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ORIGINAL ARTICLE

# Clinicopathological factors for tubulointerstitial injury in lupus nephritis

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## Abstract

**Objective** To investigate the incidence of tubulointerstitial injury in lupus nephritis (LN) and to examine clinicopathological factors that could indicate the presence of tubulointerstitial injury.

**Methods** This study included 98 patients with LN. Clinical data and the pathological results of the initial renal biopsy were collected.

**Results** The frequency of each tubulointerstitial injury parameter was over 50%, except for the interstitial edema, in the 98 patients investigated in this study. The most frequently detected tubulointerstitial injury parameter was tubular atrophy in this study. Neutrophil infiltration/karyorrhexis, wire loop lesion, and arteriosclerosis were observed frequently in patients with tubulointerstitial injuries. High serum creatinine and blood urea nitrogen (BUN) were observed more frequently in patients with tubulointerstitial injuries except tubular degeneration. The multivariable regression analysis showed a relationship between neutrophil infiltration/karyorrhexis and interstitial fibrosis/tubular degeneration, a relationship between wire loop lesion and tubulointerstitial inflammation/edema, and a relationship between arteriosclerosis and tubulointerstitial injuries (except interstitial edema). Patients with tubular degeneration had lower D-Dimer levels compared with those without. Patients with interstitial fibrosis had higher blood leukocyte counts than those without. The rate of low response to therapy was 13% among those without tubulointerstitial inflammation, but 35% in those with interstitial inflammation ($P = 0.03$).

**Conclusion** Acute and chronic renal tubulointerstitial lesions are often found along with glomerular and vascular lesions. Immune and vascular factors are probably involved in tubulointerstitial injuries. Tubulointerstitial inflammation may be the initiator of chronic renal injury and may predict response to therapy.

**Key Points**

•*To provide a theoretical basis for tubulointerstitial injury in LN.*

**Keywords** Clinicopathological factors · Lupus nephritis · Tubulointerstitial injury

## Background

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disorder of the connective tissues. It is characterized by autoantibodies that target nuclear antigens, remissions, and flare-ups, and highly variable clinical presentation, disease course, and prognosis [1]. Lupus nephritis (LN) is the most common complication of SLE, affecting about 50% of the patients with SLE [1]. It is characterized by auto-antibodies forming immune complexes that deposit into the glomeruli; those complexes promote an inflammatory response by activating the complement system and attracting inflammatory cells [2]. It is classified as class I (minimal mesangial

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glomerulonephritis) to VI (advanced sclerosing LN) according to the extent of damage [2]. The remission rate of LN is only 50–70%, and 10–20% of patients with LN will progress to end-stage renal disease within 5 years [3]. The management of Chinese patients with LN improved from 1994 to 2010, but the clinical outcomes are still suboptimal [4].

Renal pathological examination is the gold standard for the diagnosis of LN. The guidelines suggest evaluating the severity of renal damage, developing treatment plans, and determining the prognosis according to the pathological classification of LN [2]. The 2003 International Society of Nephrology and Renal Pathology (ISN/RPS) classification is widely recognized as the gold standard for the classification of LN and to guide management [5], but the published studies report conflicting data regarding the response to therapy and progression to ESRD [6]. Those conflicting data may be due to the fact that the ISN/RPS pathological classification of LN is based on glomerular injury exclusively [5]. A growing number of experts call for an improvement in the classification criteria of LN [6].

Renal tubulointerstitial injury in LN is considered to be of great value for the evaluation of the degree of renal damage and to guide management, and to determine prognosis [6–10]. Renal tubulointerstitial lesion is a candidate for inclusion in the pathological classification [11], but data regarding the clinical and pathological factors correlated with the different types of tubulointerstitial injury in LN are lacking. Glomerular injury is considered the first event leading to proteinuria and hypoxia, but proteinuria and hypoxia, in turn, lead to tubulointerstitial inflammation and fibrosis [12–14]. In addition, it is unknown whether tubulointerstitial injury is a consequence of LN or it occurs simultaneously [9, 14, 15]. It has been suggested that glomerular and tubulointerstitial injuries occur together, but that they result from different mechanisms [12, 13].

Therefore, the present study aimed to investigate the frequency of tubulointerstitial injury parameters in LN and the differences in clinicopathological factors among patients with different types of tubulointerstitial injury. The results could provide a theoretical basis for the eventual use of tubulointerstitial injury in the classification of LN.

## Materials and methods

### Patient inclusion

Clinicopathological data of patients with LN diagnosed through renal biopsy from January 2014 to December 2017 at the Fujian Provincial Hospital were retrospectively reviewed. The study was approved by the ethics committee of Fujian Provincial Hospital, Fuzhou. The pathological diagnostic criteria and classification criteria of LN were performed with reference to the ISN/RPS 2013 criteria [5]. The inclusion criteria were first confirmed LN by initial renal biopsy, the period from onset to renal biopsy was less than 1 month, without immunosuppressive treatment before renal biopsy, and complete clinical data. The exclusion criteria were no renal biopsy or clinical indicators did not support the diagnosis of LN.

### Routine management

The patients with class III, IV, III+V, or IV+V received induction immunosuppressive treatment (corticosteroids and cyclophosphamide/mycophenolate mofetil) for 6 months. The patients with class V and proteinuria above 2 g/d were given the above induction immunosuppression for 6 months, but the patients with class V but lower proteinuria were treated with an angiotensin-converting enzyme inhibitor and/or an angiotensin receptor blocker. Class II LN was treated with prednisolone at 30 mg/day.

### Data collection

All pathological examinations were originally carried out by renal pathologists. The pathological results of the renal biopsy were collected. Tubulointerstitial inflammation was defined as the presence of inflammatory cell infiltration in the interstitium [12]. Arteriosclerosis was defined as fibrous thickening and vitreous degeneration of arterioles. Karyorrhexis was defined as the presence of apoptotic, pyknotic, and fragmented nuclei. The clinical indexes reflecting liver injury, blood biochemistry, renal function, and LN activity were collected within 3 days before renal biopsy. Response after 6 months of treatment was determined. Patients with complete response and partial remission according to the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) criteria [16] were classified as the response group, while the patients without remission were classified as the low-response group.

### Statistical analysis

Statistical analysis was performed using SPSS 22.0 (IBM, Armonk, NY, USA). The continuous data with normal distribution are expressed as means ± standard deviation (SD) and were analyzed using Student's $t$ test. Continuous data with skewed distribution are expressed as quartiles (P25, P75), and were analyzed using Mann-Whitney $U$ test. Categorical data are expressed as frequencies and percentages and were analyzed using the chi square test. The clinicopathological features with significant ($P < 0.05$) differences between patients with and without tubulointerstitial injury in the univariable analyses were entered in the multivariable binary logistic regression model (forward method). The results are expressed as hazard ratio (HR) with 95% confidence intervals (CIs). Statistical significance was considered as $P < 0.05$.

