AJKD
Original Investigation

Etiology and Outcome of Crescentic Glomerulonephritis From a Single Center in China: A 10-Year Review

Shasha Chen, PhD, Zheng Tang, PhD, Haiyan Xiang, PhD, Xiaowei Li, PhD, Hao Chen, PhD, Haitao Zhang, PhD, Weixin Hu, PhD, Caihong Zeng, PhD, and Zhihong Liu, MD

Background: The disease spectrum of crescentic glomerulonephritis (GN) has been described in only a few previous studies, and detailed epidemiologic data from China are unavailable to date.

Study Design: Case series.

Setting & Participants: 528 patients with biopsy-proven crescentic GN in 2003 to 2013 from a single center.

Predictor: Crescentic GN was classified into 3 types according to immunofluorescence findings: type I was defined as linear deposition of immunoglobulins along the glomerular basement membrane; type II, as glomerular deposition of immune complex; and type III, as pauci-immune deposition.

Outcomes: Demographic, clinical, and serologic characteristics.

Results: Of 528 cases identified, 208 (39.4%) were men, with a mean age of 37.6 ± 16.4 (SD) years at kidney biopsy. 61 (11.6%) patients had type I crescentic GN, 331 (62.7%) had type II (lupus nephritis, 34.3%; immunoglobulin A [IgA] nephropathy, 17.4%), and 136 (25.8%) had type III. Proportions of patients with acute kidney injury (AKI), acute kidney diseases and disorders without AKI, and chronic kidney disease were 86.9%, 0%, and 13.1% for type I; 42.0%, 19.6%, and 38.4% for type II; and 84.6%, 2.9%, and 12.5% for type III crescentic GN, respectively. Serum antineutrophil cytoplasmic antibodies were detected in 11 (18.0%) patients with type I, 15 (4.5%) with type II, and 117 (86.0%) with type III. Anti–glomerular basement membrane antibodies were found in 60 (98.4%) patients with type I, 3 (0.9%) with type II, and 5 (3.7%) with type III. 5-year cumulative renal survival rates for patients with types I, II, and III were 17.6%, 70.1%, and 44.3%, respectively.

Limitations: Retrospective study, single-center experience.

Conclusions: Lupus nephritis may be the most common type of crescentic GN in China, followed by pauci-immune crescentic GN and IgA nephropathy. Almost half the patients presented with AKI, whereas 28.8% of cases showed chronic kidney disease. Clinical manifestations and outcomes varied according to crescentic GN type. The distinction between subtypes based on immunofluorescence and serologic findings has important implications for therapy and outcome.

Am J Kidney Dis. 67(3):376-383. © *2016 by the National Kidney Foundation, Inc.*

INDEX WORDS: Crescentic glomerulonephritis; crescents; type; etiology; antineutrophil cytoplasmic antibody (ANCA); anti-glomerular basement membrane (anti-GBM) antibody; linear deposits; immune complex; granular deposits; pauci-immune; kidney biopsy; renal pathology; renal histology; clinical follow-up; kidney survival; rapidly progressive; kidney disease; China.

Editorial, p. 355

A serious condition with rapidly progressive deterioration in kidney function,[1] crescentic glomerulonephritis (GN) is present in approximately 4% to 10% of total kidney biopsies.[2,3] Up-to-date epidemiologic data regarding kidney disease in adults are available from large national kidney biopsy registries, including those from Saudi Arabia,[4] the United States,[5] India,[6] Japan,[1] and Spain.[7] In 2003, we described the clinical features and renal histology of 172 consecutive patients with crescentic GN identified from 9,828 kidney biopsies performed at our institution from 1989 to 2001.[8] We reported that immune-complex crescentic GN was the most common type of crescentic GN in China. Since this study, we have noticed an increasing incidence of crescentic GN associated with cases of kidney biopsy. The distinction between subtypes based on immunofluorescence and serologic findings has important implications for therapy and outcome. However, to our knowledge detailed epidemiologic and clinicopathologic data from China during the past decade have not yet been published. The aim of this study was to investigate the etiology, clinicopathologic features, and outcome of histologically diagnosed crescentic GN in a large representative center from China during a 10-year period.

From the National Clinical Center of Kidney Disease, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China.

Received July 26, 2014. Accepted in revised form July 30, 2015. Originally published online September 18, 2015.

Address correspondence to Zheng Tang, PhD, 305 East Zhong Shan Road, Research Institute of Nephrology, Nanjing Jinling Hospital, 210002 Nanjing, China. E-mail: tang_dr@163.com

© 2016 by the National Kidney Foundation, Inc.

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2015.07.034

METHODS

Study Population

A total of 528 patients with biopsy-proven crescentic GN diagnosed in January 2003 to January 2013 in the renal division of Nanjing Jinling Hospital (the largest referral renal center in China) were included in this retrospective study. Patients with fewer than 10 nonsclerotic glomeruli in sampled renal tissue were excluded. Clinicopathologic and follow-up data were obtained from the electronic medical record system. This work was approved by the Ethics Committee of Jinling Hospital, and we received informed consent from all patients.

