Prediction of Renal Outcomes in Patients With Crescentic Lupus Nephritis

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Abstract: *Background:* Few studies are currently available about the renal survival and risk factors of crescentic lupus nephritis (cLN). We retrospectively analyzed data from Chinese patients with cLN in our center to identify the prognostic factors. *Methods:* One hundred twenty-four cases of biopsy-proven LN with ≥50% crescents (cLN) were included in this study. Another 100 patients with LN without crescents were randomly enrolled as a control group. Their clinicopathological data and long-term outcome were compared. *Results:* There were 101 females and 23 males with an average age of 32.0 ± 13.5 years followed for a median period of 4 years. At biopsy, the mean SCr level was 2.4 ± 2.0 mg/dL, and the mean percentage of crescents was 64.4 ± 13.3%. The renal survival rates at years 1, 3 and 5 after biopsy of cLN group and the control group were 82.3% versus 97.8%, 78.4% versus 92.6% and 70.2% versus 84.9%, respectively. Multivariate Cox regression revealed initial SCr concentration as the only independent risk factor for end-stage renal disease (hazard ratio: 1.433, $P < 0.001$). Logistic regression showed that the risk of end-stage renal disease at 5 years after biopsy increased rapidly at SCr >1.4 mg/dL and reached 90% at SCr >5.5 mg/dL. *Conclusions:* Crescentic LN had worse treatment response and lower probability of renal survival than those without crescents. Initial SCr concentration may predict kidney failure in patients with crescentic disease.

Key Indexing Terms: Crescent; Lupus nephritis; Renal survival; Risk factors. **[Am J Med Sci 2015;349(4):298–305.]**

Lupus nephritis (LN) is the one of the most common secondary disease worldwide. Crescentic LN, usually defined as the presence of crescents in over 50% of the glomeruli, is one of the most severe forms of LN and can present as a rapidly progressive glomerulonephritis (RPGN) with bad outcome and requires rapid and effective treatment.[1] LN accounted for 49.3% to 51.6% of all patients with biopsy-proven rapidly progressive crescentic glomerulonephritis, and as the most common etiology of crescentic glomerulonephritis in Thailand and Saudi.[2,3] Also in China, it is the commonest phenotype of crescentic glomerulonephritis, which occurred in 3.48% of LN, 33.9% of crescentic glomerulonephritis and 54.6% of type II (immune complex) crescentic glomerulonephritis.[4,5] A recent report from northern China has developed a simple model based on serum creatinine concentration to predict the outcomes of crescentic IgA nephrology, which showed that the association between the probability of end-stage renal disease (ESRD) and the initial SCr followed an S-shaped curve. They also assessed for another 2 types of crescentic glomerulonephritis and found that the logistic curve for anti-glomerular basement membrane (GBM) disease also fitted a typical S shape, whereas antineutrophil cytoplasmic antibody (ANCA)–associated systemic vasculitis showed a nearly linear association.[6] Many other studies are available about the significance of crescents in the treatment response and renal outcome for Henoch-Schönlein purpura nephritis,[7] IgA nephropathy,[8,9] ANCA-associated vasculitis[10] and anti-GBM disease.[11,12] However, few studies are currently available about the renal survival and risk factors of crescentic LN except few studies with small samples.[3,13–15] This study is undertaken to clarify the clinicopathological features and prognostic factors of ESRD in patients with crescentic LN.

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SUBJECTS AND METHODS

Patients

All patients with biopsy-proven LN in Nanjing Jinling Hospital from January 2003 to January 2013 were reviewed. One hundred twenty-four cases of biopsy-proven LN with ≥50% crescentic lupus nephritis (cLN) were included in this retrospective study. Another 100 LN cases without crescents during the corresponding period were regarded as a control group. The inclusion criteria were (1) diagnosed as systemic lupus erythematosus defined by the 1997 revised American Rheumatism Association criteria[16]; (2) renal biopsy confirmed LN according to the 2003 International Society of Nephrology/Renal Pathology Society classification (ISN/RPS)[17]; (3) at least 10 glomeruli on the renal biopsy specimen and crescents affecting more than 50% of the glomeruli; (4) among the total 181 patients with crescentic LN, 124 followed for more than 1 year were included in the treatment response analysis, Kaplan-Meier analysis and cox regression; 84 cases followed up for at least 5 years or until they progressed to ESRD within 5 years were included in the logistic regression.

Clinical and Laboratory Data

The data included gender, age, initial clinical manifestations, blood pressure, 24-hour urinary protein excretion, microscopic hematuria, *N*-acetyl-β-D-glucosaminidase, retinol-binding protein, urinary C3, hemoglobin, serum creatinine, eGFR, albumin, ANA, anti-dsDNA, complement C3 and C4.

Renal Pathology

Crescentic LN was defined as ≥50% of glomeruli on light microscopy having crescents (the crescent takes up over half space in Bowman's capsule).[14,18] 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).[19] The extent of interstitial inflammation by each method was semiquantitatively scored without prior knowledge of the clinical outcomes from 0 to 3, which corresponded with 0%, <10%, 10% to 25%, 25% to 50% or 50% involvement of the tubulointerstitium, respectively.[20]

Treatment

Patients with crescentic LN initially received intravenous methylprednisolone pulse therapy (0.5 g, once daily, for 3 consecutive days), followed by oral prednisone at a dose of 0.6 to 0.8 $mg \cdot kg^{-1} \cdot d^{-1}$ for 4 to 8 weeks, which was then tapered by 5 mg each week to 10 mg/d. Mycophenolate mofetil (MMF) was given at a dose of 1 to 2 g/d for 6 months and was reduced or withdrawn if side effects occurred (64 patients). Intravenous cyclophosphamide (CTX) was given for 3 to 6 months as 0.5 to 0.75 g/m^2 body surface area in monthly pulses according to a National Institutes of Health (NIH) protocol[21] (46 patients). The dosage was modified if nadir white cell counts reached 2,500 cells or less at 7 to 10 days after the infusion. The dose of tacrolimus was 0.1 to 0.15 $mg \cdot kg^{-1} \cdot d^{-1}$ administered orally in 2 divided doses and was titrated to maintain 12 hours through levels at 6 to 8 ng/mL (26 patients).