## Results

### Frequency of tubulointerstitial injury parameters in patients with LN

The characteristics of the patients are shown in Table 1. The study included 98 patients with LN (80 women and 18 men; 11–64 years of age). Among the 98 patients, 70 (71.4%) had tubular atrophy, 63 (64.3%) had tubular degeneration, 68 (69.4%) had tubulointerstitial inflammation, 10 (10.2%) had interstitial edema, and 52 (53.1%) had interstitial fibrosis. The frequencies of the renal tubulointerstitial injuries (except interstitial edema) in class II LN were all over 44%. The frequency of tubular degeneration in class II LN was 88.9%. Tubulointerstitial inflammation was observed in all patients with class IV+ V LN ($n = 21$) (Table 2). Among the 98 patients, anti-cardiolipin IgG and IgM data were available for 72 patients. For both markers, over 12 U was considered above the normal range. Among the 72 patients, seven had high IgM levels, 13 had high IgG levels, and three had high IgM and IgG levels.

### Pathological parameters according to the presence of tubulointerstitial injury

The frequencies of some chronic lesions such as glomerulosclerosis ($P = 0.01$) and arteriosclerosis ($P < 0.01$) were higher in patients with tubular atrophy compared with those without tubular atrophy. Frequencies of acute lesions such as wire loop lesion ($P < 0.001$), neutrophil infiltration/karyorrhexis ($P < 0.001$), and crescent sign ($P = 0.04$) (especially cellular crescent) were high in patients with tubular degeneration, but the frequency of arteriosclerosis was low ($P = 0.034$). Patients with tubulointerstitial inflammation showed higher frequencies of acute lesions such as wire loop lesion ($P = 0.003$), neutrophil infiltration/karyorrhexis ($P = 0.007$), endocapillary proliferative ($P = 0.001$), and chronic lesion of arteriosclerosis ($P < 0.001$). Patients with interstitial edema showed higher frequencies of acute lesions such as the double track sign ($P = 0.033$), wire loop lesion ($P < 0.001$), neutrophil infiltration/karyorrhexis ($P = 0.001$), and cellular fibrous crescent ($P < 0.001$). The frequency of arteriosclerosis ($P < 0.001$) was high in patients with interstitial fibrosis, but frequencies of acute lesions such as the double track sign ($P = 0.024$), wire loop lesion ($P < 0.001$), and neutrophil infiltration/karyorrhexis ($P < 0.001$) were low (Table 3). All tubulointerstitial injuries were observed along with neutrophil infiltration/ karyorrhexis. All tubulointerstitial injuries except tubular atrophy were observed along with the wire loop lesion. All tubulointerstitial injuries except interstitial edema were observed along with arteriosclerosis.

**Table 1** Characteristics of the patients

| | ($n = 98$) |
|---|---|
| Sex, female, *n* (%) | 80 (82) |
| Age (years) | 35 ± 13* |
| Pathological type (ISN/RPS), *n* (%) | |
| Class I | 1 (1) |
| Class II | 9 (9) |
| Class III | 8 (8) |
| Class IV | 31 (32) |
| Class V | 18 (18) |
| Class VI | 1 (1) |
| Class III + V | 9 (9) |
| Class IV + V | 21 (21) |
| Pathological types, *n* (%) | |
| Tubular atrophy | 70 (71) |
| Tubular degeneration | 63 (64) |
| Tubulointerstitial inflammation | 68 (69) |
| Interstitial edema | 10 (10) |
| Interstitial fibrosis | 52 (53) |
| Renal biopsy, *n* (%) | |
| Glomerular number | 14 ± 6* |
| Glomerulosclerosis | 47 (48) |
| Double track sign | 8 (8) |
| Wire loop | 26 (27) |
| Neutrophil infiltration/karyorrhexis | 40 (41) |
| Crescent | 30 (31) |
| Cellular crescent | 16 (16) |
| Cellular fibrous crescent | 2 (2) |
| Fibrous crescent | 21 (21) |
| Thrombotic microangiopathy | 19 (19) |
| Arteriosclerosis | 52 (53) |
| Endocapillary proliferative | 64 (65) |
| Cast | 15 (16) |
| Laboratory parameters | |
| RBC ($\times 10^9$) | 3.70 ± 0.77* |
| Hemoglobin (g/l) | 102.70 ± 27.41* |
| Leukocyte count ($\times 10^9$) | 6.12 ± 3.34* |
| Lymphocyte counts ($\times 10^9$) | 1.41 ± 0.85* |
| Monocyte counts ($\times 10^9$) | 0.40 ± 0.23* |
| Platelets ($\times 10^{12}$) | 208.57 ± 93.06* |
| Cholesterol (mmol/l) | 5.46 ± 1.83* |
| Albumin (g/l) | 27.59 ± 7.98* |
| ALT (U/l) | 14 (10.00, 21.25) # |
| BUN (mmol/l) | 6.6 (4.10, 10.85) # |
| Creatinine (μmol/l) | 74.5 (54.75, 111.00) # |
| C3 (g/l) | 0.56 (0.29, 0.74) # |
| C4 (g/l) | 0.09 (0.04, 0.18) # |
| Anti-dsDNA (titer) | 10 (0.00, 100) # |
| Antinuclear antibody (ANA)(titer) | 1000 (1000, 3200) # |
| ESR (mm/h) | 35 (21.00, 65.50) # |
| D-Dimer (mg/l) | 1.85 (0.59, 3.25) # |
| Urinary protein (g/24 h) | 2.45 (0.71, 3.93) # |
| Urine volume (L) | 2.0 (1.68, 2.50) # |
| Path cast | 0.2 (0.07, 0.54) # |

*Shown as means ± standard deviation

# Shown as medians (interquartile range)

All categorical variables are shown as *n* (%)

### Clinical parameters according to the presence of tubulointerstitial injury

Patients with tubular atrophy had elevated leukocyte count ($P = 0.012$), elevated serum creatinine (sCr) ($P = 0.006$),

**Table 2** Frequency of tubulointerstitial injury parameters in patients with LN [% (n/N)]

| Pathology type | Tubular atrophy | Tubular degeneration | Tubulointerstitial inflammation | Interstitial edema | Interstitial fibrosis |
|---|---|---|---|---|---|
| Class I ($N = 1$) | 0.0% (0/1) | 100% (1/1) | 0.0% (0/1) | 0.0% (0/1) | 0.0% (0/1) |
| Class II ($N = 9$) | 55.6% (5/9) | 88.9% (8/9) | 44.4% (4/9) | 0% (0/9) | 55.6% (5/9) |
| Class III ($N = 8$) | 75.0% (6/8) | 62.5% (5/8) | 62.5% (5/8) | 0.0% (0/8) | 75.0% (6/8) |
| Class IV ($N = 31$) | 77.4% (24/31) | 45.2% (14/31) | 74.2% (23/31) | 12.9% (4/31) | 71.0% (22/31) |
| Class V ($N = 18$) | 61.1% (11/18) | 61.1% (11/18) | 50.0% (9/18) | 5.6% (1/18) | 33.3% (6/18) |
| Class VI ($N = 1$) | 100% (1/1) | 100% (1/1) | 100% (1/1) | 0.0% (0/1) | 100% (1/1) |
| Class III+V ($N = 9$) | 66.7% (6/9) | 55.6% (5/9) | 55.9% (5/9) | 0.0% (0/9) | 44.4% (4/9) |
| Class IV+V ($N = 21$) | 81.0% (17/21) | 85.7% (18/21) | 100% (21/21) | 23.8% (5/21) | 38.1% (8/21) |
| Total ($N = 98$) | 71.4% (70/98) | 64.3% (63/98) | 69.39% (68/98) | 10.2% (10/98) | 53.1% (52/98) |

