Significance of Histological Crescent Formation in Patients with Diffuse Proliferative Lupus Nephritis

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Key Words

Crescent · Diffuse proliferative lupus nephritis ·
Clinicopathological features

Abstract

Background: Although crescentic nephritis is not rare in diffuse proliferative lupus nephritis (DPLN), little is known about the clinicopathological features in DPLN with crescents worldwide. This study was undertaken to investigate the clinicopathological features and outcome of Chinese DPLN patients with different degrees of crescents. **Methods:** 520 DPLN patients with more than 10% histological crescents (cDPLN) were enrolled in this retrospective study. They were divided into three groups: group 1 (10% ≤ crescents < 25%, n = 240), group 2 (25% ≤ crescents < 50%, n = 160), and group 3 (crescents ≥ 50%, n = 120). Another 100 patients without histological crescents were enrolled as a control group. Clinicopathological features, treatment responses, and outcomes were compared among the four groups. **Results:** There were 450 (86.6%) females and 70 (13.4%) males with an average age of 31.7 ± 11.4 years. Compared with the control group, cDPLN patients had shorter lupus nephritis duration (20.7 ± 34.1 vs. 30.4 ± 48.9 months), higher prevalence of rapidly progressive glomerulonephritis syndrome (21.8%), and gross hematuria (26.7%). Laboratory findings indicated more severe hypoproteinemia, hyperlipidemia,

and renal insufficiency; heavier proteinuria and microscopic hematuria; higher tubular injury parameters, and lower serological activity in crescentic groups. Histologically, cDPLN patients have severe glomerular and tubulointerstitial lesions as well as extensive leukocyte infiltration together with a lesser degree of immune complex deposition. The proportion of death, end-stage renal disease, and treatment failure correlates positively with the degree of histological crescents. **Conclusions:** cDPLN patients with acute onset and short disease duration mostly show severe renal manifestations, less extrarenal organ involvement, lower serological activity, serious capillary necrosis, severe tubulointerstitial inflammation, atrophy and fibrosis, prominent leukocyte infiltration, less glomerular immune complex deposition, poor treatment response, and worse renal outcome.

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Introduction

It has been reported that lupus nephritis (LN) is the commonest secondary disease of crescentic glomerulonephritis [1], occurring in 33.9% of crescentic glomerulonephritis, and 54.6% of type II (immune-complex) crescentic glomerulonephritis in Chinese patients [2, 3]. Crescentic nephritis is not rare in LN, especially in diffuse proliferative lupus nephritis (DPLN). While DPLN itself

Table 1. Demographic characteristics

	Control	Group 1 (10%≤ crescents <25%)	Group 2 (25%≤ crescents <50%)	Group 3 (crescents ≥50%)
Patients, n	100	240	160	120
Age, years	32.1±11.9	33.3±11.4 ^{a, b}	30.9±11.2	30.1±10.9
Onset age, years	28.7±10.9	29.8±11.3	28.7±11.1	27.3±10.5
Females, n	84.0	86.3	88.2	85.0
Duration of SLE, months	39.6±51.9	41.5±48.6 ^a	27.1±38.8	29.7±36.7
Duration of LN, months	30.4±48.9 ^{c, d}	29.6±43.8 ^{a, b}	14.4±23.9	15.5±24.7

^a $p < 0.05$ between group 1 and group 2. ^b $p < 0.05$ between group 1 and group 3. ^c $p < 0.05$ between control and group 2. ^d $p < 0.05$ between control and group 3.

carries a poor prognosis if timely intervention is not carried out [4], the formation of crescents further warrants rapid deterioration of renal function and a very poor outcome [5, 6]. Despite considerable improvements in the treatment of crescentic LN in recent years, 25–30% of patients will develop end-stage renal disease (ESRD), necessitating lifelong renal replacement therapy [7]. Therefore, early diagnosis and proactive intervention should be emphasized in these patients. However, there are limited detailed reports currently available concerning demographic, clinical, and pathological features in lupus patients with various degrees of histological crescents except for a few reports on DPLN patients with more than 50% glomeruli having crescents on light microscopy [8–10]. In this study, we conducted a retrospective analysis of a biopsy-proven cohort of 520 patients with more than 10% crescents in DPLN, which may shed some new light on further pathogenic and therapeutic studies.

