RESEARCH ARTICLE

Crescentic glomerulonephritis: what's different in South Asia?

A single center observational cohort study [version 1; peer review: 2 approved]

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Abstract

Background: The spectrum and outcomes of crescentic glomerulonephritis (Cr.GN) in South Asia is vastly different from that reported worldwide and there is a paucity of information. The aim of the study was to study the demography, clinical presentation, histology and predictors of longitudinal outcomes of Cr.GN in this population.

Methods: An observational cohort study of renal biopsies was performed in the largest tertiary center in South India over a period of 10 years (January 2006 to December 2015) with $\geq 50\%$ crescents on renal histology indicating Cr.GN.

Results: A total of 8645 kidney biopsies were done; 200 (2.31%) were Cr.GN. Patients were categorized into three etiological groups: anti-glomerular basement membrane (type I), immune complex (type II), and pauci-immune (type III). Type II was the most common (96, 46.5%), followed by type III (73, 38%) and type I (31, 15.5%). Female preponderance was seen across all types. About half of all patients presented with recent onset hypertension. Type II had the highest median proteinuria (4.2 (2.1-6) g/day, $p=0.06$) and the median estimated glomerular filtration rate was lowest in type I (5 (4-8) ml/min/1.73m², $p<0.001$). Among type III, anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis was seen only in ~50% of patients. Nearly one third of patients with type I were also positive for ANCA making them 'double positive'. Acute glomerular insults like tuft necrosis and chronic changes as evidenced by moderate to severe interstitial fibrosis, was a predominant feature of type I.

Conclusions: ANCA-negative pauci-immune vasculitis, as well as double positive Cr.GN, are reported for the first time in South-Asia. Renal survival was significantly worse in type I/III compared to type II.

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Types I/III, moderate to severe interstitial fibrosis and tubular atrophy, presence of oliguria/anuria and increasing percentage of crescents in renal biopsy were significant predictors of end stage kidney disease in our cohort.

Keywords

crescentic glomerulonephritis, rapidly progressive glomerulonephritis, ANCA associated vasculitis, anti-GBM disease, double positive disease, immune complex glomerulonephritis

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Introduction

Crescentic glomerulonephritis (Cr.GN) is defined histologically by the presence of extensive glomerular crescents (usually greater than 50%). Clinically, it is also known as rapidly progressive glomerulonephritis (RPGN) as it is accompanied by rapid decline in renal functions. It can occur in any glomerular disease¹ and is usually reported in about 4% to 10% of native kidney biopsies². The natural course of the disease is akin to “medical emergency”, as end stage kidney disease (ESKD) is reached in most patients within a few weeks to months³. Understanding the clinical presentation, natural history and outcomes of Cr.GN is of major concern for nephrologists worldwide. Various studies have been conducted worldwide and epidemiologic data are available from large national kidney biopsy registries, including those from the United States⁴, China², Japan⁵, Spain⁶ and Saudi Arabia⁷. Notably, pathogenesis of glomerular diseases involves a complex and as yet incompletely understood interplay between epigenetic, immunoregulatory, hormonal, and environmental factors on a background of genetic predisposition⁸. This translates into a broad spectrum of disease presentation, a variable tempo of progression and heterogenous outcomes, which are evident from these previous studies. To this end, exploring the features of Cr.GN in a South Asian population, a genetically and demographically diverse group of individuals, may help to provide useful insights into the causality, and predictors of severe outcomes. Our aim was to study the demography, clinical presentation, histology and predictors of longitudinal outcomes of Cr.GN in this population.

Methods

Study design, setting and participants

This was an observational retrospective cohort study performed at the outpatient and inpatient services of the Department of Nephrology, Christian Medical College Vellore, India.

We included all patients (≥ 18 years) who underwent native renal biopsy at our centre between January 2006 to December 2015 and had $\geq 50\%$ crescents on renal histology. There were no other inclusion or exclusion criteria.

Data collection

Data on patients' demographic profile, clinical features, biochemical parameters, histopathology, treatments, morbidity and mortality were retrieved from the electronic patient records (Clinical WorkStation) maintained in the hospital. Follow-up clinical and outcome data with regards to their serum creatinine, dialysis requirement, and complications were collected for each follow-up visit until August 2016. During the index and follow-up visits, patients were classified into chronic kidney disease (CKD) stages as per estimated glomerular filtration rate (eGFR) calculated by CKD-EPI equation⁹.

Data definitions. Cr.GN was defined as the presence of $\geq 50\%$ glomerular crescents as the principal histologic finding. Patients were categorized into three groups on the basis of etiology of Cr.GN; type I, anti- glomerular basement membrane (GBM) Cr.GN; type II, immune complex Cr.GN; type III, pauci-immune Cr.GN.

Microhematuria was defined as >5 red blood cells per high power field. Proteinuria was assessed from 24-hour timed collection as is the standard practice in our center. Interstitial fibrosis and tubular atrophy (IFTA) was classified as follows: focal, $<25\%$; moderate, $25\text{--}50\%$; and severe, $>50\%$.