and elevated BUN ($P = 0.006$). Patients with tubular degeneration had lower sCr ($P = 0.011$), lower BUN ($P = 0.019$), lower D-Dimer ($P = 0.002$), and higher ESR ($P = 0.048$). Patients with tubulointerstitial inflammation had elevated sCr ($P < 0.001$), elevated BUN ($P = 0.002$), and elevated proteinuria ($P = 0.044$). Patients with interstitial edema had elevated ESR ($P = 0.046$). Patients with interstitial fibrosis had elevated leukocyte count ($P = 0.017$), elevated sCr ($P < 0.001$), elevated BUN ($P < 0.001$), and elevated D-Dimer ($P = 0.037$). All tubulointerstitial injuries except interstitial edema were found along with sCr and BUN (Table 3).

## Multivariable logistic regression for clinicopathological features and tubulointerstitial injury

The clinicopathological features with significant differences ($P < 0.05$) in the univariable analyses were entered in a multivariable binary logistic regression model (forward method). Patients with glomerulosclerosis (HR = 3.63, 95% CI 1.18–11.16, $P = 0.02$) and arteriosclerosis (HR = 10.64, 95% CI 3.21–35.32, $P < 0.001$) had a higher hazard of tubular atrophy. Patients with neutrophil infiltration/karyorrhexis (HR = 84.03, 95% CI 8.46–834.71, $P < 0.001$), arteriosclerosis (HR = 0.30, 95% CI 0.10–0.89, $P = 0.03$), and lower D-dimer (HR = 0.75, 95% CI 0.58–0.98, $P = 0.04$) had higher hazard of tubular degeneration. Patients with endocapillary proliferation (HR = 3.02, 95% CI 1.02–8.95, $P = 0.046$), arteriosclerosis (HR = 6.33, 95% CI 2.21–18.12, $P = 0.001$), and wire loop lesion (HR = 6.02, 95% CI 1.11–32.56, $P = 0.04$) had higher hazard of tubulointerstitial inflammation. Patients with the wire loop lesion (HR = 15.56, 95% CI 3.04–79.69, $P = 0.001$) had a higher hazard of interstitial edema. Patients with neutrophil infiltration/karyorrhexis (HR = 0.12, 95% CI 0.04–0.37, $P < 0.001$), arteriosclerosis (HR = 5.27, 95% CI 1.84–15.10, $P = 0.002$), and higher cast (HR = 10.68, 95% CI 1.67–68.35, $P = 0.01$) had higher hazard of interstitial fibrosis (Table 4).

## Rates of low response to therapy

Response after 6 months of treatment was determined and analyzed according to the presence of different types of tubulointerstitial injury. After 6 months of treatment, 28 patients had a low response to therapy. The rate of low response was 29%. Patients with tubulointerstitial inflammation had a higher rate of low response to therapy ($P = 0.03$), while there were no differences in patients with the other tubulointerstitial injury (tubular degeneration, $P = 0.216$; tubular atrophy, $P = 0.089$; interstitial edema, $P = 0.99$; and interstitial fibrosis, $P = 0.117$) (Fig. 1).

# Discussion

The results showed that the frequency of each tubulointerstitial injury parameter (except for the interstitial edema) was over 50% in the 98 patients investigated in this study. The most frequently detected tubulointerstitial injury parameter was tubular atrophy in this study. This is supported by previous studies [7]. The present study also showed that tubulointerstitial inflammation occurred in all 21 cases of class

