (μmol/L)	154 ± 130	96 ± 94	0.05
dsDNA-IU/ml*	549 (119-1536)	246 (58-882)	0.33
Serum Complement 3 (mg/ml)	0.42 (0.31-0.81)	0.86 (0.5-1.11)	0.06
Serum Complement 4 (mg/ml)	0.07 (0.04-0.14)	0.22 (0.11-0.34)	0.02
Activity index			
Mean ± SD	10.2 ± 3.6	2.4 ± 3.0	0.0001
Median (IQR)	10 (7-13)	1 (0-4)	
Chronicity index			
Mean ± SD	4.1 ± 2.1	3.2 ± 2.0	
Median (IQR)	4 (2-6)	3 (2-4)	
Crescents-n (%)	10 (40%)	3 (11.1%)	0.02
Interstitial Inflammation	22 (88%)	12 (44.4%)	0.007

*The data are expressed as the median (interquartile range). Anti-dsDNA, anti-double-stranded DNA antibodies. HPF, high-power field. The *P* values were calculated with the use of the Kruskal-Wallis test for continuous variables and with the chi-square test and Fisher's exact test for categorical variables. ISN/RPS, International Society of Nephrology and Renal Pathology Society.

Table 3. Comparison of response to therapy and remission status between those with and without necrosis among patients with lupus nephritis

	Necrosis	No Necrosis	*P*
Number of patients-n (%)	25 (48.1%)	27 (51.9%)	
Remission Status			
Complete	10 (40%)	14 (51.9%)	0.1
Partial	4 (16%)	7(25.9%)	0.9
No remission	11(44%)	6 (22.2%)	0.007
Doubling of serum creatinine or ESRD-n (%)	8 (32%)	4 (14.8%)	0.01
Activity index			
Mean ± SD	4.4 ± 4.5	3.2 ± 4.4	
Median (IQR)	2 (2-6)	1 (0-4)	0.08
Chronicity index			
Mean ± SD	6.7 ± 2.3	3.8 ± 2.6	
Median (IQR)	7 (5-8)	4 (1-6)	0.0002

ESRD, end-stage renal disease; IQR, interquartile range.

cyclophosphamide for the maintenance phase of therapy.

Necrotic lesions were reported in 25 patients (48.1%) with PLN. Two groups were classified according to necrotic lesions at the time of the baseline renal biopsy, as shown in **Table 2**. The patients with necrotic lesions had a higher baseline serum creatinine and 24-hour urine protein (**Table 2**). Urine sediments were more active among those with necrosis, as were higher serological markers of ANA and anti-DNA.

Using light microscopy, it was found that there were more patients with necrotic lesions in ISN/RPS class IV than in ISN/RPS class III (**Table 2**). The activity indices at the baseline biopsy were significantly higher among the patients with necrotic lesions; however, the chronicity indices were not different between the two groups at the baseline biopsy. There were more cellular, fibro-cellular crescents, and interstitial inflammation in the patients with necrotic lesions (**Table 2**).

The management protocols for the two groups were not different. Cyclophosphamide was

used in 48% of the necrotic lesions and 52% of those without necrosis. Similarly, there was no difference in the cumulative dosage of cyclophosphamide between the two groups. Furthermore, there were no differences in the number of patients who received mycophenolate mofetil for induction therapy.

Complete remission was observed in 40 versus 51.9% of patients, partial remission was observed in 16% versus 25.9% of patients, and there was no response in 44% versus 22% of patients with and without necrotic lesions, respectively (*P* values of 0.1, 0.9, and 0.007, respectively) (**Table 3**).

Furthermore, the renal outcome of doubling the serum creatinine was observed in 14.8% of patients with no necrosis compared with 32% in patients with necrosis ($P = 0.01$) after a median follow-up of 8.8 years (mean 7.4 ± 3.3 years) (**Table 3**).

There were no differences in the baseline chronicity indices between those with and without necrosis. In the repeat biopsy, the median renal chronicity index among those with necrosis was 7 (IQR): 5 to 8), whereas it was 4 (IQR: 1 to 6) for those without necrosis ($P = 0.002$) (**Table 3**).

Discussion

Immunosuppression is of fundamental importance to the long-term survival of patients with systemic lupus erythematosus. Over the last 50 years, there have been great advances in our knowledge of the immune system and the potential therapeutic targets for pharmacological intervention, leading to improved patient and renal survival. Despite this, a significant proportion of patients continue to have a suboptimal or no response and develop chronic kidney disease [14, 15]. Clinicians need to tailor therapy to suit the individual patient characteristics and to balance the advantages and disadvantages of these treatments. Thus, it is important to understand the various predictors that impact the outcome and the optimization of therapy. In this study, we examined the clinical significance of necrotizing lesions in lupus nephritis.

According to the latest American College of Rheumatology guidelines for the management of lupus nephritis, the presence of any crescents on a renal biopsy sample are considered to indicate crescentic LN, with a recommendation of more aggressive immunosuppressive regimens [16]. This is because the presence of crescents indicates a poorer prognosis, even with the appropriate treatment [17].

We evaluated the presence of necrotic lesions and their impact on clinical presentation and response to treatment. Those with necrotic lesions have a higher proteinuria with worse renal function at the time of presentation. The most important finding of our study is the reduced probability of remission and the progression to worsening renal function and permanent kidney damage.

To date, there is no study that stratifies patients based on the presence of necrotic lesions or crescents. One recent retrospective study suggested that mycophenolate mofetil is at least as effective as high doses of cyclophosphamide in crescentic class IV LN [18].

Three phases of immunosuppression therapy can be recognized in the management of patients with lupus nephritis: induction, maintenance, and withdrawal. The clinician's decisions to move from one phase to another are solely based on clinical and biochemical parameters, which are not sufficiently sensitive to predict the disease activity. We have shown previously that biopsy at the end of the maintenance phase of therapy has great diagnostic and prognostic value [10]. The most appropriate times for repeated serial biopsy are at baseline, at the end of induction therapy, and prior to the withdrawal of immunosuppressive treatment. Similarly, we have shown that the severity of interstitial inflammation does reflect long-term outcomes, and based on the present study, necrotic lesions should be considered when choosing the appropriate immunosuppressive medications [11]. It is most likely that more aggressive immunosuppressive treatments of patients with necrotic lesions are needed, possibly using combinations of standard immunosuppressives with biological therapies to avoid permanent renal damage.

Our study has several limitations including a retrospective methodology, which is vulnerable to the loss of information and particularly to the loss of follow-up information. In addition, this study had a relatively modest sample size of LN

biopsies. Despite these limitations, it is proposed that clinical, biochemical, and histological parameters should be included for individualizing treatment decisions, with more early and frequent assessments of the response to therapy.

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Disclosure of conflict of interest

None.

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