Qualitative and semiquantitative determination of anti-nuclear antibody (ANA) in serum was done manually by EUROIMMUN Mosaic Hep-20-10 indirect immunofluorescence test (IIFT). The test was done with a sample dilution starting point of 1:100. It is graded on a scale of 1+ to 5+. The sensitivity of the test was 100% with a specificity of 96%. Quantitative determination of anti-double stranded DNA (anti-dsDNA) in serum was done by Anti-dsDNA-NcX ELISA (IgG). The upper limit of the normal range (cut-off) was 100 IU/ml. Anti-neutrophil cytoplasmic antibodies (ANCA) were determined by measuring anti-myeloperoxidase (anti-MPO) and anti-proteinase3 (anti-PR3). Quantitative determination of anti-MPO was done by Anti-Myeloperoxidase ELISA (IgG) test kit. The upper limit of the normal range (cut-off) is 20 RU/ml. The ELISA had a sensitivity of 93.3% and a specificity of 99.8%. Quantitative determination of anti-PR3 was done by Anti-PR3-hn-hr ELISA (IgG). The upper limit of the normal range (cut-off) was 20 RU/ml. The ELISA had a sensitivity of 94% and a specificity of 99%. The tests kits for antibodies were from EUROIMMUN, Luebeck, Germany.

Quantitative determination of complement factors (C3 and C4) was done by means of endpoint nephelometry on the BN ProSpec System by Siemens Health Care Diagnostics Products, Marburg, Germany. Antisera used were liquid animal sera produced by immunization of rabbits with highly purified human complement factors (C3c or C4). The following reference intervals applied for serum samples from healthy adults: C3/C3c, 0.9–1.8 g/L; C4/C4c, 0.1–0.4 g/L.

Statistical analysis

Data are presented as mean $\pm$ standard deviation or medians (interquartile range) or frequency and percent (%) according to the types and distribution of variables. Differences among groups of normally distributed variables were analyzed by t test or one-way analysis of variance (ANOVA). Post-hoc comparisons were performed using t-test with Bonferroni correction. Differences among groups of non-parametric variables were analyzed by Mann–Whitney U-test or the Kruskal-Wallis Test. Categorical variables were compared using chi-squared or Fisher's exact test. Multivariable logistic regression was used to identify predictors of ESKD.

Statistical calculations were performed using SPSS software for Windows, version 21.0 (SPSS Inc., Chicago, IL) and graphs were made using Graph Pad Prism 7.0e (Graph Pad Software Inc., San Diego, CA). A *P* value of <0.05 was taken as significant.

Ethical considerations

Approval was obtained from the Institutional Review Board (Silver, Research and Ethics Committee) of the Christian Medical

College, Vellore, India (IRB 9090 dated 06.10.2014). Waiver of informed consent was obtained from the ethics committee as the study was retrospective and used de-identified patient information from electronic records.

Results

Demography

A total of 8645 kidney biopsies were done at our center from January 2006 to December 2015, of which 200 had Cr.GN (2.31%). The most common cause of Cr.GN was type II (96, 46.5%), followed by type III (73, 38%), and type I (31, 15.5%). The various etiologies of Cr.GN are depicted in Figure 1. Females constituted 60% of the patients with a female: male ratio of 1.5:1. Female preponderance was seen across all three types of Cr.GN. The mean age of presentation for all types was 40.6 ± 14.6 years, with the highest mean age of presentation seen in patients with type III Cr.GN. Demographic and baseline clinical and laboratory parameters of the study population are summarized in Table 1.

Clinical and laboratory features

Non-visible hematuria was near universal (95%). More than half of the patients (56%) were oliguric at presentation. Anuria at presentation was seen in 10% patients. Oliguria and anuria were

more common in type I Cr.GN patients (oliguria in 74%, $p=0.08$; anuria in 16%, $p=0.04$) who also had significantly more uremic symptoms (64%, $p=0.006$). About half of all the three types presented with recent onset hypertension. Among extra-renal symptoms, skin lesions and arthritis were rare in type I, but hemoptysis was seen only in type I and III Cr.GN.

Type II Cr.GN had the highest median proteinuria (4.2 ($2.1-6$) g/day, $p=0.06$), lowest serum albumin (2.8 ± 0.8 g/dL, $p < 0.001$) and highest serum cholesterol levels (214 ± 73 mg/dL, $p=0.04$). The median eGFR was 9 ($5-17$) ml/min/1.73m² and was lowest in type I Cr.GN (5 ($4-8$) ml/min/1.73m², $p < 0.001$) with the lowest mean Hb (7.6 ± 2 g/dL, $p=0.003$).

Serum complement levels were low in nearly 50% patients with Cr.GN (low C3 in 43% and low C4 in 11%), predominantly in those with type II Cr.GN ($p < 0.001$). Interestingly, low C3 levels were also found in about 25% patients with either type I or type III Cr.GN. Low C4 levels, on the other hand was seen only in type II Cr.GN. Though ANA was positive to various extents in all types of Cr.GN (23% in type I, 9% in type II & 47% in type III), dsDNA positivity was seen only type II Cr.GN (33%). Among type III Cr.GN, ANCA associated vasculitis (AAV) was seen only in 50% patients (anti-MPO 24%; anti-PR3 26.3%).