**Table 3** Clinical and pathological factors according to LN lesions

| | Tubular atrophy | | | Tubular degeneration | | | Tubulointerstitial inflammation | |
|---|---|---|---|---|---|---|---|---|
| | Yes ($n = 70$) | No ($n = 28$) | *P* | Yes ($n = 63$) | No ($n = 35$) | *P* | Yes ($n = 68$) | No ($n = 30$) |
| Sex, female (%) | 80% (56) | 86% (24) | 0.578 | 84% (53) | 77% (27) | 0.423 | 84% (57) | 77% (23) |
| Age (years)* | 36 ± 13 | 30 ± 11 | 0.067 | 35 ± 13 | 34 ± 14 | 0.741 | 36 ± 12 | 32 ± 14 |
| Pathological parameters | | | | | | | | |
| Glomerular number | 15 ± 5 | 12 ± 6 | 0.410 | 14 ± 6 | 15 ± 4 | 0.543 | 15 ± 5 | 13 ± 7 |
| Glomerulosclerosis | 59% (41) | 21% (6) | *0.001* | 43% (27) | 57% (20) | 0.208 | 54% (37) | 33% (10) |
| Double track sign | 4% (3) | 18% (5) | *0.041* | 11% (7) | 3% (1) | 0.253 | 9% (6) | 7% (2) |
| Wire loop | 23% (16) | 36% (10) | 0.213 | 40% (25) | 3% (1) | *< 0.001* | 35% (24) | 7% (2) |
| Neutrophil infiltration/ karyorrhexis | 34% (24) | 57% (16) | *0.044* | 62% (39) | 3% (1) | *< 0.001* | 50% (34) | 20% (6) |
| Crescent | 30% (21) | 32% (9) | 0.814 | 38% (24) | 17% (6) | *0.04* | 37% (25) | 17% (5) |
| Cellular crescent | 17% (12) | 14% (4) | 1 | 22% (14) | 6% (2) | *0.045* | 21% (14) | 7% (2) |
| Cellular fibrous crescent | 3% (2) | 0% (0) | 1 | 3% (2) | 0% (0) | 0.536 | 3% (2) | 0% (0) |
| Fibrous crescent | 20% (14) | 25% (7) | 0.594 | 27% (17) | 11% (4) | 0.08 | 25% (17) | 13% (4) |
| Arteriosclerosis | 19% (13) | 21% (6) | *< 0.001* | 25% (16) | 9% (3) | *0.034* | 24% (16) | 10% (3) |
| Thrombotic microangiopathy | 69% (48) | 14% (4) | 0.78 | 44% (28) | 69% (24) | 0.06 | 66% (45) | 27% (8) |
| Endocapillary proliferative | 69% (48) | 57% (16) | 0.349 | 65% (41) | 66% (23) | 1 | 76% (52) | 40% (12) |
| Cast | 17% (12) | 11% (3) | 0.544 | 17% (11) | 11% (4) | 0.563 | 19% (13) | 7% (2) |
| Laboratory parameters | | | | | | | | |
| Erythrocyte count ($\times 10^9$)* | 3.68 ± 0.78 | 3.76 ± 0.77 | 0.646 | 3.71 ± 0.72 | 3.68 ± 0.86 | 0.875 | 3.67 ± 0.70 | 3.76 ± 0.92 |
| Hemoglobin (g/l)* | 103.21 ± 23.26 | 101.41 ± 36.26 | 0.770 | 103.21 ± 28.00 | 101.77 ± 26.70 | 0.805 | 102.47 ± 20.61 | 103.21 ± 39.13 |
| Leukocyte count ($\times 10^9$)* | 6.54 ± 3.69 | 5.07 ± 1.94 | *0.012* | 5.90 ± 3.48 | 6.52 ± 3.08 | 0.369 | 6.41 ± 3.61 | 5.46 ± 2.56 |
| Lymphocyte count ($\times 10^9$)* | 1.43 ± 0.83 | 1.35 ± 0.91 | 0.665 | 1.40 ± 0.94 | 1.44 ± 0.68 | 0.810 | 1.38 ± 0.86 | 1.48 ± 0.85 |
| Monocyte count ($\times 10^9$)* | 0.40 ± 0.24 | 0.40 ± 0.24 | 0.900 | 0.38 ± 0.23 | 0.43 ± 0.24 | 0.313 | 0.41 ± 0.25 | 0.38 ± 0.21 |
| Platelet count ($\times 10^{12}$)* | 200.61 ± 81.82 | 228.46 ± 117.13 | 0.182 | 218.52 ± 102.44 | 190.66 ± 71.12 | 0.157 | 198.65 ± 86.83 | 231.07 ± 103.09 |
| Cholesterol (mmol/l)* | 5.55 ± 1.78 | 5.21 ± 1.97 | 0.135 | 5.32 ± 1.88 | 5.70 ± 1.75 | 0.334 | 5.60 ± 1.84 | 5.13 ± 1.81 |
| Albumin (g/l)* | 27.99 ± 8.11 | 26.61 ± 7.69 | 0.264 | 27.94 ± 7.77 | 26.97 ± 8.41 | 0.569 | 26.71 ± 7.94 | 29.60 ± 7.74 |
| ALT (U/l) # | 13 (10.00, 21.00) | 16 (11.25, 23.75) | 0.198 | 14 (11.00, 22.00) | 12 (9.00, 21.00) | 0.819 | 13 (10.00, 20.75) | 16 (12.00, 22.00) |
| BUN (mmol/l) # | 7.8 (4.68, 11.78) | 5.56 (2.73, 7.65) | *0.006* | 5.7 (3.60, 9.80) | 8.3 (6.10, 12.00) | *0.011* | 8.05 (5.53, 13.70) | 4.05 (2.78, 6.53) |
| sCr (μmol/l) # | 81.6 (57.50, 137.25) | 65.5 (42.75, 79.00) | *0.006* | 66.00 (53.00, 94.00) | 94 (68.00, 141.00) | *0.019* | 81 (60.25, 151.00) | 64 (42.75, 85.25) |
| Complement 3 (g/l) # | 0.56 (0.28, 0.73) | 0.53 (0.28, 0.76) | 0.869 | 0.58 (0.33, 0.77) | 0.39 (0.22, 0.68) | 0.115 | 0.50 (0.29, 0.68) | 0.62 (0.30, 0.84) |
| Complement 4 (g/l) # | 0.09 (0.04, 0.18) | 0.09 (0.04, 0.16) | 0.943 | 0.1 (0.05, 0.15) | 0.07 (0.03, 0.22) | 0.950 | 0.11 (0.04, 0.20) | 0.07 (0.04, 0.14) |
| Anti-dsDNA (titer) # | 21 (0.00, 100) | 10 (0.00, 100.00) | 0.552 | 10 (0.00, 100.00) | 32 (0.00, 100) | 0.899 | 10 (0.00, 100.00) | 21 (0.00, 100.00) |
| Antinuclear antibody (ANA) (titer) # | 1000 (1000, 3200) | 2100 (1000, 3200) | 0.243 | 1000 (1000, 3200) | 1000 (320, 3200) | 0.495 | 1000 (1000, 3200) | 1000 (830, 3200) |
| ESR (mm/h) # | 35 (21.00, 63.00) | 40 (21.00, 102.75) | 0.276 | 40 (23.00, 73.00) | 25 (20.00, 56.00) | *0.048* | 36.5 (21.25, 66.5) | 33.5 (21.00, 61.25) |
| D-Dimer (mg/l) # | 1.95 (0.58, 3.27) | 1.44 (0.61, 2.8) | 0.558 | 1.19 (0.49, 2.48) | 2.49 (1.44, 3.89) | *0.002* | 1.8 (0.68, 3.18) | 1.89 (0.57, 3.36) |
| Proteinuria (g/24 h) # | 2.55 (0.93, 3.93) | 1.55 (0.53, 3.95) | 0.457 | 1.6 (0.60, 3.50) | 3.3 (1.50, 4.00) | 0.069 | 2.9 (0.84, 4.35) | 1.5 (0.51, 2.70) |
| Urine volume (L) # | 2.07 (1.70, 2.60) | 1.90 (1.50, 2.32) | 0.071 | 2 (1.6, 2.50) | 2.04 (1.70, 2.50) | 0.598 | 2.05 (1.70, 2.60) | 1.9 (1.53, 2.25) |
| Urinary path cast# | 0.17 (0.02, 0.58) | 0.28 (0.08, 0.53) | 0.491 | 1.2 (0.07, 0.50) | 0.2 (0.07, 0.80) | 0.693 | 0.23 (0.07, 0.53) | 0.17 (0.00, 0.58) |