Methods

Patients

The clinicopathological characteristics of 520 biopsy-proven DPLN patients with more than 10% crescents (cDPLN) diagnosed between 2000 and 2010 in Nanjing Jinling Hospital were retrospectively reviewed. The inclusion criteria were: (1) diagnosed as systemic lupus erythematosus (SLE) as defined by the 1997 revised American Rheumatism Association criteria [11], (2) renal biopsy-confirmed DPLN according to the 2003 International Society of Nephrology/Renal Pathology Society classification [12], and (3) at least 10% of the glomeruli having crescents ('extracapillary cells more than two layers thick involving ≥25% of the glomerular circumference'). Reasons for exclusion were: (1) <10 nonsclerotic glomeruli in sampled renal tissue, (2) biopsy aged <18 years, (3) class IV LN mixed with other histological types such as IV+V or IV+III, and (4) life-threatening complications such as pancreatitis, gastrointestinal hemorrhage, se-

vere infection, severe cardiovascular disease, and bone marrow insufficiency. According to the degree of histological crescents, the cDPLN patients were divided into three subgroups: group 1 (10%≤ crescents <25%, $n = 240$), group 2 (25%≤ crescents <50%, $n = 160$), and group 3 (crescents ≥50%, $n = 120$). Another 100 DPLN patients without crescent formation were regarded as a control group. The clinicopathological features, treatment response and renal function deterioration were compared among the four groups.

Renal Pathology

Percutaneous renal biopsy was carried out under ultrasound guidance. DPLN was defined as >50% of glomeruli on light microscopy having segmental or global endocapillary or extracapillary glomerulonephritis as well as mesangial involvement [12]. Pathological parameters such as activity indexes (AI) and chronic indexes (CI) were approached by renal pathologists using a modification of an earlier reported system involving semiquantitative scoring of specific biopsy features [13]. Tubulointerstitial lesions including tubular atrophy and interstitial fibrosis as well as interstitial inflammation were semiquantitatively graded as none (0), mild (1), moderate (2), or severe (3) [14]. Immunofluorescence for deposition of IgG, IgA, IgM, C3, C1q, and fibrin deposits was semiquantitatively graded from 0 to 4+ according to the intensity of fluorescence.

Definitions

Complete remission was defined as urinary protein excretion <0.3 g/day, normal urinary sediment, and normal or stable renal function (within 10% of normal eGFR if previously abnormal renal function). Partial remission was defined as a urinary protein excretion within the range of 0.3–2.9 g/day with a stable or improved renal function [15]. Treatment failure was defined as a sustained 25% increase in serum creatinine, an increase in proteinuria, or a reduction in proteinuria but not to the extent of complete or partial remission. A relapse was defined as persistent increase in proteinuria >1 g/day after complete remission or a doubling of proteinuria with values >2 g/day after achieving partial remission, or recurrence of active urinary sediment and/or an increase of ≥25% in serum creatinine [16]. ESRD was defined as a serum creatinine >6 mg/dl (>528 mmol/l), or the initiation of renal replacement therapy [17].

Table 2. Clinical and laboratory features of renal damage

	Control	Group 1 (10%≤ crescents <25%)	Group 2 (25%≤ crescents <50%)	Group 3 (crescents ≥50%)
UAB, %	46.6	33.5	19.4	20.8
NS, %	19.4	28.2	23.5	15.8
RPGN, %	1	6.4	24.1	42.5
CRF, %	6.8	10.6	9.4	1.7
Gross hematuria, %	12.3	22.6	27.6	31.7
BUN, mg/dl	25.9±17.1 ^{a-c}	32.5±21.1	35.4±28.2	39.6±24.1
SCr, mg/dl	1.3±2.0 ^{b, c}	1.5±1.4 ^{d, e}	2.0±2.0	2.4±2.2
Urine protein, g/day	3.0±2.9 ^{b, c}	3.6±2.9 ^e	4.4±3.3	4.8±3.3
Urinary sediment, ×10 ⁴ /ml	307.8±822.7	700.5±2,846.1	524.1±1,018.4	784.0±1,794.0
Urinary C3, mg/l	4.3±4.6 ^{a-c}	8.5±0.6 ^e	11.1±1.0	12.8±1.4
NAG, U/g·Cr	46.6±35.9 ^{a-c}	58.9±41.0 ^e	70.7±46.9	74.9±46.0
RBP, mg/l	3.0±5.2 ^{a-c}	6.0±11.4 ^e	9.9±19.5	11.7±17.4