Figure 1. Etiologies of crescentic glomerulonephritis (Cr.GN). GBM, glomerular basement membrane; ANCA, anti-neutrophil cytoplasmic antibodies; AAV, ANCA associated vasculitis.

Table 1. Demography, baseline clinical and laboratory characteristics of the study population.

Characteristic	All types (n=200)	Type I Cr.GN (anti-GBM) (n=31)	Type II Cr.GN (immune complex) (n=93)	Type III Cr.GN (pauci-immune) (n=76)	P value
Age (years, mean±SD)	40.6±14.6	37.5±12.2	37.8±14.6	45.3±14.3	0.03[@], 0.003[#]
Gender (male:female (ratio))	80:120 (0.67)	12:19 (0.63)	36:57 (0.63)	32:44 (0.73)	0.89
Renal symptoms (n (%))					
Oliguria	112 (56)	23 (74.2)	50 (53.8)	39 (51.3)	0.08
Anuria	20 (10)	5 (16.1)	4 (4.3)	11 (4.5)	0.03
Visible hematuria	25 (12.5)	6 (19.4)	9 (9.7)	10 (13.2)	0.38
Non-visible hematuria	190 (95)	29 (93.5)	90 (96.8)	71 (93.4)	0.55
Hypertension	100 (50)	15 (48.4)	51 (54.8)	34 (44.7)	0.42
Uremic symptoms	84 (42)	20 (64.5)	30 (32.3)	34 (44.7)	0.006
Extra-renal symptoms (n (%))					
Skin lesions	24 (12)	0	16 (17.2)	8 (10.5)	0.006
Arthritis	40 (20)	6 (19.4)	18 (19.4)	16 (21.1)	0.96
Hemoptysis	19 (9.5)	4 (12.9)	0	15 (19.7)	<0.001
Diabetes mellitus (n, %)	14 (7)	0	5 (5.4)	9 (11.8)	0.03
Hemoglobin (g/dL, mean±SD)	8.6±2.1	7.6±1.9	9±2	8.5±2.1	0.003^{\$}
Total leucocyte (cells*10 ⁹ /L, mean±SD)	9.9±4.5	9.3±3.9	9.8±5.2	10.3±3.7	0.57
Serum cholesterol (mg/dL, mean±SD, n)	199.7±73.8 (123)	205.3±101.8 (15)	213.9±73.2 (62)	178.8±59.6 (46)	0.04[#]
Serum albumin (g/dL, mean±SD)	3±0.7	3.2±0.6	2.8±0.8	3.1±0.5	0.008^{\$}, 0.005[#]
24-hour proteinuria (g/day, median (IQR), n)	3.5 (1.8-5.6) (187)	3.3 (2-5.8) (26)	4.2 (2.1-6) (89)	2.8 (1.3-4.3) (72)	0.06
Serum creatinine (mg/dL, mean±SD)	6.9±4.4	10.6±5.5	5.1±3.2	7.6±4.1	<0.001^{@\$}, 0.001[#]
CKD-EPI eGFR (ml/min/1.73m ² , median (IQR))	9 (5-16.8)	5 (4-8)	14 (8-25.5)	7 (5-12)	<0.001^{@#}
CKD stages at baseline (n (%))					
Stage 2 Yes	7 (3.5)	0	6 (6.5)	1 (1.3)	<0.001
Stage 3 Yes	19 (9.5)	1 (3.2)	13 (14)	5 (6.6)	
Stage 4 Yes	34 (17)	0	24 (25.8)	10 (13.2)	
Stage 5 Yes	52 (26)	6 (19.4)	21 (22.6)	25 (32.9)	
Stage 5D Yes	88 (44)	24 (77.4)	29 (31.2)	35 (46.1)	
Serum complements (mg/dL, n/N (%))					
Low C3	84/196 (42.9)	7/31 (22.6)	59/90 (65.6)	18/75 (24)	<0.001
Low C4	21/196 (10.7)	0	20/90 (22.2)	1/75 (1.3)	<0.001
Serology (n/N (%))					
ANA Yes	51/176 (29)	7/31 (22.6)	38/80 (47.5)	6/65 (9.2)	<0.001
Anti- dsDNA Yes	25/146 (17.1)	0	25/75 (33.3)	0	<0.001
ANCA Yes	54 (31.8)	10/31 (32.3)	6/64 (9.4)	38/76 (50)	<0.001
Anti-MPO-ANCA Yes	28/143 (19.6)	7/25 (28)	3/50 (6)	18/68 (26.5)	<0.001
Anti-PR3-ANCA Yes	26/143 (18.2)	3/25 (12)	3/50 (6)	20/68 (29.4)	<0.001

Abbreviations: Cr.GN, crescentic glomerulonephritis; eGFR, estimated glomerular filtration rate (calculated using the CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula); C3, complement C3; C4, complement C4; ANA, anti-nuclear antibody; Anti- dsDNA, anti-double stranded DNA antibody; ANCA, anti-neutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3; GBM, glomerular basement membrane.

P value is significant at <0.05 between [@]Type 1 and Type III, [#]Type II and Type III, ^{\$}Type 1 and Type II analyzed by One-way ANOVA with Bonferroni correction.