**Table 3** (continued)

| | Tubulointerstitial inflammation | Interstitial edema | | | Interstitial fibrosis | | |
|---|---|---|---|---|---|---|---|
| | *P* | Yes (*n* = 10) | No (*n* = 88) | *P* | Yes (*n* = 52) | No (*n* = 36) | *P* |
| Sex, female (%) | 0.408 | 80% (8) | 82% (72) | 1 | 75% (39) | 89% (41) | 0.115 |
| Age (years)* | 0.149 | 33 ± 12 | 35 ± 13 | 0.739 | 36 ± 14 | 33 ± 12 | 0.241 |
| Pathological parameters | | | | | | | |
| Glomerular number | 0.247 | 11 ± 4 | 15 ± 6 | *0.024* | 15 ± 4 | 14 ± 7 | 0.586 |
| Glomerulosclerosis | 0.079 | 70% (7) | 45% (40) | 0.188 | 56% (29) | 39% (18) | 0.11 |
| Double track sign | 1 | 30% (3) | 6% (5) | *0.033* | 2% (1) | 15% (7) | *0.024* |
| Wire loop | *0.003* | 80% (8) | 20% (18) | *< 0.001* | 12% (6) | 43% (20) | *< 0.001* |
| Neutrophil infiltration/ karyorrhexis | *0.007* | 90% (9) | 35% (31) | *0.001* | 23% (12) | 61% (28) | *< 0.001* |
| Crescent | 0.058 | 30% (3) | 31% (27) | 1 | 31% (16) | 30% (14) | 1 |
| Cellular crescent | 0.137 | 30% (3) | 15% (13) | 0.207 | 17% (9) | 15% (7) | 1 |
| Cellular fibrous crescent | 1 | 100% (10) | 2% (2) | *< 0.001* | 4% (2) | 0% (0) | 0.497 |
| Fibrous crescent | 0.286 | 20% (2) | 22% (19) | 1 | 19% (10) | 24% (11) | 0.672 |
| Arteriosclerosis | *< 0.001* | 30% (3) | 18% (16) | 0.078 | 13% (7) | 26% (12) | *< 0.001* |
| Thrombotic microangiopathy | 0.167 | 90% (9) | 63% (55) | 0.402 | 73% (38) | 30% (14) | 0.132 |
| Endocapillary proliferative | *0.001* | 60% (6) | 52% (46) | 0.746 | 65% (34) | 65% (30) | 1 |
| Cast | 0.139 | 20% (2) | 15% (13) | 0.648 | 25% (13) | 4% (2) | *0.005* |
| Laboratory parameters | | | | | | | |
| Erythrocyte count ($\times 10^9$)* | 0.602 | 3.56 ± 0.55 | 3.72 ± 0.79 | 0.559 | 3.79 ± 0.86 | 3.70 ± 0.67 | 0.966 |
| Hemoglobin (g/l)* | 0.922 | 99.60 ± 16.87 | 103.05 ± 28.41 | 0.708 | 102.31 ± 25.67 | 103.14 ± 29.53 | 0.882 |
| Leukocyte count ($\times 10^9$)* | 0.139 | 7.01 ± 4.19 | 6.02 ± 3.25 | 0.378 | 6.86 ± 3.77 | 5.29 ± 2.57 | *0.017* |
| Lymphocyte count ($\times 10^9$)* | 0.569 | 1.63 ± 1.51 | 1.38 ± 0.75 | 0.623 | 1.46 ± 0.86 | 1.35 ± 0.84 | 0.520 |
| Monocyte count ($\times 10^9$)* | 0.544 | 0.40 ± 0.36 | 0.40 ± 0.22 | 0.943 | 0.41 ± 0.21 | 0.39 ± 0.26 | 0.684 |
| Platelet count ($\times 10^{12}$)* | 0.112 | 185.40 ± 69.80 | 211.20 ± 95.3 | 0.409 | 203.79 ± 85.32 | 213.98 ± 101.78 | 0.591 |
| Cholesterol (mmol/l)* | 0.243 | 4.97 ± 1.43 | 5.51 ± 1.87 | 0.376 | 5.52 ± 1.77 | 5.39 ± 1.92 | 0.734 |
| Albumin (g/l)* | 0.098 | 24.9 ± 7.94 | 27.9 ± 7.97 | 0.262 | 26.58 ± 7.97 | 28.74 ± 7.92 | 0.182 |
| ALT (U/l) # | 0.297 | 15 (10.5, 21.00) | 14 (10, 21.75) | 0.916 | 12 (9.00, 21.00) | 14 (11.00, 22.00) | 0.231 |
| BUN (mmol/l) # | *< 0.001* | 6.85 (3.68, 18.13) | 6.6 (4.30, 10.68) | 0.907 | 9.15 (5.05, 13.90) | 5.35 (3.10, 7.30) | *< 0.001* |
| sCr (μmol/l) # | *0.002* | 73 (53.00, 185.25) | 74.5 (55.00, 110.75) | 0.967 | 96 (65.75, 171.00) | 64.5 (47.75, 80.00) | *< 0.001* |
| Complement 3 (g/l) # | 0.214 | 0.4 (0.28, 0.48) | 0.59 (0.28, 0.77) | 0.72 | 0.58 (0.24, 0.78) | 0.50 (0.29, 0.69) | 0.588 |
| Complement 4 (g/l) # | 0.266 | 0.09 (0.03, 0.12) | 0.09 (0.04, 0.18) | 0.359 | 0.09 (0.33, 0.21) | 0.09 (0.04, 0.14) | 0.729 |
| Anti-dsDNA (titer) # | 0.886 | 21 (7.50, 320.00) | 10 (0.00, 100.00) | 0.504 | 10 (0.00, 100.00) | 21 (0.00, 100.00) | 0.640 |
| Antinuclear antibody (ANA) (titer) # | 0.617 | 1000 (1000, 1550) | 1000 (320, 3200) | 0.950 | 1000 (320, 3200) | 1000 (1000, 3200) | 0.470 |
| ESR (mm/h) # | 0.688 | 56.5 (37.25, 85.75) | 33 (21.00, 65.00) | *0.046* | 31 (21.00, 59.75) | 43 (21.75, 71.50) | 0.174 |
| D-Dimer (mg/l) # | 0.853 | 1.12 (0.52, 3.99) | 1.87 (0.61, 3.18) | 0.819 | 2.09 (1.19, 3.30) | 1.12 (0.43, 3.04) | *0.037* |
| Proteinuria (g/24 h) # | *0.044* | 3.1 (1.35, 5.88) | 2.2 (0.67, 3.80) | 0.224 | 2.68 (1.49, 4.15) | 1.49 (0.63, 3.53) | 0.095 |
| Urine volume (L) # | 0.134 | 1.75 (1.48, 2.63) | 2.0 (1.70, 2.50) | 0.514 | 1.95 (1.63, 2.48) | 2.0 (1.68, 2.53) | 0.724 |
| Urinary path cast# | 0.678 | 0.20 (0.11, 1.43) | 0.2 (0.07, 0.53) | 0.563 | 0.2 (0.07, 0.65) | 0.23 (0.08, 0.50) | 0.813 |

**ALT*, glutamic-pyruvic transaminase; *BUN*, blood urea nitrogen; *sCr*, serum creatinine; *Anti-dsDNA*, anti-double-stranded DNA; *ESR*, erythrocyte sedimentation rate

*Shown as means ± standard deviation

# Shown as medians (interquartile range)

All categorical variables are shown as *n* (%)

**Table 4** Multivariable logistic regression for clinicopathological features and tubulointerstitial injury

| | HR | 95% CI | *P* value |
|---|---|---|---|
| Tubular atrophy | | | |
| Glomerulosclerosis | 3.634 | 1.183–11.161 | 0.024 |
| Arteriosclerosis | 10.639 | 3.205–35.318 | < 0.001 |
| Tubular degeneration | | | |
| Neutrophil infiltration/ karyorrhexis | 84.030 | 8.459–834.712 | < 0.001 |
| Arteriosclerosis | 0.295 | 0.098–0.893 | 0.031 |
| D-Dimer | 0.754 | 0.579–0.983 | 0.037 |
| Tubulointerstitial inflammation | | | |
| Endocapillary proliferative | 3.020 | 1.020–8.945 | 0.046 |
| Arteriosclerosis | 6.331 | 2.212–18.121 | 0.001 |
| Wire loop lesion | 6.019 | 1.114–32.559 | 0.037 |
| Interstitial edema | | | |
| Wire loop lesion | 15.556 | 3.036–79.693 | 0.001 |
| Interstitial fibrosis | | | |
| Neutrophil infiltration/ karyorrhexis | 0.117 | 0.037–0.372 | < 0.001 |
| Arteriosclerosis | 5.272 | 1.841–15.095 | 0.002 |
| Cast | 10.677 | 1.668–68.353 | 0.012 |
| Leukocyte count | 1.159 | 0.993–1.353 | 0.061 |

IV+V LN. Even in patients with class II LN, in which the typical glomerular lesions are mild, the incidence of tubulointerstitial injury was still high (up to 88.9%), and more than 50% of the patients with class II LN had tubular atrophy as chronic injury. Those results suggest that glomerular and tubulointerstitial lesions coexist in many patients, but not in all of them, as Yu et al. have shown [9]. Therefore, as suggested by Yu et al. [9], the ISN/RPS classification could also reflect tubulointerstitial lesions based on the glomerular lesions, but the ISN/RPS classification focuses on the glomerular lesions and the tubulointerstitial lesions could also be helpful for determining the prognosis of those patients.