Pathologic Studies

All biopsy specimens were examined by light microscopy, and immunofluorescence was reviewed by 2 nephropathologists (CZ and HC) blinded to patient outcome. Lupus nephritis was diagnosed and classified based on the International Society of Nephrology/Renal Pathology Society classification.[9] Tubulointerstitial lesions, including tubular atrophy and interstitial fibrosis, were semiquantitatively graded as none (0), mild (1), moderate (2), or severe (3).[10] The extent of interstitial inflammation by each method was semiquantitatively scored (without prior knowledge of clinical outcomes) from 0 to 3, which corresponded to 0%, <20%, 20% to 50%, or >50% involvement of the tubulointerstitium, respectively.[11]

Definitions

Crescentic GN was defined as more than half the total glomeruli affected by large crescents, as assessed by light microscopy.[12,13] Immunofluorescence microscopy was used to determine the type of crescentic GN. Type I included cases of anti–glomerular basement membrane (anti-GBM) disease characterized by linear deposits of antibodies along the GBM. Type II was a heterogeneous group of primary or secondary glomerular diseases with granular deposits of immunoglobulins and complement fractions on the glomerular tuft. Type III was defined as the absence of immune deposits in kidney tissue.[5,14,15]

Clinical presentations included acute kidney injury (AKI), acute kidney diseases and disorders (AKD) without AKI, and chronic kidney disease (CKD). AKI was defined as an increase in creatinine level by 0.3 mg/dL (26.5 mmol/L) within 48 hours or a percentage increase in serum creatinine ≥ 50% (1.5-fold from baseline) within 7 days or urine volume ≤ 0.5 mL/kg/h for 6 hours. CKD was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or markers of kidney damage for more than 3 months (including nephrotic syndrome, asymptomatic urinary abnormalities, or nephritic syndrome). AKD without AKI was defined as eGFR < 60 mL/min/1.73 m^2 for less than 3 months or a decrease in eGFR ≥ 35% or an increase in creatinine level > 50% or markers of kidney damage for less than 3 months.[16]

Decreased eGFR was defined as eGFR < 60 mL/min/1.73 m^2. Nephrotic syndrome was defined as proteinuria with protein excretion > 3.5 g/d and serum albumin level < 35 g/dL, with eGFR ≥ 60 mL/min/1.73 m^2. Asymptomatic urinary abnormalities were defined as proteinuria with protein excretion < 3.5 g/d and/or hematuria with more than 3 red blood cells per high-power field, without edema, hypertension, or decreased eGFR. Nephritic syndrome was defined as hematuria, proteinuria (protein excretion < 3.5 g/d), hypertension, and edema, with eGFR ≥ 60 mL/min/1.73 m^2. The life-table end point was defined as chronic kidney failure (ie, eGFR < 15 mL/min/1.73 m^2, initiation of dialysis therapy that continued for >3 months, or transplantation).[17] Serum creatinine was measured by an enzymatic method and recalibrated to standardized creatinine measurements. eGFR was calculated with the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.[18] eGFR categories included ≥90, 60 to 89, 30 to 59, 15 to 29, and <15 mL/min/1.73 m^2.[19]

Statistical Analysis

All data were analyzed using the statistical software SPSS, version 19.0 (IBM). Quantitative data were expressed as mean ± standard deviation or median with interquartile range. All parameters were compared by χ^2 test or Fisher test for categorical data and *t* test, 1-way analysis of variance, or Kruskal-Wallis test for continuous data. Kaplan-Meier curves and log-rank test were used to analyze and compare time from entry to chronic kidney failure (renal survival). $P < 0.05$ was considered significant.

RESULTS

Etiology, Demographics, and Kidney Manifestations

A total of 528 patients with biopsy-proven crescentic GN diagnosed January 2003 to January 2013 were recruited for this retrospective study, accounting for 1.56% (528 of 33,747) of the total nontransplant kidney biopsies in this period. The disease composition of crescentic GN was as follows: 181 (34.3%) had lupus nephritis, 136 (25.8%) had pauci-immune nephritis, 92 (17.4%) had immunoglobulin A (IgA) nephropathy, 61 (11.6%) had anti-GBM kidney disease, 39 (7.4%) had Henoch-Schönlein purpura nephritis, 11 (2.1%) had membranoproliferative glomerulonephritis, 5 (0.9%) had idiopathic crescentic glomerulonephritis, 2 (0.4%) had hepatitis B virus–associated nephritis, and 1 (0.2%) had focal segmental glomerulosclerosis (Table S1, available as online supplementary material).