UAB = Abnormal urinalysis; NS = nephrotic syndrome; RPGN = rapidly progressive glomerulonephritis syndrome; RBP = retinol-binding protein. ^a $p < 0.05$ between control and group 1. ^b $p < 0.05$ between control and group 2. ^c $p < 0.05$ between control and group 3. ^d $p < 0.05$ between group 1 and group 2. ^e $p < 0.05$ between group 1 and group 3.

Statistical Analysis

All data were analyzed by using statistical software SPSS 19.0. Quantitative data were expressed as means ± SD. All parameters were compared by a χ^2 test or Fisher's exact test for categorical data, and Student's *t* test or a one-way analysis of variance for continuous data. A Spearman test was used for correlation analysis. Statistical significance was considered as $p < 0.05$.

Results

General Condition

There were 450 (86.6%) females and 70 (13.4%) males with an average age and onset age of 31.6 ± 11.3 and 28.8 ± 11.1 years, respectively. The duration of SLE and LN were 34.5 ± 42.9 and 20.7 ± 34.1 months, respectively. Group 1 showed a higher average age and disease-onset age than the other groups (table 1).

Clinical and Laboratory Features of Renal Damage

As shown in table 2, cDPLN patients more frequently manifested with rapidly progressive glomerulonephritis syndrome (21.8%), gross hematuria (26.7%), nephrotic syndrome (23.4%), and chronic renal failure (CRF; 7.9%). Their average levels of urea nitrogen and creatinine at renal biopsy were 35.3 ± 23.6 versus 25.8 ± 17.1 mg/dl and 1.9 ± 1.9 versus 1.2 ± 1.9 mg/dl, respectively, compared with the control group. Groups 1 and 2 had a higher proportion of CRF than the control group ($p = 0.261$, $p =$

0.412), and group 3 had a lower proportion of CRF than the control group ($p = 0.12$). A positive correlation existed among the levels of urea nitrogen ($p < 0.01$), creatinine ($p < 0.01$), proteinuria ($p < 0.001$), NAG (n-acetyl- β -D-glucosaminidase; $p < 0.001$), retinol-binding protein ($p < 0.001$), and urine C3 with the degree of crescents (table 2).

Immunological Characteristics

In the 520 cDPLN patients, the rates of positive ANA, ds-DNA, Sm, RNP, SSA, SSB, ACL, LA, and ANCA were 98.3, 68.8, 21.7, 27.1, 50.9, 13.4, 29.9, 2.6, and 3.1%, respectively. A negative correlation of albumin ($p < 0.001$) and rate of positive RNP ($p < 0.001$) was found with the crescent ratio among the four groups, while the rate of positive LA ($p < 0.001$) and ANCA ($p = 0.071$) increased with the rising ratio of crescents. Lower values of globulin ($p < 0.001$), cryoglobulin ($p = 0.376$), IgG ($p = 0.001$), ANA ($p = 0.08$), and ds-DNA titers ($p = 0.64$), a lower ratio of positive Sm ($p = 0.003$) and ACL ($p < 0.001$), and higher levels of C3 ($p = 0.022$) and C4 ($p = 0.004$) were observed in the cDPLN groups (table 3).