In LN, anti-dsDNA antibodies either bind to chromatin or to cross-reactive antigens on the surface of renal cells or extracellular matrix [17]. Previous studies suggested links between anti-dsDNA antibody deposition and tubulointerstitial fibrosis in LN through the accumulation of matrix proteins [18–20]. The intraglomerular accumulation of fibronectin can be the result of plasma fibronectin capture and local synthesis [20–22]. Anti-dsDNA are able to induce the synthesis of fibronectin through PKC-α, PKC-β1, and PKC-βII phosphorylation and TGF-β1 secretion [19], while increased fibronectin synthesis by proximal renal tubular epithelial cells involves increased ERK, p38 MAPK, Jun N-terminal Kinase (JNK), PKC-α, and PKC-βII activation, but not PKC-βI, all of them inducing the secretion of TGF-β1, IL-6, IL-8, monocyte chemoattractant protein 1 (MCP-1), and tumor necrosis factor-alpha (THF-α) [23]. Therefore, it can be hypothesized that tubulointerstitial damage may occur

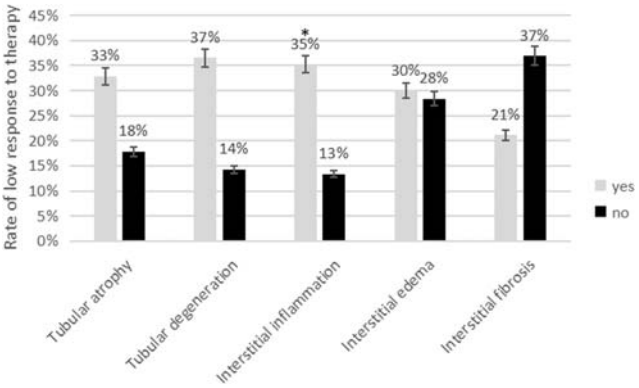


**Fig. 1** Rate of low response to therapy by tubulointerstitial injury (*$P < 0.05$)

independently from glomerular damage and that the two categories of lesions involve different mechanisms [9, 14, 15]. This is supported by Yu et al. [9], who showed that not all patients with glomerular lesions developed concomitant tubulointerstitial lesions. Based on murine studies, Davidson et al. [14] showed that numerous pathways participated in the development of LN and suggested that those pathways should be identified in each case of LN in order to individualize the treatments. Indeed, those mechanisms include Th cell activation, B cell activation, anti-dsDNA secretion, and TLR expression and inflammation through IFN-α, IL-6, IL-17, and IL-21 [24–28], among others, and not all mechanisms are necessarily activated at the same time within a given individual. Therefore, drugs that modulate inflammation could play roles in the management of tubulointerstitial lesions. For example, mycophenolic acid (MPA) could be used as a treatment against tubulointerstitial inflammation and fibrosis through its direct action on tubular epithelial cells [29–31]. Nevertheless, all those studies, including the present one, included patients with glomerular lesions, and it should be interesting to observe patients with tubulointerstitial lesions only.

Previous studies showed that tubulointerstitial inflammation might indicate the progression of an ongoing injury [8, 32]. Recent basic studies showed that tubulointerstitial inflammation drives the progression of chronic kidney disease (CKD) [33–37]. The reason why the frequencies of acute and chronic renal injury parameters are higher in patients with tubulointerstitial inflammation may be that tubulointerstitial inflammation is not only a sign indicating acute renal injury but also a force driving acute renal injury toward chronic injury.

Abnormality of some clinical indicators is often more serious in specific tubulointerstitial lesions. These clinical indicators mainly reflect the renal injury (sCr, BUN, and urinary protein) and inflammation (leukocyte count), while other markers reflecting liver function (ALT, ALB, and cholesterol), hematology (erythrocyte, hemoglobin, and platelet), and activity of LN (complements, anti-dsDNA, and ESR) showed no such relationship. This is supported by the literature [8, 38]. Nevertheless, there are exceptions. For example, the levels of

Cr and BUN in the tubular degeneration group were lower than in the patients without tubular degeneration. It is interesting that LN patients without tubular degeneration seem to have higher sCr and BUN levels. Maybe tubular degeneration is not only a consequence of LN but also a sign of renal injury repair.

After multivariable regression analysis based on clinicopathological factors, patients with high leukocyte count still had a higher hazard of interstitial fibrosis. As for the pathologic indexes, patients displaying neutrophil infiltration/karyorrhexis, wire loop lesion, and arteriosclerosis had a higher hazard of at least two tubulointerstitial injuries. It seems that patients with immune factors (elevated leukocyte count, neutrophil infiltration/karyorrhexis, and wire loop lesion) and vascular factors (arteriosclerosis) had a higher hazard of tubulointerstitial injuries. As for leukocyte count, Wu et al. demonstrated a pathogenic role for leukocyte chemotaxis involving collectin-11, a recently described soluble C-type lectin, in the development of interstitial fibrosis in an animal study [39]. Specifically, collectin-11 promotes leukocyte recruitment and fibroblast proliferation in a carbohydrate-dependent manner [39]. Collectin-11-deficient mice showed markedly decreased tubulointerstitial fibrosis compared with wild type ones [39]. It would be valuable to explore the potential role of immune and vascular factors in the development of tubulointerstitial injuries.

Previous studies have identified LN patients with tubulointerstitial inflammation as being at the greatest risk for progression to renal failure, while there was no relationship between the probability of remission and tubulointerstitial inflammation [7, 8]. In the present study, to minimize the confounding factors, we included patients with LN confirmed using renal biopsy, with renal biopsy within 1 month of symptom onset, and without immunosuppressive treatment before renal biopsy. After evaluating the response to therapy in the first 6 months of treatment, we found that the rate of low response to therapy was significantly higher in patients with tubulointerstitial inflammation. It suggests that LN patients with tubulointerstitial inflammation should receive more aggressive treatment to achieve better renal outcomes. Of note, tubulointerstitial inflammation is one of the most favorable prognostic factors for kidney survival [40–42]. Additional studies are needed to investigate how to improve tubulointerstitial inflammation, as well as how to improve the impact of tubulointerstitial inflammation on renal prognosis.