Of 528 patients with crescentic GN, 208 (39.4%) were men and 320 (60.6%) were women, with an average age of 37.6 ± 16.4 (standard deviation) years at biopsy (Table 1). The median interval between onset of the disease and kidney biopsy was 2 (range, 1-6) months. Female predominance was observed in type II crescentic GN, whereas types I and III were almost equally distributed between sexes. There were clear incidence peaks for crescentic GN: in those aged 14 to 24 and 45 to 54 years in the type I group, 14 to 44 years in the type II group, and 45 years or older in the type III group. Among all 528 cases, clinical presentations of crescentic GN included AKI in 58.1%, AKD without AKI in 13.1%, and CKD in 28.8%; 35.4% needed dialysis at the time of kidney biopsy; and 71.0% had decreased eGFRs at presentation (mean baseline eGFR, 40.6 ± 38.6 mL/min/1.73 m^2). In patients with type III, and especially type I with acute onset, crescentic GN mostly presented with AKI. Those with type I had higher rates of gross hematuria and oliguria and higher serum creatinine levels. Those with type II had a younger age, longer disease duration, greater female predominance, lower serum creatinine levels, higher amount of proteinuria, and more severe hypoproteinemia; they also had highly variable clinical presentations ranging from

Table 1. Baseline Demographic and Kidney Manifestations of Patients With Crescentic GN

	Total (N = 528)	Type I (n = 61)	Type II (n = 331)	Type III (n = 136)	P
Age, y	37.6 ± 16.4	40.6 ± 17.0	32.4 ± 13.8	48.8 ± 16.1	<0.001[a-c]
Male sex	208 (39.4)	33 (54)	111 (33.5)	64 (47.1)	0.001[a,c]
Duration of disease, mo	2 [1.0-6.0]	1 [0.6-2.0]	3 [1.0-12.0]	1 [1.0-2.0]	<0.001[a,c]
Albumin, g/L	29.3 ± 6.2	31.9 ± 4.9	27.6 ± 6.3	32.3 ± 4.9	<0.001[a,c]
Proteinuria, g/d	3.2 [1.6-5.4]	1.9 [1.0-4.6]	4.0 [2.4-6.5]	1.8 [1.1-3.3]	<0.001[a-c]
Urine RBC count, $\times 10^4$/mL	420 [125-1,250]	1,200 [616-1,913]	345 [80-1,225]	426.5 [175.0-1,150.0]	<0.001[a,b]
Scr, μmol/L	324 ± 267	611 ± 282	223 ± 204	440 ± 255	<0.001[a,c]
eGFR, mL/min/1.73 m^2	40.6 ± 38.6	12.6 ± 13.2	54.5 ± 40.7	19.5 ± 20.0	<0.001[a-c]
Hypertension	231 (43.8)	33 (54)	142 (42.9)	56 (41.2)	0.2
Gross hematuria	221 (42.1)	48 (79)	123 (37.2)	50 (37.6)	<0.001[a,b]
Oliguria	104 (19.7)	37 (61)	31 (9.4)	36 (26.5)	<0.001[a-c]
AKI	307 (58.1)	53 (87)	139 (42.0)	115 (84.6)	
AKD without AKI	69 (13.1)	0 (0)	65 (19.6)	4 (2.9)	
CKD	152 (28.8)	8 (13)	127 (38.4)	17 (12.5)	

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range].

Abbreviations: AKD, acute kidney diseases and disorders; AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; RBC, red blood cell; Scr, serum creatinine.

[a]$P < 0.05$ between types I and II.

[b]$P < 0.05$ between types I and III.

[c]$P < 0.05$ between types II and III.

AKI to AKD without AKI to CKD. Those with type III had the lowest levels of proteinuria and compared with type II, had lower eGFRs.

Laboratory Features

Patients with type I crescentic GN had more severe anemia and kidney tubular injury parameters (including *N*-acetyl-β-D-glucosaminidase [NAG], retinol binding protein, and complement 3 [C3] enzyme) than the other groups (Table 2). Patients with type II crescentic GN presented with higher hemoglobin levels and more severe hypocomplementemia. Those with type III had better tubular function and more frequently had detectable antineutrophil cytoplasmic antibodies (ANCAs) than those with type II crescentic GN. ANCA was detected in 11 (18.0%) patients with type I, 15 (4.5%) with type II, and 117 (86.0%) with type III crescentic GN ($P < 0.001$). Anti-GBM antibodies were detectable in 60 (98.4%) patients with type I, 3 (0.9%) with type II, and 5 (3.7%) with type III crescentic GN ($P < 0.001$).