Renal Pathological Characteristics

The mean scores of AI and CI in cDPLN patients compared with the control group were 10.6 ± 4.1 versus 6.7 ± 3.4 and 2.3 ± 1.9 versus 1.7 ± 2.1 . In cDPLN patients, besides cellular ($p < 0.001$), fibrocellular ($p < 0.001$), and

Table 3. Immunological characteristics

	Control	Group 1 (10%≤ crescents <25%)	Group 2 (25%≤ crescents <50%)	Group 3 (crescents ≥50%)
Alb, g/l	29.5±7.2 ^{a, b}	27.9±7.0 ^{c, d}	25.8±5.7	24.7±5.9
Glo, g/l	26.8±7.9 ^{a, b, e}	23.5±6.5	24.0±7.2	23.3±6.5
CG, mg/l	380.6±297.7	322.3±192.7	316.5±238.2	329.2±353.8
IgG, g/l	13.9±9.2 ^{a, b, e}	10.4±5.6	10.5±6.7	10.4±5.7
ANA (1:n)	654.3±581.4 ^{a, e}	524.5±528.8	480.3±540.3	537.7±543.3
ds-DNA (1:n)	25.7±33.1	19.1±32.8	25.7±85.4	24.4±42.6
Positive ACL, %	48.1	36.7	23.5	28.3
Positive LA, %	0.9	0.5	8.3	17.6
Positive ANCA, %	0	2.2	2.3	5.8
C3, g/l	0.434±0.248 ^b	0.499±0.245	0.494±0.225	0.545±0.356
C4, g/l	0.106±0.126	0.118±0.089	0.135±0.107	0.159±0.163

^a $p < 0.05$ between the control group and group 2. ^b $p < 0.05$ between the control group and group 3. ^c $p < 0.05$ between group 1 and group 2. ^d $p < 0.05$ between group 1 and group 3. ^e $p < 0.05$ between the control group and group 1.

fibrous crescents ($p < 0.001$), the percentage of cases with capillary necrosis ($p < 0.001$), score of interstitial inflammation ($p < 0.001$), and AI ($p < 0.001$) increased along with the rising ratio of crescents. The scores of acute tubulointerstitial lesions ($p = 0.103$) and chronic tubulointerstitial lesions ($p < 0.001$) were higher in the cDPLN groups than in the control group. Group 1 had the most severe acute tubulointerstitial lesions ($p = 0.113$) and the highest ratio of glomerular sclerosis ($p = 0.186$).

Immunofluorescence indicated that the average peripheral capillary loop intensity of IgG, IgA, IgM, C3, and C1q deposition was lower in cDPLN patients than those in the control group, and the differences in IgG, IgA, and IgM reached statistical significance ($p < 0.001$, $p < 0.001$, and $p = 0.008$, respectively; table 4).

Renal Infiltrating Cells Analysis

cDPLN patients, especially in group 3, had significantly higher numbers of infiltrating CD4 and CD8+ T cells in the renal interstitium than the control group. Interstitium infiltrating CD68+ T cells increased in proportion to the degree of histological crescents ($p < 0.01$; table 5).

Extrarenal Manifestations

The average SLE Disease Activity (SLE-DAI) score [18, 19] of cDPLN patients was 15.2 ± 5.7 . The main extrarenal manifestation included arthritis (54.6%), hypertension (51.3%), anemia (49.4%), and malar rash (46.5%). The ratio of hypertension ($p < 0.001$) and anemia ($p <$

0.001) were in positive proportion to the percentage of crescents. A higher SLE-DAI score ($p = 0.021$), higher proportion of serositis ($p = 0.043$), malignant hypertension ($p = 0.510$), and TTP/HUS ($p = 0.057$) were observed in the cDPLN groups than those in the control group, but not completely proportional to the ratio of crescent in total glomeruli. Group 1 exhibited the highest ratio of malignant hypertension ($p < 0.01$), TTP/HUS ($p = 0.094$), and malar rash ($p = 0.069$) (data not shown).

Follow-Up

A total of 620 DPLN patients were treated with a flexible strategy, mainly based on high-dose corticosteroids and cytotoxic agents for induction and maintenance after biopsy. There was no significant difference in the treatment algorithm among the four groups. The follow-up time ranged from 1 month to 10 years. In the cDPLN groups, 28 patients (5.6%) died of renal disease, 32 patients (6.1%) reached ESRD, 101 patients (19.4%) developed CRF, and 357 patients (68.7%) maintained normal renal function. The proportion of death and ESRD correlated positively with the degree of histological crescents. Excluding those with serum creatinine exceeding 4.5 mg/dl or followed for less than 60 months, it was found that 320 cDPLN patients had a lower complete remission rate after longer time of treatment. It was found that the higher the percentage of histological crescents, the lower the proportion of patients showing a good response to immune-suppressive therapy during follow-up (table 6).