Nearly one third patients with type I Cr.GN (32%) showing linear staining in immunofluorescence were also positive for ANCA (anti-MPO 22.5%; anti-PR3 9.7%) making them 'double positive Cr.GN'.

Histopathological features

Characteristic histopathological features noted in kidney biopsies have been summarized in Table 2. The highest percentage of glomeruli with crescents was seen in type I ($83 \pm 17\%$, $p=0.001$) followed by type III ($74 \pm 19\%$) and type II ($69 \pm 18\%$). The most common type of crescents in all three groups was fibrocellular. Glomerular proliferative lesions, as evidenced by mesangial hypercellularity (68%, $p=0.02$), endocapillary proliferation (100%) and neutrophilic exudation (50%, $p=0.01$), were predominantly seen in type II Cr.GN. Severe glomerular insults, such as tuft necrosis, was a predominant feature of type I (32%, $p=0.002$) and type III Cr.GN (25%). Chronicity, as evidenced by moderate to severe IFTA, was predominant in type I Cr.GN (68%; $p=0.02$).

Treatment differences

Standard treatment protocols as per KDIGO 2012¹⁰ guidelines were followed for all patients. Nearly half of the patients required dialysis at presentation, with significantly more in type I and type III Cr.GN (81% & 62% respectively, $p<0.001$).

About one fifth of patients received therapeutic plasma exchange (PLEX), and this was significantly more in type I and type III Cr.GN (42% and 26% respectively, $p<0.001$). The frequency and indications of PLEX are summarized in Table 3. Immunosuppression with/without PLEX was given in 90% of patients with significantly more in type II and III Cr.GN (92% and 91% respectively, $p<0.001$).

Patient and renal outcomes

The mean follow-up period was 9.4 ± 15 months. Table 4 summarizes the outcomes observed in three types of Cr.GN. In the entire cohort, nearly half (45%) developed ESKD, requiring renal replacement therapy. This was significantly more in type I (77%, $p<0.001$). Overall mortality rate was 4% and did not vary significantly between the groups. Sepsis was found to be the most common cause of death.

Type III Cr.GN: ANCA associated vasculitis (AAV) vs. ANCA negative vasculitis

The group of patients with type III Cr.GN was subdivided into AAV (38, 51%) and ANCA negative (37, 49%) vasculitis. Characteristic features of the two groups are summarized in Table 5. AAV was associated with a significantly higher mean age ($p=0.01$), presence of extra renal manifestations of fever (50%, $p=0.02$), hemoptysis (39%, $p<0.001$) leukocytosis

Table 2. Histopathology characteristics of the study population.

Characteristic	All types (n=200)	Type I Cr.GN (anti-GBM) (n=31)	Type II Cr.GN (immune complex) (n=93)	Type III Cr.GN (pauci-immune) (n=76)	P value
Number of glomeruli (median (IQR))	9 (6-12)	11 (6-15)	9 (6-11)	9.5 (6-12)	0.46
Number of sclerosed glomeruli (median (IQR))	1 (0-3)	0 (0-6)	1 (0-3)	1 (0-4)	0.23
Crescents (%; mean $\pm$ SD)	73.2 $\pm$ 18.9	83 $\pm$ 16.7	69.2 $\pm$ 18.1	74.2 $\pm$ 19.4	0.001[§]
Predominant type (n (%))					0.17
Cellular	49 (24.5)	5 (16.1)	22 (23.7)	22 (29)	
Cellular to fibro-cellula	40 (20)	10 (32.3)	18 (19.3)	12 (15.8)	
Fibrocellular	88 (44)	10 (32.3)	46 (49.5)	32 (42.1)	
Fibrous	23 (11.5)	6 (19.4)	7 (7.5)	10 (13.2)	
Glomerular lesions (n (%))					
Mesangial proliferation Yes	116 (58)	13 (41.9)	63 (67.7)	40 (52.6)	0.02
Inter-capillary mesangial sclerosis Yes	16 (8)	6 (19.3)	3 (3.2)	7 (9.2)	0.02
Endocapillary proliferation Yes	79 (100)	-	79 (100)	-	
Neutrophilic infiltration Yes	79 (39.5)	9 (29)	47 (50.5)	23 (30.3)	0.01
Tuft necrosis Yes	37 (18.5)	10 (32.2)	8 (8.6)	19 (25)	0.002
Glomerular thrombosis Yes	3 (1.5)	0	3 (3.2)	0	0.1
IFTA Moderate/Severe Yes (n (%))	100 (50)	21 (67.7)	38 (40.9)	41 (53.9)	0.02
Vascular (n (%))					
Necrosis Yes	7 (3.5)	1 (3.2)	3 (3.2)	3 (3.9)	0.96
Arterio(lo)sclerosis Yes	55 (23)	12 (38.7)	27 (29)	16 (21.1)	0.95

Abbreviations: IFTA, interstitial fibrosis and tubular atrophy; Cr.GN, crescentic glomerulonephritis; GBM, glomerular basement membrane.

P value is significant at <0.05 between * Type 1 and Type III, # Type II and Type III, [§]Type 1 and Type II analyzed by One-way ANOVA with Bonferroni correction.