We divided type I crescentic GN into 2 subgroups according to ANCA test results, as shown in Table S2. ANCA-positive patients more frequently had gross

Table 2. Laboratory and Serologic Data By Type of Crescentic GN

	Total (N = 528)	Type I (n = 61)	Type II (n = 331)	Type III (n = 136)	P
Hemoglobin, g/dL	9.3 ± 2.3	8.2 ± 2.0	9.8 ± 2.4	8.5 ± 1.7	<0.001[a-c]
NAG, U/g[d]	70.6 ± 45.3	75.4 ± 43.9	73.7 ± 46.5	60.9 ± 41.4	0.02[c]
RBP, mg/L	12.6 ± 15.5	23.6 ± 15.2	13.3 ± 12.9	10.7 ± 15.8	<0.001[a,c]
Urinary C3, mg/L	12.1 ± 11.9	18.5 ± 12.1	12.1 ± 11.9	9.9 ± 10.8	<0.001[a,b]
C3, g/L	0.77 [0.53-0.99]	0.89 [0.79-1.09]	0.62 [0.44-0.93]	0.87 [0.72-1.02]	<0.001[a,c]
C4, g/L	0.19 [0.12-0.25]	0.23 [0.17-0.28]	0.16 [0.10-0.21]	0.24 [0.18-0.28]	<0.001[a,c]
ANCA positive	143 (27.1)	11 (18)	15 (4.5)	117 (86.0)	<0.001[a-c]
MPO-ANCA positive	124 (23.5)	11 (18)	13 (3.9)	100 (73.5)	<0.001
PR3-ANCA positive	24 (4.5)	1 (2)	5 (1.5)	18 (13.2)	<0.001
Anti-GBM positive	68 (12.9)	60 (98)	3 (0.9)	5 (3.7)	<0.001[a-c]

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range].

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; C3, complement 3; C4, complement 4; GBM, glomerular basement membrane; GN, glomerulonephritis; MPO, myeloperoxidase; NAG, *N*-acetyl-β-D-glucosaminidase; PR3, proteinase 3; RBP, retinol binding protein.

[a]$P < 0.05$ between types I and II.

[b]$P < 0.05$ between types I and III.

[c]$P < 0.05$ between types II and III.

[d]Denominator of unit refers to grams of creatinine.

hematuria and a lower proportion of glomeruli with crescents and capillary necrosis than ANCA-negative patients. We also subdivided type III crescentic GN by ANCA test results, as shown in Table S3. ANCA-positive patients were older and had a lower amount of proteinuria, higher proportion of glomerular sclerosis, more capillary necrosis, and lower percentage of patients with CKD stages 1 to 2 than ANCA-negative patients.

Extrarenal Manifestations

Main extrarenal manifestations varied substantially among the 3 types of crescentic GN (Table S4). Patients with type I had higher frequencies of hematologic disorders (62.3%), fever (50.8%), gastrointestinal symptoms (36.1%), hemoptysis (34.4%) and serositis (34.4%). Those with type II had higher frequencies of skin rash (38.7%) and arthralgia (34.4%). Patients with type III crescentic GN had higher frequencies of pneumonia (35.3%) and nasal symptoms (28.7%).

Pathologic Features

As shown in Table S5, mean overall percentages of glomeruli with crescents, cellular crescents, fibrocellular crescents, and fibrotic crescents among the 528 patients with crescentic GN were 67.6% ± 15.8%, 20.9% ± 23.9%, 31.4% ± 24.8%, and 11.9% ± 22.4%, respectively. Among the 3 crescentic GN types, patients with type I had higher percentages of glomeruli with crescents, global sclerosis, severe tubular atrophy/necrosis, and interstitial fibrosis/inflammation than the other groups. Patients with type II crescentic GN had lower percentages of global sclerosis and fibrotic crescents and less tubular atrophy/necrosis and interstitial fibrosis/inflammation and capillary necrosis. Type III patients had more capillary necrosis and a greater frequency of severe interstitial inflammation.

Outcome and Renal Survival

By the end of follow-up, the overall distribution of patients by CKD stage (using the CKD-EPI creatinine equation for staging) was as follows: stage 1, 22.0%; stage 2, 14.0%; stage 3, 15.5%; stage 4, 13.4%; and stage 5, 35.0% (Table 3). Patients with type I crescentic GN experienced the most severe declines in kidney function because this group had the highest proportion of individuals with CKD stages 3 to 5 at last follow-up. Type II had the highest proportion of patients with CKD stages 1 to 2 at last follow-up.

As shown in Fig 1A, patients with type I crescentic GN had the worst renal survival, whereas type II patients had the best renal prognosis ($P < 0.001$). The 5-year cumulative renal survival rates of types I, II, and III were 17.6%, 70.1%, and 44.3%, respectively. Fig 1B depicts the renal survival of patients categorized by type of crescentic GN and subdivided (for types I and III) according to serologic criteria. The 5-year cumulative renal survival rates of type I crescentic GN with and without ANCAs were 13.3% and 20.7%; of type III crescentic GN with and without ANCAs, 44.4% and 51.9%.