This study has several limitations. First, it was a retrospective study, which is vulnerable to missing data. Second, the study included a relatively small sample of LN biopsies, and the degree of tubulointerstitial lesions could not be further analyzed. Finally, the efficacy of the final treatment response was judged according to the ACR/EULAR criteria, but when the patients were grouped, those with a complete response and partial remission according to the ACR/EULAR criteria were classified as the response group, while the patients without remission were classified as the low-response group. This grouping had to be adopted because the number of patients was relatively small, and to reduce the statistical error. Despite these limitations, this study provides evidence for the clinicopathological factors found along with tubulointerstitial injury and the potential predictive value of tubulointerstitial inflammation, which is important for exploring how tubulointerstitial injury affects the development of LN. It is necessary to expand the sample size of each pathological type further and obtain long-term follow-up to confirm these results.

## Conclusion

Tubulointerstitial injury is common in LN, and obvious tubulointerstitial injury can be observed when the glomerular lesion is not serious. Acute and chronic renal tubulointerstitial lesions are found, along with glomerular and vascular lesions. Abnormal immune and vascular indexes are found along with tubulointerstitial injuries. Tubulointerstitial inflammation may be the initiator of chronic renal injury and predicts the response to therapy.

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### Compliance with ethical standards

**Disclosures** None.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee at which the studies were conducted (IRB approval number K2018-03-003) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## References

1. Pokroy-Shapira E, Gelernter I, Molad Y (2014) Evolution of chronic kidney disease in patients with systemic lupus erythematosus over a long-period follow-up: a single-center inception cohort study. Clin Rheumatol 33(5):649–657. https://doi.org/10.1007/s10067-014-2527-0
2. Lewis EJ, Schwartz MM (2010) Lupus nephritis. Oxford University Press, Oxford
3. Anders HJ, Rovin B (2016) A pathophysiology-based approach to the diagnosis and treatment of lupus nephritis. Kidney Int 90(3):493–501. https://doi.org/10.1016/j.kint.2016.05.017
4. Shao SJ, Hou JH, Xie GT, Sun W, Liang DD, Zeng CH, Zhu HX, Liu ZH (2019) Improvement of outcomes in patients with lupus nephritis: management evolution in Chinese patients from 1994 to 2010. J Rheumatol. https://doi.org/10.3899/jrheum.180145

5. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, Balow JE, Bruijn JA, Cook T, Ferrario F, Fogo AB, Ginzler EM, Hebert L, Hill G, Hill P, Jennette JC, Kong NC, Lesavre P, Lockshin M, Looi LM, Makino H, Moura LA, Nagata M, International Society of Nephrology Working Group on the Classification of Lupus N, Renal Pathology Society Working Group on the Classification of Lupus N (2004) The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int 65 (2):521–530. doi:https://doi.org/10.1111/j.1523-1755.2004.00443.x
6. Parikh SV, Alvarado A, Malvar A, Rovin BH (2015) The kidney biopsy in lupus nephritis: past, present, and future. Semin Nephrol 35(5):465–477. https://doi.org/10.1016/j.semnephrol.2015.08.008
7. Hsieh C, Chang A, Brandt D, Guttikonda R, Utset TO, Clark MR (2011) Predicting outcomes of lupus nephritis with tubulointerstitial inflammation and scarring. Arthritis Care Res (Hoboken) 63(6): 865–874. https://doi.org/10.1002/acr.20441
8. Alsuwaida AO (2013) Interstitial inflammation and long-term renal outcomes in lupus nephritis. Lupus 22(14):1446–1454. https://doi.org/10.1177/0961203313507986
9. Yu F, Wu LH, Tan Y, Li LH, Wang CL, Wang WK, Qu Z, Chen MH, Gao JJ, Li ZY, Zheng X, Ao J, Zhu SN, Wang SX, Zhao MH, Zou WZ, Liu G (2010) Tubulointerstitial lesions of patients with lupus nephritis classified by the 2003 International Society of Nephrology and Renal Pathology Society system. Kidney Int 77(9):820–829. https://doi.org/10.1038/ki.2010.13
10. Pagni F, Galimberti S, Galbiati E, Rebora P, Pietropaolo V, Pieruzzi F, Smith AJ, Ferrario F (2016) Tubulointerstitial lesions in lupus nephritis: international multicentre study in a large cohort of patients with repeat biopsy. Nephrology (Carlton) 21(1):35–45. https://doi.org/10.1111/nep.12555
11. Yu F, Haas M, Glassock R, Zhao MH (2017) Redefining lupus nephritis: clinical implications of pathophysiologic subtypes. Nat Rev Nephrol 13(8):483–495. https://doi.org/10.1038/nrneph.2017.85
12. Clark MR, Trotter K, Chang A (2015) The pathogenesis and therapeutic implications of tubulointerstitial inflammation in human lupus nephritis. Semin Nephrol 35(5):455–464. https://doi.org/10.1016/j.semnephrol.2015.08.007
13. Trotter K, Clark MR, Liarski VM (2016) Overview of pathophysiology and treatment of human lupus nephritis. Curr Opin Rheumatol 28(5):460–467. https://doi.org/10.1097/BOR.0000000000000319
14. Davidson A, Aranow C (2010) Lupus nephritis: lessons from murine models. Nat Rev Rheumatol 6(1):13–20. https://doi.org/10.1038/nrrheum.2009.240
15. Yung S, Chan TM (2017) Molecular and immunological basis of tubulo-interstitial injury in lupus nephritis: a comprehensive review. Clin Rev Allergy Immunol 52(2):149–163. https://doi.org/10.1007/s12016-016-8533-z
16. Bertsias GK, Tektonidou M, Amoura Z, Aringer M, Bajema I, Berden JH, Boletis J, Cervera R, Dorner T, Doria A, Ferrario F, Floege J, Houssiau FA, Ioannidis JP, Isenberg DA, Kallenberg CG, Lightstone L, Marks SD, Martini A, Moroni G, Neumann I, Praga M, Schneider M, Starra A, Tesar V, Vasconcelos C, van Vollenhoven RF, Zakharova H, Haubitz M, Gordon C, Jayne D, Boumpas DT, European League Against R, European Renal Association-European D, Transplant A (2012) Joint European League Against rheumatism and European renal association-European Dialysis and Transplant association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 71(11):1771–1782. https://doi.org/10.1136/annrheumdis-2012-201940
17. Krishnan MR, Wang C, Marion TN (2012) Anti-DNA autoantibodies initiate experimental lupus nephritis by binding directly to the glomerular basement membrane in mice. Kidney Int 82(2):184–192. https://doi.org/10.1038/ki.2011.484
18. Yung S, Zhang Q, Chau MK, Chan TM (2015) Distinct effects of mycophenolate mofetil and cyclophosphamide on renal fibrosis in NZBWF1/J mice. Autoimmunity 48(7):471–487. https://doi.org/10.3109/08916934.2015.1054027
19. Yung S, Zhang Q, Zhang CZ, Chan KW, Lui SL, Chan TM (2009) Anti-DNA antibody induction of protein kinase C phosphorylation and fibronectin synthesis in human and murine lupus and the effect of mycophenolic acid. Arthritis Rheum 60(7):2071–2082. https://doi.org/10.1002/art.24573
20. Baelde HJ, Eikmans M, van Vliet AI, Bergijk EC, de Heer E, Bruijn JA (2004) Alternatively spliced isoforms of fibronectin in immune-mediated glomerulosclerosis: the role of TGFbeta and IL-4. J Pathol 204(3):248–257. https://doi.org/10.1002/path.1653
21. van Vliet AI, van Alderwegen IE, Baelde HJ, de Heer E, Bruijn JA (2002) Fibronectin accumulation in glomerulosclerotic lesions: self-assembly sites and the heparin II binding domain. Kidney Int 61(2):481–489. https://doi.org/10.1046/j.1523-1755.2002.00159.x
22. Bergijk EC, Baelde HJ, De Heer E, Killen PD, Bruijn JA (1995) Specific accumulation of exogenous fibronectin in experimental glomerulosclerosis. J Pathol 176(2):191–199. https://doi.org/10.1002/path.1711760213
23. Yung S, Ng CY, Ho SK, Cheung KF, Chan KW, Zhang Q, Chau MK, Chan TM (2015) Anti-dsDNA antibody induces soluble fibronectin secretion by proximal renal tubular epithelial cells and downstream increase of TGF-beta1 and collagen synthesis. J Autoimmun 58:111–122. https://doi.org/10.1016/j.jaut.2015.01.008
24. Doreau A, Belot A, Bastid J, Riche B, Trescol-Biemont MC, Ranchin B, Fabien N, Cochat P, Pouteil-Noble C, Trolliet P, Durieu I, Tebib J, Kassai B, Ansieau S, Puisieux A, Eliaou JF, Bonnefoy-Berard N (2009) Interleukin 17 acts in synergy with B cell-activating factor to influence B cell biology and the pathophysiology of systemic lupus erythematosus. Nat Immunol 10(7):778–785. https://doi.org/10.1038/ni.1741
25. Ramanujam M, Wang X, Huang W, Liu Z, Schiffer L, Tao H, Frank D, Rice J, Diamond B, Yu KO, Porcelli S, Davidson A (2006) Similarities and differences between selective and nonselective BAFF blockade in murine SLE. J Clin Invest 116(3):724–734. https://doi.org/10.1172/JCI26385
26. Gilliet M, Cao W, Liu YJ (2008) Plasmacytoid dendritic cells: sensing nucleic acids in viral infection and autoimmune diseases. Nat Rev Immunol 8(8):594–606. https://doi.org/10.1038/nri2358
27. Chaturvedi A, Dorward D, Pierce SK (2008) The B cell receptor governs the subcellular location of toll-like receptor 9 leading to hyperresponses to DNA-containing antigens. Immunity 28(6):799–809. https://doi.org/10.1016/j.immuni.2008.03.019
28. Christensen SR, Shlomchik MJ (2007) Regulation of lupus-related autoantibody production and clinical disease by toll-like receptors. Semin Immunol 19(1):11–23. https://doi.org/10.1016/j.smim.2006.12.005
29. Chan TM, Li FK, Tang CS, Wong RW, Fang GX, Ji YL, Lau CS, Wong AK, Tong MK, Chan KW, Lai KN (2000) Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou nephrology study group. N Engl J Med 343(16):1156–1162. https://doi.org/10.1056/NEJM200010193431604
30. Chan TM, Tse KC, Tang CS, Mok MY, Li FK, Hong Kong Nephrology Study G (2005) Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. J Am Soc Nephrol 16(4):1076–1084. https://doi.org/10.1681/ASN.2004080686
31. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, Petri M, Gilkeson GS, Wallace DJ, Weisman MH, Appel GB (2005) Mycophenolate mofetil or intravenous cyclophosphamide