Table 3. Treatment characteristics of study population.

Characteristic	All types (n=200)	Type I Cr.GN (anti-GBM) (n=31)	Type II Cr.GN (immune complex) (n=93)	Type III Cr.GN (pauci-immune) (n=76)	P value
IS Yes (n (%))	177 (88.5)	22 (71)	86 (92.5)	69 (90.8)	0.01
Steroids alone Yes	43 (21.5)	2 (35.5)	29 (31.2)	12 (15.8)	0.003
Steroids plus cyclophosphamide Yes	100 (50)	18 (58.1)	33 (35.4)	49 (64.5)	
Steroids plus other IS Yes	33 (16.5)	1 (3.2)	24 (25.8)	8 (10.5)	
PLEX with IS Yes	37 (18.5)	12 (38.7)	5 (5.4)	20 (26.3)	<0.001
without IS Yes	1 (0.5)	1 (3.2)	0	0	
PLEX indications (n (%))					
Hemoptysis Yes	2 (1)	1 (3.2)	0	1 (1.3)	<0.001
Renal failure Yes	26 (13)	10 (32)	5 (5.4)	11 (14.5)	
Both Yes	11 (5.5)	3 (9.7)	0	8 (10.5)	
Hemodialysis (n (%))	104 (52)	25 (80.6)	32 (34.4)	47 (61.8)	< 0.001

Abbreviations: IS, immunosuppression; PLEX, plasma exchange; IS, immunosuppression; CR.GN, crescentic glomerulonephritis; GBM, glomerular basement membrane.

Table 4. Outcomes at follow-up for study population.

Characteristic	All types (n=200)	Type I Cr.GN (anti-GBM) (n=31)	Type II Cr.GN (immune complex) (n=93)	Type III Cr.GN (pauci-immune) (n=76)	P value
Follow-up (months, mean±SD)	9.4±15.5	4.6±8.3	10±15.1	10.6±17.8	0.17
Serum creatinine at last follow-up (mg/dL, mean±SD, n)	3.7±3.5 (95)	7.2±5.8 (6)	3.4±3.3 (49)	3.5±3.1 (40)	0.03[®], 0.04[†]
eGFR (CKD-EPI) at last follow-up (ml/min/1.73m ² , median (IQR), n)	27.5 (11.3-54.5) (95)	11 (4-34) (6)	32 (42.3-33.8) (49)	24.5 (14-43) (40)	0.07
eGFR change from baseline (n/N (%))					
eGFR loss & no change in CKD stage	11/105 (11.6)	3/6 (50)	3/49 (6.1)	5/40 (12.5)	0.25
eGFR loss & change in CKD stage	10/105 (10.5)	0	6/49 (12.2)	4/40 (10)	
eGFR gain & no change in CKD stage	24/105 (25.3)	1/6 (16.7)	13/49 (26.5)	10/40 (13.2)	
eGFR gain & change in CKD stage	50/105 (52.6)	2/6 (33.3)	27/49 (55.1)	21/40 (52.5)	
ESKD	89 (44.5)	24 (77.4)	28 (30.1)	38 (50)	<0.001
Hemodialysis (n (%))	87 (43.5)	24 (77.4)	28 (30.1)	35 (46)	<0.001
Infections (n (%))	34 (17)	5 (16.1)	19 (20.4)	10 (13.2)	0.45
Death	9 (4.5)	0	4 (4.3)	5 (6.6)	0.17

Abbreviations: eGFR, estimated glomerular filtration rate (calculated using the CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula); ESKD, end stage kidney disease; Cr.GN, crescentic glomerulonephritis; GBM, glomerular basement membrane.

P value is significant at <0.05 between [®] Type 1 and Type III, [†] Type II and Type III, [‡] Type 1 and Type II analyzed by One-way ANOVA with Bonferroni correction.

(11.2±4.5 cells*10⁹/L, p=0.03), severe histology, as evidenced by fibrous/ fibrocellular crescents (84%, p=0.009), tuft necrosis (37%, p=0.02), and greater requirement of PLEX (45%, p<0.001). However, the median 24-hour proteinuria (3.7 (2.1–6.7) g/day, p=0.001) and serum cholesterol (206.7±61 mg/dL, p=0.003) was higher in ANCA negative

vasculitis. Rates of ESKD and renal survival did not differ between the two groups (Table 5 and Figure 2).

Double antibody positive Cr.GN

Among those with type I Cr.GN (n=31), there were 10 'double positive' patients (32.3%) with positive ANCA serologies

Table 5. Type III Cr.GN: characteristics of AAV and ANCA negative vasculitis.