Table 3. Outcome and Renal Survival of Patients With Crescentic GN

	Total (n = 528)	Type I (n = 61)	Type II (n = 331)	Type III (n = 136)	P
Follow-up, mo	28.0 ± 32.9	11.6 ± 12.1	32.4 ± 13.8	25.9 ± 33.8	<0.001[a,b]
Treatment					
RRT	216 (40.9)	57 (93)	79 (23.9)	80 (58.8)	<0.001[a-c]
IV MP pulse therapy	432 (81.8)	50 (82)	262 (79.2)	120 (88.2)	0.07[c]
Status at last follow-up					
Scr, μmol/L	319 ± 308	588 ± 271	246 ± 192	375 ± 284	<0.001[a-c]
eGFR, mL/min/1.73 m^2	48.3 ± 42.8	19.8 ± 2.5	44.0 ± 2.4	30.9 ± 2.7	<0.001[a-c]
CKD stage					
1	116 (22.0)	2 (3)	104 (31.4)	10 (7.4)	
2	74 (14.0)	0 (0)	62 (18.7)	12 (8.8)	
3	82 (15.5)	4 (7)	52 (15.7)	26 (19.1)	
4	71 (13.4)	8 (13)	37 (11.2)	26 (19.1)	
5	185 (35.0)	47 (77)	76 (23.0)	62 (45.6)	
5-y renal survival rate	55.0	17.6	70.1	44.3	<0.001[a]

Note: Values for categorical variables are given as number (percentage) or percentage; values for continuous variables, as mean ± standard deviation.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; IV, intravenous; MP, methylprednisolone; RRT, renal replacement therapy; Scr, serum creatinine.

[a] $P < 0.05$ between types I and II.

[b] $P < 0.05$ between types I and III.

[c] $P < 0.05$ between types II and III.

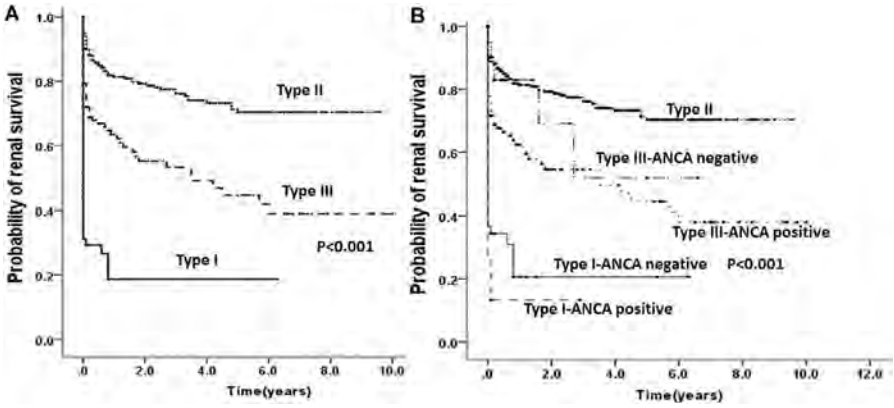

Figure 1. Renal survival in patients by crescentic glomerulonephritis type based on (A) histopathologic criteria and (B) including subdivisions of types I and III based on serologic criteria. Abbreviation: ANCA, antineutrophil cytoplasmic antibody.

DISCUSSION

Crescentic GN remains one of the leading histologic diagnoses associated with acute or rapidly progressive kidney failure.[6] There is a paucity of reports from China[8,20] and few series from other parts of the world. We previously analyzed data from 172 Chinese patients with crescentic GN in our center to characterize the clinical spectrum of crescentic GN during 1989 to 2001[8]; however, the sample was small and clinicopathologic information was limited. This report provides more extensive and detailed information about the occurrence and outcome of biopsy-diagnosed crescentic GN in 33,747 nontransplant-related biopsies performed during the past 10 years in the biggest renal center in China.

Crescents can occur with most forms of primary GN and also are associated with various systemic diseases. Among 33,747 kidney biopsies examined, the most frequent primary glomerular disease was IgA nephritis and the most prevalent secondary glomerular disease was lupus nephritis. Of note, in the present study, we also observed a limited number of instances of crescents associated with unusual disease entities, such as light-chain kidney disease, Alport syndrome, membranous nephropathy, focal segmental glomerulosclerosis, diabetic nephritis, and minimal change disease. These biopsy specimens had various percentages of crescents, usually with <50% of glomeruli having crescents, thus highlighting the need for considering these diseases as a cause of GN with crescents with decreased eGFR and the importance of performing an early kidney biopsy for accurate diagnosis and appropriate therapeutic decisions.

The spectrum of crescentic GN varied substantially among groups stratified by age and sex. Similar to previous reports,[4,20] patients with anti-GBM disease (type I crescentic GN) were mainly middle-aged men with worse prognoses, and most had oliguria or hemoptysis and extensive glomerular crescent formation pathologically. Patients with immune complex–mediated crescentic GN (type II) were mainly young or middle-aged women and many had nephrotic syndrome, but nevertheless they showed good response to intensive immunosuppressive therapy. Patients with pauci-immune crescentic GN (type III) were mainly middle-aged or elderly with multisystem involvement and had a relatively good response to intensive immunosuppressive therapy.

Almost half the patients in our cohort had AKI as their clinical presentation, but it was remarkable that clinical presentations also included AKD in 13.1% and CKD in 28.8%, which were most commonly seen in patients with type II crescentic GN. Therefore, timely kidney biopsy should be emphasized for patients with decreased eGFRs, asymptomatic urinary abnormalities, and nephrotic syndrome without kidney atrophy in a kidney ultrasound to facilitate early diagnosis and proper treatment.