Table 4. Renal pathological characteristics

	Control	Group 1 (10%≤ crescents <25%)	Group 2 (25%≤ crescents <50%)	Group 3 (crescents ≥50%)
Glomeruli, n	26.7±10.3 ^{b, c}	26.1±11.7 ^{d, e}	22.9±8.7	21.7±9.5
<i>Light microscope</i>				
Glomerular sclerosis, %	7.8±14.2	9.0±15.6 ^e	7.1±12.0	5.7±10.1
Segmental sclerosis, %	1.8±7.9	0.9±3.2	1.1±5.0	0.7±4.9
Crescents, %	0 ^{a-c}	19.0±6.0 ^{d, e}	37.2±5.2 ^f	64.5±14.0
Cellular crescents, %	0 ^{a-c}	8.0±8.4 ^{d, e}	13.35±15.4 ^f	21.72±25.0
Fibrocellular crescents, %	0 ^{a-c}	10.2±8.4 ^{d, e}	20.5±16.1 ^f	39.2±25.4
Fibrous crescents, %	0 ^{a-c}	0.9±3.5 ^{d, e}	3.3±9.0 ^f	5.4±13.7
Capillary necrosis, %	19.8	33.3	48.2	59.2
Wire loops, %	44.3	41.3	25.3	25.8
Capillary microthrombi, %	31.1	27.5	24.7	28.3
Acute tubulointerstitial lesion	0.7±0.7 ^a	1.0±0.7 ^e	0.8±0.8	0.8±0.8
Chronic tubulointerstitial lesion	0.5±0.7 ^{a-c}	0.9±0.9	0.9±0.9	0.8±0.9
Interstitial inflammation	0.9±0.4 ^{a-c}	1.0±0.5 ^{d, e}	1.2±0.6 ^f	1.3±0.7
<i>Immunofluorescence</i>				
IgG	2.0±0.2 ^{a-c}	1.8±0.4 ^d	1.6±0.7	1.7±0.6
IgA	1.5±0.6 ^{a-c}	1.3±0.5	1.1±0.5	1.2±0.5
IgM	1.4±0.5 ^{a, b}	1.2±0.4	1.2±0.5	1.2±0.5
C3	2.0±0.3	1.91±0.40	1.9±0.6	1.9±0.5
C4	1.1±0.8	0.98±0.7 ^{d, e}	1.2±0.6	1.4±0.61
C1q	1.5±0.5	1.5±0.5	1.4±0.6	1.5±0.5
AI score	6.7±3.3 ^{a-c}	9.1±3.4 ^e	9.9±4.1 ^f	11.6±4.7
CI score	1.70±2.13 ^{a-c}	2.27±1.78	2.20±2.01	2.33±2.00

^a p < 0.05 between control and group 1. ^b p < 0.05 between control and group 2. ^c p < 0.05 between control and group 3. ^d p < 0.05 between group 1 and group 2. ^e p < 0.05 between group 1 and group 3. ^f p < 0.05 between group 2 and group 3.

Table 5. Renal infiltrating cells analysis

	Control	Group 1 (10%≤ crescents <25%)	Group 2 (25%≤ crescents <50%)	Group 3 (crescents ≥50%)
CD4+ in interstitium (/mm ²)	119.3±79.8 ^{a-c}	170.2±133.9	165.4±86.3	184.9±111.6
CD8+ in interstitium (/mm ²)	116.3±80.2 ^{a-c}	177.8±124.3	177.9±80.5	197.7±113.6
CD68+ in glomeruli (/glo)	17.9±16.5	17.6±31.5	22.3±58.8	12.9±10.5
CD68+ in interstitium (/mm ²)	238.3±211.2 ^{a-c}	391.5±271.6	443.8±301.3	496.4±424.0

^a p < 0.05 between control and group 1. ^b p < 0.05 between control and group 2. ^c p < 0.05 between control and group 3.