Characteristic	ANCA neg. vasculitis(n=37)	AAV(n=38)	P value
Age (years, mean(SD))	41±13.3	49.4±14.4	0.01
Gender (male:female (ratio))	15:22 (0.68)	16:22 (0.73)	0.89
Renal symptoms (n (%))			
Oliguria	20 (54.1)	18 (47.4)	0.56
Anuria	6 (16.2)	4 (10.5)	0.52
Hypertension	19 (51.4)	14 (36.8)	0.21
Uremic symptoms	18 (48.6)	15 (39.5)	0.42
Extra-renal symptoms (n (%))			
Skin lesions	3 (8.1)	5 (13.2)	0.71
Arthritis	5 (13.5)	11 (28.9)	0.1
Hemoptysis	0	15 (39.5)	<0.001
Fever	9 (24.3)	19 (50)	0.02
Hemoglobin (g/dL, mean±SD)	8.8±2.7	8.2±2	0.19
Total leucocyte (cells*10 ⁹ /L, mean±SD)	9.3±2.5	11.2±4.5	0.03
Serum cholesterol (mg/dL, mean±SD, n)	206.7±61.1	155.3±47.9	0.003
Serum Albumin (mg/dL, mean±SD)	3.1±0.5	3.1±0.6	0.79
24-hour proteinuria (g/day, median (IQR), n)	3.7 (2.1-6.7)	2.1 (0.9-3.5)	0.001
Serum creatinine (mg/dL, mean±SD)	7.1±4	7.9±4.3	0.39
CKD-EPI eGFR (ml/min/1.73m ² , median (IQR))	9 (5.5-16)	7 (4-10.3)	0.11
Serum complements (mg/dL, n/N (%))			
Low C3	12 (32.4)	6 (16.2)	0.1
Low C4	1 (2.7)	0	1
Crescents (%; mean±SD)	74.8±20.5	73±18.3	0.7
Predominant type (n (%))			
Cellular	16 (43.2)	6 (15.8)	0.009
Fibrocellular or fibrous	21 (56.8)	32 (84.2)	
Glomerular lesions (n (%))			
Mesangial proliferation Yes	20 (54.1)	20 (52.6)	0.9
Neutrophilic infiltration Yes	12 (32.4)	11 (28.9)	0.74
Tuft necrosis Yes	5 (13.5)	14 (36.8)	0.02
IFTA Moderate/Severe Yes (n, (%))	20 (54.1)	20 (52.6)	0.9
Vascular (n (%))			
Necrosis Yes	1 (2.7)	2 (5.3)	0.57
Arterio(lo)sclerosis Yes	26 (70.3)	21 (55.3)	0.18
Treatment (n (%))			
Immunosuppression Yes	33 (89.2)	36 (94.7)	0.38
PLEX Yes	3 (8.1)	17 (44.7)	<0.001
Outcomes			
Serum creatinine at last follow-up (mg/dL, mean±SD, n)	4±4.2, 18	3.1±1.9, 22	0.42
eGFR at last follow-up (ml/min/1.73m ² , median (IQR), n)	29 (17.8-51.7), 18	21.6 (13.2-34.7), 22	0.09
ESKD	20 (54.1)	17 (44.7)	0.42
Death	0	5 (13.2)	0.07

Abbreviations: ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate (calculated using the CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula); ESKD, end stage kidney disease; C3, complement C3; C4, complement C4; IFTA, interstitial fibrosis and tubular atrophy; PLEX, plasma exchange; ESKD, end stage kidney disease; Cr.GN, crescentic glomerulonephritis; GBM, glomerular basement membrane.

Figure 2. Kaplan-Meier estimates for renal survival in types of crescentic glomerulonephritis and their subgroups.

(anti-MPO 7; anti-PR3 3). Renal survival was significantly worse in this group ($p=0.002$) compared to AAV but similar to type I Cr.GN (Figure 2).

Predictors of severe outcomes

We analyzed various risk factors which predicted the development of ESKD at follow-up in this cohort (Table 6). In an adjusted regression analysis, type I/type III Cr.GN, moderate to severe

IFTA, presence of oliguria/anuria and increasing percentage of crescents in renal biopsy were significant predictors of ESKD at follow-up.

Kaplan-Meier estimates of renal survival differed significantly between the three groups (Figure 2) but did not differ in any subgroups (Figure 2). Patient survival was similar in all three groups (Figure 3).

Table 6. Significant predictors of ESKD at follow-up.

Risk factors	Univariate P value	Multivariable regression			
		Exp (B)	95% C.I.		P value
			Lower	Upper	
Gender	0.22				
Renal symptoms					
Oliguria Yes	<0.001	3.4	1.7	6.7	<0.001
Anuria Yes	0.004				
Uremic symptoms Yes	<0.001				
Extra-renal symptoms					
Skin lesions No	0.038				
Arthritis No	0.014				
Serum creatinine (mg/dL)	<0.001				
CKD-EPI eGFR (ml/min/1.73m ²)	<0.001				
Normal C3	0.66				
Normal C4	0.04				
Serology					
ANA neg.	0.014				
Anti- dsDNA pos.	0.07				
ANCA pos.	0.68				
Percentage of crescents	<0.001	1.02	1.005	1.04	0.01
Glomerular lesions					
Mesangial proliferation No	0.01				
Predominant type of crescents					
Cellular Yes	0.28				
Vascular					
Necrosis Yes	0.022				
Interstitial					
IFTA Moderate/Severe Yes	<0.001	3.4	1.8	6.5	<0.001
Type I/III Cr.GN	<0.001	2.7	1.4	5.1	0.003
Immunosuppression No	0.003				
PLEX Yes	0.1				
Hemodialysis at index visit discharge Yes	<0.001				

Abbreviations: ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; C3, complement C3; C4, complement C4; IFTA, interstitial fibrosis and tubular atrophy; PLEX, plasma exchange; CR.GN, crescentic glomerulonephritis; eGFR, estimated glomerular filtration rate (calculated using the CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula).