In pathologic findings, mean proportions of glomeruli showing crescents were 80.6% in anti-GBM disease, 63.1% in immune complex–mediated GN, and 73.2% in pauci-immune GN; crescents involving >80% glomeruli were seen in 55.7%, 14.5%, and 39.0% of the 3 types, respectively. Proportions of cellular crescents, segmental sclerosis, and fibrocellular crescents were similar among the 3 groups.

The etiology and clinicopathologic and outcome data for crescentic GN vary considerably among different countries. In Table 4, our findings are compared with reports of crescentic GN from Saudi Arabia,[4] China,[8,20] the United States,[5] India,[6] Japan,[1] and Spain.[7] The most striking differences can be seen in the etiology, renal loss, and risk factors for end-stage renal disease. In our group, the most common pathologic type of crescentic GN was lupus nephritis, followed by pauci-immune crescentic GN. This is similar to results from Saudi Arabia,[4] but different from those of some other regions, including Spain,[7] the United States,[5] Northern China,[20] India,[6] and Japan,[1]

Table 4. Comparison of the Current Study's Findings With 7 Other Reports on Crescentic GN

	Oudah[4]	Lin[20]	Jennette[5]	Gupta[6]	Koyama[1]	Lopez-Gomez[7]	Tang[8]	Current study
No.	72	106	632	46	1,772 RPGN	860 ARF	172	528
Years	2001-2009	2000-2007		2008-2010	1989-2007	1994-2006	1985-2001	2003-2013
Country	Saudi Arabia	China	United States	India	Japan	Spain	China	China
% of biopsies with crescentic GN	38%	2.81%		3%		34.7%	1.75%	1.56%
Crescentic GN type								
Anti-GBM	0%	16.0%	15%	0%	6.1%	12.5%	8.7%	11.6%
Immune complex	68%	40.6%	24%	28%	2%	20.2%	68.6%	62.7%
LN	49%	14.6%					34.3%	34.3%
Pauci-immune	26%	43.4%	60%	72%	64%	67.2%	22.7%	25.8%
Mean age, y	35.6	45.2	47	27.6	57.5-64.7[a]	63	33.5	37.6
Sex, M:F	30:42	57:5	308:319	22:24	839:933	1.5	68:104	208:320
Hypertension		61.3%		48%		53.1%	61.6%	43.8%
Baseline Scr, μmol/L	247.5	—[b]	238.7	583.4	362.4	450.8	362.4	335.9
Proteinuria, g/d	8.8	4.2	7.0	2.53	2.2	1.5		1.9
ANCA+		38.7%					9.9%	27.1%
Anti-GBM+		17.9%						12.9%
Scr at last f/u, μmol/L	112.2							318.2
Dialysis-dependent at last f/u	34%			52%				33.9%
Proportion of glomeruli with crescents	37.6%	Cellular 36.2%; fibrous 14.5%		75.8%				67.7%
Sclerotic glomeruli	25.2%							12.7%
ESRD risk factors	Sclerosed glomeruli, ATN, Bowman membrane thickening, vasculopathy			Arteriolar fibrinoid necrosis	Scr, age, lung involvement, serum CRP			Oliguria, Scr, anti-GBM+, sclerosed glomeruli, crescents, interstitial inflammation

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; ARF, acute renal failure; ATN, acute tubular necrosis; CRP, C-reactive protein; ESRD, end-stage renal disease; f/u, follow-up; GBM, glomerular basement membrane; GN, glomerulonephritis; LN, lupus nephritis; RPGN, rapidly progressive glomerulonephritis; Scr, serum creatinine.

[a]Age range.

[b]Scr not given; estimated glomerular filtration rate was 14.5 mL/min/1.73 m^2.

in which pauci-immune crescentic GN was found to be the predominant type. The report from Oudah et al[4] had the highest percentage of crescentic GN in total biopsies and the highest serum creatinine concentrations; these results are understandable given that these authors defined crescentic GN as "nephritis with at least 20% of glomeruli having crescents," whereas all other studies defined crescentic GN as having ≥50% of glomeruli with crescents.[6,8,20] The initial average serum creatinine concentration in our group was lower than that in Spain[7] and India,[6] but similar to that in the United States[5] and Japan.[1] The average amount of proteinuria was lower than that in Saudi Arabia[4] and the United States.[5] Percentages of our cases that were positive for ANCAs and anti-GBM antibodies were similar to the report from Northern China.[20] Similar percentages of patients requiring dialysis during follow-up were found in our group and the report of Oudah et al.[4]