Discussion

We have previously analyzed data from Chinese patients with crescentic nephritis in our center to characterize the clinical spectrum of crescentic glomerulonephritis. LN was demonstrated to be the commonest cause of

secondary disease of crescentic glomerulonephritis in Chinese patients, occurring in 33.9% of crescentic nephritis cases and 54.6% of type II (immune-complex) crescentic glomerulonephritis cases [2, 3]. Crescents were considered a critical factor in the histologic classification for Henoch-Schönlein purpura nephritis as they signifi-

Table 6. Treatment response and outcome

	Control	Group 1 (10%≤ crescents <25%)	Group 2 (25%≤ crescents <50%)	Group 3 (crescents ≥50%)
<i>Induction treatment, %</i>				
MMF + FK506 + P	27.3	22.2	12.7	16.7
MMF	29.5	28.5	40.2	28.8
FK506	0	4.2	5.9	4.5
CTX	28.4	39.6	24.5	39.4
<i>Maintenance treatment, %</i>				
MMF + FK506 + P	9.3	9.2	4.0	12.7
MMF	26.7	20.6	29.3	22.2
FK506	0	0.7	0	0
CTX	0	2.7	0	3.2
<i>Treatment response, %</i>				
CR	78.3	66.7	61.8	74.2
1-year	40	47.9	52	54.5
2-year	73	62.5	56.9	62.1
3-year	74.8	66.7	59.8	68.2
PR	18.3	25	29.4	15.2
TF	3.5	8.3	8.8	10.6
Relapse rate	37.8	41.7	49.5	31.7
<i>Outcome, n (%)</i>				
Death	1 (1.1)	5 (1.9)	10 (6.4)	13 (11.2)
ESRD	2 (2.2)	10 (4.3)	10 (6.4)	12 (10.2)
CRF	13 (13.2)	45 (18.6)	29 (18.4)	27 (22.4)
Normal renal function	83 (83.5)	180 (75.2)	110 (68.8)	67 (56.1)

CR = Complete remission; PR = partial remission; TF = treatment failure.

cantly affect symptomatology and long-term outcome of the disease [20]; likewise, crescents may be helpful to define the severity of renal disease, guide the choice of treatment, and predict the prognosis of patients with crescentic LN.

The present study showed that DPLN was the major pathological type of LN with histological crescent formation, affecting 44.9% of initial biopsies with more than 10% of sampled glomeruli. cDPLN more frequently manifested with rapidly progressive glomerulonephritis syndrome, CRF, and gross hematuria than those without crescents, which is consistent with our earlier study [8]. Group 3 developed the lowest rate of CRF as this group mostly presented with acute onset, rapid progression, and severe symptoms such as gross hematuria, oliguria, and hypertension. Therefore, the time between presentation of LN and biopsy/treatment was usually shorter than for other groups, and this group mostly received timely nephrologist consultation as well as early and intensive intervention.

Similar to findings from another report which showed that DPLN patients with more than 50% crescents had a more serious laboratory and pathological presentation [9], our study indicated that DPLN patients with more than 10% histological crescents had more severe hypo-proteinemia, hyperlipidemia, and renal insufficiency, heavier proteinuria and hematuria, and higher levels of tubular injury parameters. Immunologically, lower serological activity and a higher rate of positive LA and ANCA were observed in these patients. On pathologic evaluation, apart from the proportion of cellular crescents, fibrocellular and fibrous crescents, significantly higher scores of AI, CI, interstitial inflammation activity indexes, acute and chronic tubulointerstitial lesion activity indexes, as well as a higher rate of capillary necrosis, were identified in cDPLN patients than in those without crescents.

There is evidence supporting the notion that there are at least two mechanisms leading to glomerular damage in severe proliferative LN: a pauci-immune-mediated