for lupus nephritis. N Engl J Med 353(21):2219–2228. https://doi.org/10.1056/NEJMoa043731
32. Zappitelli M, Duffy CM, Bernard C, Gupta IR (2008) Evaluation of activity, chronicity and tubulointerstitial indices for childhood lupus nephritis. Pediatr Nephrol 23(1):83–91. https://doi.org/10.1007/s00467-007-0619-7
33. Wang Y, Chang J, Yao B, Niu A, Kelly E, Breeggemann MC, Abboud Werner SL, Harris RC, Zhang MZ (2015) Proximal tubule-derived colony stimulating factor-1 mediates polarization of renal macrophages and dendritic cells, and recovery in acute kidney injury. Kidney Int 88(6):1274–1282. https://doi.org/10.1038/ki.2015.295
34. Baek JH, Zeng R, Weinmann-Menke J, Valerius MT, Wada Y, Ajay AK, Colonna M, Kelley VR (2015) IL-34 mediates acute kidney injury and worsens subsequent chronic kidney disease. J Clin Invest 125(8):3198–3214. https://doi.org/10.1172/JCI81166
35. Edeling M, Ragi G, Huang S, Pavenstadt H, Susztak K (2016) Developmental signalling pathways in renal fibrosis: the roles of Notch, Wnt and Hedgehog. Nat Rev Nephrol 12(7):426–439. https://doi.org/10.1038/nrneph.2016.54
36. Tan RJ, Zhou D, Zhou L (2011) Liu Y (2014) Wnt/beta-catenin signaling and kidney fibrosis. Kidney Int Suppl 4(1):84–90. https://doi.org/10.1038/kisup.2014.16
37. Chung AC, Lan HY (2011) Chemokines in renal injury. J Am Soc Nephrol 22(5):802–809. https://doi.org/10.1681/ASN.2010050510
38. Hill GS, Delahousse M, Nochy D, Mandet C, Bariety J (2001) Proteinuria and tubulointerstitial lesions in lupus nephritis. Kidney Int 60(5):1893–1903. https://doi.org/10.1046/j.1523-1755.2001.00017.x
39. Wu W, Liu C, Farrar CA, Ma L, Dong X, Sacks SH, Li K, Zhou W (2018) Collectin-11 promotes the development of renal tubulointerstitial fibrosis. J Am Soc Nephrol 29(1):168–181. https://doi.org/10.1681/ASN.2017050544
40. Tanaka K, Tanabe K, Nishii N, Takiue K, Sugiyama H, Wada J (2017) Sustained tubulointerstitial inflammation in kidney with severe leptospirosis. Intern Med 56(10):1179–1184. https://doi.org/10.2169/internalmedicine.56.8084
41. Joyce E, Glasner P, Ranganathan S, Swiatecka-Urban A (2017) Tubulointerstitial nephritis: diagnosis, treatment, and monitoring. Pediatr Nephrol 32(4):577–587. https://doi.org/10.1007/s00467-016-3394-5
42. Rankin AJ, Kipgen D, Geddes CC, Fox JG, Milne G, Mackinnon B, McQuarrie EP (2019) Assessment of active tubulointerstitial nephritis in non-scarred renal cortex improves prediction of renal outcomes in patients with IgA nephropathy. Clin Kidney J 12(3):348–354. https://doi.org/10.1093/ckj/sfy093