Anti-GBM antibodies and ANCAs appearing together in crescentic GN is a common phenomenon, occurring in approximately one-fourth to one-third of patients with anti-GBM antibodies and to a much smaller degree in patients with ANCAs.[5,21-24] In this large cohort, we describe 15 (2.8%) patients with both ANCAs and anti-GBM antibodies ("double positive"); the prevalence of positive anti-GBM antibodies in patients with pauci-immune crescentic GN was 0.37% (5 of 136) and the prevalence of positive ANCAs in anti-GBM disease was 18% (11 of 61). We observed that anti-GBM antibodies were more commonly accompanied by myeloperoxidase-specific ANCAs than by proteinase 3–specific ANCAs. Consistent with previous studies, the current study provides further evidence to support the phenomena that double-positive patients are older than those with only anti-GBM antibodies,[21,23,25-27] have more severe renal damage,[28] and have myeloperoxidase-ANCA predominance.[26,29] However, our findings differ from some earlier reports of male predominance in double-positive patients.[23,25-27] The multisystem involvement we observed in the double-positive group is similar to findings in patients in the pauci-immune crescentic GN group, whereas renal manifestations clinically and histologically resemble those in patients with anti-GBM antibodies, as has been previously reported.[28,30] Moreover, the prognosis of double-positive patients in our study was remarkably worse than that for patients with anti-GBM disease and pauci-immune crescentic GN; none of these patients recovered kidney function despite immunosuppression therapy and plasma exchange. This finding is consistent with recent studies,[21,27,28] but discrepant with earlier reports.[25,26,31]

We found a significant difference between ANCA-negative vasculitis and ANCA-positive vasculitis. Compared with the 113 patients with ANCA-positive pauci-immune crescentic GN, the 18 patients with undetectable ANCAs were younger at disease onset and had fewer constitutional symptoms, much less extrarenal involvement (eg, lung, ear, nose, joint, and nervous system), lower serum creatinine levels, lower dependency on dialysis, higher urinary protein levels, higher nephrotic syndrome prevalence, a significantly higher percentage of normal glomeruli, and less capillary necrosis. In our study, patients with negative ANCA test results had better kidney disease outcomes, which is contrary to the report by Chen et al[32] from Northern China.

In conclusion, lupus nephritis may be the most common type of crescentic GN in China, and anti-GBM disease and pauci-immune crescentic GN are not rare in China. Clinical manifestations and outcomes vary by crescentic GN type. The distinction between subtypes based on immunofluorescence and serologic findings has important implications for therapy and outcome.

ACKNOWLEDGEMENTS

Support: National Key Technology R&D Program (2011BAI10B04), Jiangsu Province basic research project of Natural Science Foundation (BK20131327).

Financial Disclosure: The authors declare that they have no other relevant financial interests.

Contributions: Research idea and study design: SC, ZT; data acquisition: SC, HX, XL; data analysis and interpretation: SC, HC; statistical analysis: SC; supervision or mentorship: HZ, WH, CZ, ZL. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. ZT takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

SUPPLEMENTARY MATERIAL

Table S1: Etiology of crescentic glomerulonephritis.

Table S2: Clinicopathologic characteristics and patient outcome, type I, with and without ANCA.

Table S3: Clinicopathologic characteristics and patient outcome, type III, with and without ANCA.

Table S4: Extrarenal manifestations by crescentic GN type.

Table S5: Pathologic features by crescentic GN type.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2015.07.034) is available at www.ajkd.org

REFERENCES

1. Koyama A, Yamagata K, Makino H, et al. A nationwide survey of rapidly progressive glomerulonephritis in Japan: etiology, prognosis and treatment diversity. *Clin Exp Nephrol*. 2009;13:633-650.

2. Pettersson E, Sundelin B, Heigl Z. Incidence and outcome of pauci-immune necrotizing and crescentic glomerulonephritis in adults. *Clin Nephrol*. 1995;43:141-149.

3. Panichi V, Pasquariello A, Innocenti M, et al. The Pisa experience of renal biopsies, 1977-2005. *J Nephrol*. 2007;20:329-335.

4. Oudah N, Al Duhailib Z, Alsaad K, et al. Glomerulonephritis with crescents among adult Saudi patients outcome and its predictors. *Clin Exp Med*. 2012;12:121-125.

5. Jennette JC. Rapidly progressive crescentic glomerulonephritis. *Kidney Int*. 2003;63:1164-1177.

6. Gupta R, Singh L, Sharma A, Bagga A, Agarwal SK, Dinda AK. Crescentic glomerulonephritis: a clinical and histomorphological analysis of 46 cases. *Indian J Pathol Microbiol*. 2011;54:497-500.

7. Lopez-Gomez JM, Rivera F; Spanish Registry of Glomerulonephritis. Renal biopsy findings in acute renal failure in the cohort of patients in the Spanish Registry of Glomerulonephritis. *Clin J Am Soc Nephrol*. 2008;3:674-681.

8. Tang Z, Wu Y, Wang Q, et al. Clinical spectrum of diffuse crescentic glomerulonephritis in Chinese patients. *Chin Med J*. 2003;116:1737-1740.