Figure 3. Kaplan-Meier estimate for patient survival in types of crescentic glomerulonephritis.

Discussion

Cr.GN is one of the leading causes of rapidly progressive renal failure. There are a few studies of Cr.GN from South Asia but there is dearth of data on the different types of Cr.GN and their outcomes.

In this study Cr.GN accounted for 2.3% of all biopsies conducted over a period of 10 years, which is comparable to previously reported rates of Cr.GN from India^{11,12}. Type II Cr.GN was found to be the most common type, which is unique to the Asian continent. Various studies conducted in different parts of the world have shown type III Cr.GN to be the most common^{5,13}. However studies from China, Saudi Arabia and a smaller Indian study have reported type II Cr.GN to be the most common^{2,11,14}. Reasons cited for increased incidence of

type II Cr.GN in these parts have been an increased incidence of infections and a higher prevalence of IgA nephropathy. Lupus nephritis (45%) is the most common cause of type II Cr.GN, followed by infection related GN (24%) and IgA nephropathy (23%) in our cohort. This is similar to one of the largest reviews of Cr.GN from China, in which lupus nephritis was listed as most common cause of type II Cr.GN (34%) followed by IgA nephropathy (17%)².

Gender differences in Cr.GN have mostly been observed in type II Cr.GN with female preponderance. The gender distribution has been variable in type I and type III Cr.GN in different studies^{2,11,13–15}. As is already known and established in other studies, patients with type I Cr.GN had the most severe renal failure at presentation. However, in this study, more than half of the patients with type II and III Cr.GN also presented with severe renal failure, highlighting the dramatic presentation in this patient population. These rates are much higher than previously reported^{2,15}.

Serum complement C3 levels have been shown to be low in type I and type III Cr.GN in addition to type II Cr.GN. This was confirmed in our study. However, we found no cases of low C4 levels in type I and III Cr.GN, highlighting that the alternate complement pathway has a role in the pathogenesis of these GNs. Our observed rates of ANCA seropositivity in type III Cr.GN are much lower than those reported in other studies^{2,15}. An earlier study from India also reported similar rates of ANCA seropositivity¹⁶. ANCA negative vasculitis could be attributed to other antibodies, such as anti-endothelial cell antibodies, or to cell mediated immune mechanisms, which lead to neutrophilic activation¹⁷. The high prevalence of ANCA negative vasculitis in this cohort highlights the need for research into its pathogenesis to elucidate factors specific to our population.

Subgroup analysis of type III Cr.GN revealed important differences between AAV and ANCA negative vasculitis groups, which, to the best of our knowledge, is reported for the first time from India. Similar to our study, younger age of onset and lower prevalence of systemic involvement in ANCA negative vasculitis has been reported from other parts of the world^{18–21}. Chen *et al.*¹⁹ also observed a higher level of proteinuria in this group, similar to our study. Although chronic lesions on kidney biopsy were more prevalent in ANCA negative vasculitis in these studies, we found a higher prevalence of fibrous/fibrocellular crescents and tuft necrosis in the AAV group. Data on renal outcomes has been variable, with few studies showing comparable outcomes in the two groups^{20,21}, which is similar to our study and others showing poorer renal outcome in ANCA negative vasculitis^{18,19}.

Levy *et al.*²² reported a prevalence of ANCA positivity of nearly 30% in type I Cr.GN with predominance of anti-MPO ANCA. They concluded that these patients had a poor prognosis when presenting with severe disease and initially behaved more like anti-GBM disease than vasculitis with low rates of recovery from renal failure. On the other hand McAdoo *et al.*²³

in their retrospective analysis of double antibody positive cases found that such patients had shared characteristics of AAV and anti-GBM disease. Double positive patients had a greater likelihood of independence from dialysis despite more chronicity compared to patients with anti-GBM disease and long term renal survival was intermediate compared to the single-positive patients. Our prevalence of 'double positive Cr.GN' was similar to Levi *et al.*²² with intermediate risk for renal survival.

At the end of the follow-up period, almost half of the patients had developed ESKD in our study. Renal survival was worst in type I Cr.GN. Similar rates of renal survival were reported by Chen *et al.*² Previously reported rates of renal failure from India varied between 46–60%^{11,16}. Different studies have identified various risk factors for ESKD: sclerosed glomeruli, acute tubular necrosis, vasculopathy⁷, arteriolar fibrinoid necrosis¹⁶, serum creatinine, age, lung involvement, serum c-reactive protein⁵, oliguria, crescents and interstitial inflammation².