Definitions

RPGN is defined as oliguria, 50% loss of renal function over 3 months and active urinary sediment including red blood cell casts or gross hematuria. Complete remission was defined as urinary protein excretion <0.4 g/d, normal urinary sediment and normal or stable renal function (within 10% of normal creatinine if previously abnormal renal function). Partial remission was defined as a urinary protein excretion within the range of 0.4 to 3 g/d with a stable or improved renal function.[22] 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 (1) proteinuric flare: persistent increase in proteinuria >1.0 g/d after CR or a doubling of proteinuria with values >2 g/d after achieving PR. (2) Nephritic flare: recurrence of active urinary sediment and/or an increase of ≥25% in serum creatinine. The end point of life table was defined as ESRD (a serum creatinine >6 mg/dL or the initiation of renal replacement therapy for at least 3 months or undergone renal transplantation).[23] Chronic kidney disease (CKD) was defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months or more, irrespective of cause. Normal renal function was defined as creatinine ≤1.24 mg/dL (110 μmol/L).

Statistical Analyses

All data were analyzed by using statistical software SPSS 19.0. All parameters were compared by the χ^2 test or Fisher's exact test for categorical data and the Student's *t* test or 1-way analysis of variance for continuous data. For the analysis of length of time from entry to ESRD (renal survival), product-limit life table distributions were compared with the Kaplan-Meier method. Cox hazard regression model was used to evaluate clinical, laboratory and histologic predictors of progression to ESRD. A *P* value <0.05 was considered significant. The cumulative probability of ESRD at 5 years after renal biopsy was calculated using logistic regression. The function to calculate the probability of this event was as follows:

$$P = \frac{e^{-a+b\times}}{1+e^{-a+b\times}}$$

where *P* is the probability of ESRD at 5 years after renal biopsy, and x is the baseline SCr concentration (mg/dL) that was identified as an independent risk factor for ESRD on multivariate Cox analysis. Using this equation, we calculated the values of SCr at which the probability of ESRD was 20% and 90%. The high-risk threshold of the initial SCr concentration was the value at which the cumulative probability of ESRD at 5 years reached 90%. The low-risk threshold of initial SCr concentration was the value at which the cumulative probability of ESRD at 5 years was less than 20%.

RESULTS

Prevalence

During January 2003 and January 2013 in Nanjing Jinling Hospital, a total of 3,044 patients were diagnosed as LN, 55.2% of these patients (1,679) had different degree of crescents in glomeruli, including 181 patients with more than 50% crescents. The distribution of various types of LN with crescents ≥50% in glomeruli mainly included ISN classes IV (60.8%), III (4.4%), V + III (3.9%) and V + IV (30.9%), as depicted in (Table 1).

Baseline Clinical, Laboratory and Pathological Characteristics

Among the 124 cLN patients, 101 (81.5%) were females and 23 (17.5%) were males, with an average age of 32.0 ± 13.5 years old. In cLN patients, there was a significantly shorter LN duration ($P = 0.003$), higher proportion of RPGN ($P < 0.001$), hypertension ($P = 0.012$), gross hematuria ($P = 0.043$), severe hypoproteinemia ($P < 0.001$), heavier proteinuria ($P < 0.001$) and microscopic hematuria ($P < 0.001$), severe tubular injury parameters ($P < 0.001$), lower titers of ANA ($P = 0.001$) and higher rate of positive ANCA ($P = 0.021$). ANCA was detected in 103 cLN patients, among whom 9 patients were ANCA positive, with an average titer of 109.7, mainly had ANCA specificity for myeloperoxidase (MPO) (8/9). On pathological examination, the average percentage of crescents, cellular, fibrocellular and fibrous crescents were 64.4% ± 13.3%, 22.2% ± 25.1%, 35.8% ± 25.1% and 6.4% ± 14.8%, respectively, in cLN patients. Lower intensity of capillary deposition of IgA ($P < 0.001$), IgG ($P < 0.001$), IgM ($P < 0.001$), C3 ($P = 0.001$), C1q ($P = 0.011$), higher number of infiltrating $CD4^+$ ($P < 0.001$), CD8+ ($P < 0.001$) and $CD68^+$ ($P < 0.001$) T cells in renal interstitium were observed in crescentic group than those in the control group. Besides, 9 patients (7.3%) were diagnosed with TMA on pathology (Table 2).

Treatment Response and Outcome

There was no significant difference in treatment regimen between the 2 groups, except that much higher rate of crescentic LN patients received renal replacement therapy (7 with plasma exchange, 6 with immune adsorption, 43 with CRRT, 12 with hemodialysis) and intravenous methylprednisolone pulse therapy than those without crescents.

Compared with controls, cLN patients had significantly lower rate of clinical remission (CR + PR) (58.8% versus 95.5%, $P < 0.001$) with longer duration (13.2 ± 7.9 versus

TABLE 1. The distribution of pathological types of lupus nephritis patients with and without crescentic nephritis

	Crescent ≥ 50%, n	Crescent = 0%, n
Number of biopsies	181	100
Class II	0	0
Class III	8	0
Class IV	110	83
Class V/V + III/V + IV	0/7/56	0/0/17