9. Weening JJ, D'Agati DV, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int*. 2004;65:521-530.

10. Solez K, Axelsen R, Benediktsson H, et al. International standardization of criteria for the histologic diagnosis of renal allograft rejection: the Banff working classification of kidney transplant pathology. *Kidney Int*. 1993;44: 411-411.

11. Hsieh C, Chang A, Brandt D, Guttikonda R, Utset TO, Clark MR. Predicting outcomes of lupus nephritis with tubulointerstitial inflammation and scarring. *Arthritis Care Res*. 2011;63:865-874.

12. Harris AA, Falk RJ, Jennette JC. Crescentic glomerulonephritis with a paucity of glomerular immunoglobulin localization. *Am J Kidney Dis*. 1998;32:179-184.

13. Nachman P, Jennette J, Falk R. Primary glomerular disease. In: Brenner BM, ed. *Brenner & Rectors The Kidney*. Philadelphia, PA: Saunders; 2008:987-1066.

14. Moroni G, Ponticelli C. Rapidly progressive crescentic glomerulonephritis: early treatment is a must. *Autoimmun Rev*. 2014;13:723-729.

15. Couser WG. Rapidly progressive glomerulonephritis: classification, pathogenetic mechanisms, and therapy. *Am J Kidney Dis*. 1988;11:449-464.

16. Eknoyan G, Lameire N, Eckardt K, Kasiske B; Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2:1-138.

17. Korbet SM, Lewis EJ, Schwartz MM, Reichlin M, Evans J, Rohde RD. Factors predictive of outcome in severe lupus nephritis. *Am J Kidney Dis*. 2000;35:904-914.

18. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150: 604-612.

19. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*. 2011;80:17-28.

20. Lin W, Chen M, Cui Z, Zhao MH. The immunopathological spectrum of crescentic glomerulonephritis: a survey of 106 patients in a single Chinese center. *Nephron Clin Pract*. 2010;116: c65-c74.

21. Levy JB, Hammad T, Coulthart A, Dougan T, Pusey CD. Clinical features and outcome of patients with both ANCA and anti-GBM antibodies. *Kidney Int*. 2004;66:1535-1540.

22. Lionaki S, Jennette JC, Falk RJ. Anti-neutrophil cytoplasmic (ANCA) and anti-glomerular basement membrane (GBM) autoantibodies in necrotizing and crescentic glomerulonephritis. *Semin Immunopathol*. 2007;29:459-474.

23. Hellmark T, Segelmark M, Wieslander J. Anti-GBM antibodies in Goodpasture syndrome; anatomy of an epitope. *Nephrol Dial Transplant*. 1997;12:646-648.

24. Kalluri R, Wilson C, Weber M, et al. Identification of the alpha 3 chain of type IV collagen as the common autoantigen in antibasement membrane disease and Goodpasture syndrome. *J Am Soc Nephrol*. 1995;6:1178-1185.

25. Jayne DR, Marshall PD, Jones SJ, Lockwood CM. Autoantibodies to GBM and neutrophil cytoplasm in rapidly progressive glomerulonephritis. *Kidney Int*. 1990;37(3):965-970.

26. Bosch X, Mirapeix E, Font J, et al. Prognostic implication of anti-neutrophil cytoplasmic autoantibodies with myeloperoxidase specificity in anti-glomerular basement membrane disease. *Clin Nephrol*. 1991;36:107-113.

27. Rutgers A, Slot M, van Paassen P, van Breda Vriesman P, Heeringa P, Tervaert JWC. Coexistence of anti-glomerular basement membrane antibodies and myeloperoxidase-ANCAs in crescentic glomerulonephritis. *Am J Kidney Dis*. 2005;46: 253-262.

28. Zhao J, Yang R, Cui Z, Chen M, Zhao M-H, Wang H-Y. Characteristics and outcome of Chinese patients with both anti-neutrophil cytoplasmic antibody and antiglomerular basement membrane antibodies. *Nephron Clin Pract*. 2007;107:c56-c62.

29. Weber M, Andrassy K, Pullig O, Koderisch J, Netzer K. Antineutrophil-cytoplasmic antibodies and antiglomerular basement membrane antibodies in Goodpasture's syndrome and in Wegener's granulomatosis. *J Am Soc Nephrol*. 1992;2: 1227-1234.

30. Srivastava A, Rao G, Segal P, Shah M, Geetha D. Characteristics and outcome of crescentic glomerulonephritis in patients with both antineutrophil cytoplasmic antibody and anti-glomerular basement membrane antibody. *Clin Rheumatol*. 2013;32:1317-1322.

31. Segelmark M, Hellmark T, Wieslander J. The prognostic significance in Goodpasture's disease of specificity, titre and affinity of anti-glomerular-basement-membrane antibodies. *Nephron Clin Pract*. 2004;94:c59-c68.

32. Chen M, Yu F, Wang S-X, Zou W-Z, Zhao M-H, Wang H-Y. Antineutrophil cytoplasmic autoantibody–negative pauci-immune crescentic glomerulonephritis. *J Am Soc Nephrol*. 2007;18: 599-605.