process leading to the damage occurring in segmental lesions, and a peripheral capillary wall immune aggregate-mediated process in global lesions [21–28]. These reports have raised the possibility of a mechanism akin to pauci-immune necrotizing vasculitis for necrotizing and crescentic LN. Our results expand on these earlier observations in a large cohort of DPLN patients with extensive crescent formation with detailed clinical, laboratory, histology, and prognosis data. The percentage of capillary necrosis and positive ANCA correlated perfectly with the ratio of histological crescents. Besides, a lower ratio of hypocomplementemia, positive Sm, ACL, lower levels of ANA, ds-DNA, cryoglobulin, IgG, and serum CD20+ cells were observed in cDPLN patients. Moreover, less subendothelial ‘wire loop’ deposits, capillary microthrombi, and a lower intensity of peripheral capillary IgG, IgA, IgM, C3, and C1q deposition in cDPLN patients were observed. Though cell-mediated immunity plays a key role in crescent formation, with the increasing rate of crescent and uremia state, the humoral immunity response may be relatively suppressed, which could be proven by decreasing levels of complement, immunoglobulin, cryoglobulins, and CD20+ cells, thus resulting in less mature B cells and less production of autoantibodies, as well as less immune complex deposit in renal tissues. Our results, therefore, favor the interpretation that DPLN with crescents appears to be the result of two distinct pathogenetic mechanisms.

Glomerular crescents are a histopathologic marker of severe renal injury, characterized by disruption in the integrity of the glomerular capillary wall, leading to macrophage and T cell infiltration into the Bowman space, and further exacerbate the inflammatory process and glomerular injury [29]. We have previously demonstrated that monocytes (CD68+ cells) and T cells play a dominant role in the formation of crescents and contribute to the development of diffuse crescentic glomerulonephritis [1, 30]. T cells could initiate autoimmunity, antigen recognition, and macrophage recruitment and activation. These macrophages subsequently release proinflammatory cytokines which result in cell proliferation, recruitment of more macrophages, and upregulation of adhesion molecule expression [31, 32]. In this study, higher infiltrating numbers of CD4+, CD8+, and CD68+ cells were observed in renal tissues of crescentic glomerulonephritis compared with that in controls, and these may serve as useful markers for the active lesions in patients with crescentic DPLN.

It is generally assumed that a greater percentage of crescent formation in glomeruli will lead to the identifica-

tion of more severe clinicopathological features. Surprisingly, however, we found that DPLN patients with 10–25% crescents in some aspects had more severe features than those with $\geq 50\%$ crescents in glomeruli. Patients in this group had the longest SLE duration, highest age, and highest disease-onset age in our study. The prevalence of CRF, malignant hypertension, and TTP/HUS was markedly higher than in all other groups. Furthermore, they had the most severe glomerular sclerosis, acute tubulointerstitial lesions, vascular lesions, most prominent interstitial CD4+ infiltration, and the highest degree of microscopic hematuria. On one hand, this group of patients may not present with acute onset, rapid progression, and severe symptoms, and thus the diagnosis and treatment may be delayed. On the other hand, although both cellular and humoral immunity are suppressed in patients with renal insufficiency, we accordingly speculate that the degree of immune suppression may not be perfectly associated with the degree of renal damage. In addition, tubulointerstitial and vascular lesions were quite prominent in this group, which played a pivotal role in the development and prognosis of LN. In clinical work, much emphasis should be placed on this group of patients, and a specific mechanism remains to be further studied in the future.

Although there are no well-established guidelines for the treatment of crescentic glomerulonephritis in patients with LN, most authors, including the ACR/EULAR guidelines, recommend intensive immunosuppressive therapy on the therapeutic basis of proliferative LN [6, 33]. Our study demonstrated that the degree of histological crescents will have implications on treatment response and renal function deterioration in DPLN owing to severe clinical manifestations, serious pathological changes, and a higher AI and CI score. Therefore, we suggest that more aggressive treatment should be given to DPLN patients with histological crescents.

There were some limitations to this study. Firstly, this was a retrospective single-center study. Based on the patients’ financial conditions and different physicians’ clinical experiences, all patients were treated with a flexible strategy and without the exact unified medicines and duration. Secondly, there were difficulties in collecting and comparing previous medicines, treatment failures, and previous renal biopsy data before biopsy because many clinicopathological data were lost or incomplete. Thirdly, though we figured out that crescentic nephritis is most common in class IV LN, patients with class III, IV+III, and IV+V can also present with histological crescents under microscopy, but were excluded from this study.

Therefore, a future well-designed prospective multicenter study is required to evaluate the long-term prognosis of LN patients with various degrees of histological crescents.

Disclosure Statement

The authors have no conflict of interest to declare.

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