Conclusion

We were able to analyse detailed demographic, clinical, serological and pathological features of our cohort. Strengths of our study include its large sample size, the inclusion and comparison of ANCA negative vasculitis as well as 'double positive Cr.GN' patients, of which there is no previously reported data from India. We highlight several important clinical practice points, in particular type II Cr.GN may present with a severe renal failure similar to type III Cr.GN. However, the response to treatment and outcomes were much more favourable and appropriate treatment should be initiated at the earliest. Prevalence of ANCA negative vasculitis was much higher in our population and hence kidney biopsy is mandatory in a case of suspected RPGN with negative serologies. Type I/type III Cr.GN, moderate to severe IFTA, presence of oliguria/anuria, and increasing percentage of crescents in renal biopsy were significant predictors of ESKD at follow-up in our cohort. Our study has also been able to identify areas of further research: search for pathways of alternate complement activation in type I and III Cr.GN and to explore the pathogenesis and factors responsible for increased prevalence of ANCA negative vasculitis in our population. The limitations of the study are that it is a single centre and it was retrospective in nature.

Data availability

Underlying data

Figshare: Crescentic GN_repository.xlsx, <https://doi.org/10.6084/m9.figshare.12479402.v4>²⁴.

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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Stephen Holdsworth

Immunology Department, Monash Health, Clayton, Australia

This is a well performed study of rapidly progressive Crescentic Glomerulonephritis (Cr.GN) from a single hospital in South India. The study surveyed 8645 renal biopsies from 2006-2015 and studied 200 patients who had a biopsy showing Cr.GN (>50% crescentic glomeruli).

The frequency of this disease amongst biopsied patients with glomerulonephritis (2.3%) is a lower frequency than has been found in other large studies. However this was a relatively large group (200) enabling more confidence in the data collected.

Relatively to other large studies there were several significant observations. The relative frequency of infection as an underlying disease was unusually high. There was also a relatively higher than expected frequency of Lupus Nephritis.

The other unexpected findings were the high percentage of ANCA negative patients amongst the Type III pauci immune group. These two groups, (Type III ANCA positive and negative), were similar in most clinical and biochemical features except for the observation that ANCA negative patients were significantly younger, had significantly less extra renal disease especially haemoptysis. Consequently they had significantly less plasma exchange treatment. Their biopsies showed less glomerulosclerosis and full glomerular tuft necrosis and they had a strong trends to outcomes with less loss of renal function and death.

The frequency of Type I, anti GBM disease group was, as expected, infrequent. Only 21 patients had "pure" anti-GBM disease but the number of double positive (10 patients with Type I anti GBM disease and concurrently Type III classification) significantly raised the percentage of patients with anti GBM disease. If we deleted these 10 double positive patients from the Type III group this "Pure Type III" group would now fall to 68 and the number of ANCA positive patients in this "Pure Type III group" would fall to 28. Therefore the percentage of "pure Type III" patients ANCA positive would fall to 41%. This is a remarkably low frequency of ANCA positivity in Type III Cr.GN patients. It would be interesting to see how many of these patients ("Pure" anti GBM disease, "Pure Type III and" double positive) had circulating anti-GBM antibodies.

Regarding treatment and outcomes there was an unexpected use of prednisolone alone amongst a group of patients who may have benefitted from immunosuppression with drugs including Rituximab, Mycophenolate and azathioprine. Having made this observation it is important to say that the overall outcomes seem to be similar to those reported in other large patient surveys.

This is an important study that has demonstrated several novel differences in this group of Cr.GN patients not seen in other large studies. A validation study, also from Southern India, has the potential to strengthen these findings.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

No source data required

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Immunology.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 27 Jul 2020

Suceena Alexander, Christian Medical College, Vellore, India

Dear Dr Stephen

Thank you for your review and comments. I have addressed the reasons for steroid alone treatment in some patients with Cr.GN in my response to Dr. Salama's comments.

Regards
Suceena Alexander

Competing Interests: None

Reviewer Report 21 July 2020

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Alan Salama

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This is an interesting description of a large case series of patients with crescentic nephritis from Southern India. The predominance of immune complex disease is as previously reported and in keeping with higher levels of infection related disease, SLE and IgA. The most interesting features are the high rates of ANCA negative pauci immune GN. The cause of this is uncertain and warrants more investigation, especially as many patients were also hypocomplementaemic - begging the question if these are more like pauci immune lupus like disease or if the immunoglobulin staining was verified by repeat staining. However, the nature of the antigen (and antibody if one exists) would be of great interest. These are experiments beyond the scope of this work, but are intriguing.

There were many patients treated with steroids alone across all groups (up to a third of group 1 and 2) which is not recommended in KDIGO and would be worth investigating the reasons for, as that may account for some of the ESRD.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

No source data required

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Immune mediated kidney disease, autoimmunity, glomerulonephritis.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 23 Jul 2020

Suceena Alexander, Christian Medical College, Vellore, India

Dear Dr Alan Salama

Thank you for your review and comments. With regards to the steroid alone treatment in group I (anti-GBM), the treatment table shows 2/31 which is 6.5%. The percentage shown in the bracket is a typo and we apologise for the error. In Group II (immune complex), the major reasons for steroid alone treatment were chronicity and severe IFTA on biopsy and the presence of concomitant infections as most were infection related glomerulonephritis.

Regards

Suceena Alexander

Competing Interests: None