The Outcome of Pauci-immune Crescentic Glomerulonephritis and Its Prognostic Factors; A single Center Case Series

Neda Najafi,[1] Shahrzad Ossareh,[1] Mitra Mehrazma,[2,3] Mohsen Vahedi[4]

[1]Nephrology Section, Department of Medicine, Hasheminejad Kidney Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[2]Department of Pathology, Hasheminejad Kidney Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
[3]Oncopathology Research Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[4]Department of Biostatistics and Epidemiology, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran

Keywords. crescentic glomerulonephritis, pauci-immune glomerulonephritis, CKD, kidney survival, cyclophosphamide

Introduction. Pauci-immune crescentic glomerulonephritis (GN) is the most common cause of rapidly progressive GN in adults. The aim of this study was to determine the outcome of patients with pauci-immune crescentic GN and risk factors of the development of end-stage kidney disease (ESKD) in these patients.
Methods. This case series study was carried on 120 patients with pauci-immune crescentic GN biopsied in our center betwen 1998 and 2016. Inclusion criteria were age > 16 years, at least one crescentic glomerulus, maximally 1+ deposition of immunoglobulins and complement components at fluorescent microscopy, and at least 6 months follow-up. The main outcomes were ESKD and death.
Results. The study population included 120 patients with pauci-immune crescentic GN (mean age was 47 ± 17 years and 49.1% male). There was no significant difference in outcome between patients with diffuse or focal crescentic GN. Seventy-two patients (60%) developed ESKD and 31 patients (25.8%) died. The need for dialysis at admission, lower baseline hemoglobin and GFR and GFR at four months and high percentage of glomerulosclerosis and interstitial fibrosis had a significant relationship with low kidney survival ($P < .05$). The rate of ESKD was higher in patients who did not receive cyclophosphamide therapy, due to focal crescentic GN or high chronicity, compared to patients who received it (70.7 vs. 28.5%, $P < .001$).
Conclusion. In our study, a high percentage of patients with pauci-immune crescentic GN developed ESKD. Low first GFR and high chronicity in biopsy were associated with lower kidney survival. Failure to administer cyclophosphamide in seemingly limited or advanced cases, together with late referral may have led to poor prognosis.

IJKD 2024;18:9-17
www.ijkd.org
DOI: 10.52547/ijkd.7545

Original Paper

INTRODUCTION

Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome characterized by features of glomerular disease in urinalysis and progressive reduction in kidney function within a period of weeks to months.[1] It is most commonly characterized by extensive crescent formation, i.e., extracapillary proliferation of parietal cells in the Bowman's space. According to previous studies, the frequency of diffuse crescentic glomerulonephritis (GN) and

pauci-immune crescentic GN among all kidney biopsies is 5.8 and 10%, respectively.[2,3] Based on the findings of immunofluorescent microscope, three types of crescentic GN are defined.[1] Type 1 is characterized by linear antibody deposition along the glomerular basement membrane and is defined as anti-GBM disease. Type 2 consists of a heterogeneous group of primary and secondary glomerular diseases characterized by granular deposition of immunoglobulins and complement components in the glomeruli and is defined as immune complex crescentic GN. Type 3 is characterized by the absence of deposition of immunoglobulins and complement fragments in the glomeruli and is defined as pauci-immune crescentic GN.[1]

Pauci-immune crescentic GN is the most common cause of RPGN, especially in the elderly and white race, and can lead to end-stage kidney disease (ESKD). However, with appropriate treatment, remission occurs in more than 50% of the patients who have a glomerular filtration rate (GFR) of less than 10 mL/min at admission. Therefore, invasive immunosuppressive therapy is recommended for all patients.[4]

With a high percentage of crescent formation i.e. more than 80%, and especially in the presence of circumferential crescents and advanced kidney failure, unresponsiveness to therapy is very likely.[1] On the other hand, focal crescentic GN, i.e., non-circumferential crescents in less than 50% of glomeruli, is accompanied by a slower course and may even undergo spontaneous remission. Some pathologists believe that only crescent formation in more than 50% of glomeruli is known as crescentic GN, while others consider 10 to 50 percent crescent formation as crescentic GN.[1] Despite these general definitions, the presence of only one crescentic glomerulus on biopsy of patients with ANCA-associated GN, is considered as extracapillary GN.[5]Approximately 90% of patients with pauci-immune crescentic GN are positive for anti-neutrophil cytoplasmic antibody (ANCA).[5]

In 2010, Berden classified ANCA-associated GN according to patient outcome as: 1) Focal : ≥ 50% normal glomeruli, 2) Crescentic: ≥ 50% of glomeruli with cellular or fibro- cellular crescents, 3) Mixed: < 50% normal glomeruli, < 50% crescentic glomeruli and < 50% globally sclerotic glomeruli, and 4) sclerotic: ≥ 50% globally sclerotic glomeruli. According to this classification, the worst to best prognoses are seen in sclerotic, mixed, crescentic and focal categories, respectively.[6]

This study was designed to determine the outcome and risk factors of ESKD in patients suffering from pauci-immune crescentic GN.

MATERIALS AND METHODS

This case series was performed on 120 patients, with pauci-immune crescentic GN, who underwent biopsy in Hasheminejad kidney center (HKC), between 1998 and 2018.

Inclusion criteria were patients aged over 16 years, having at least one crescentic glomerulus in the pathology sample, maximal deposition of 1+ immunoglobulins, complements in the glomeruli in immune fluorescent microscopy, and having passed at least six months from the diagnosis of crescentic GN. Exclusion criteria was the lack of follow-up information of the patients.

"Active crescent percentage" was defined as the percentage of cellular and fibrocellular crescents to total number of non-sclerotic glomeruli and "total crescent percentage" was defined as the total number of crescentic glomeruli to total number of glomeruli. The primary outcomes were defined as ESKD and death. Secondary outcomes were defined as complete remission, i.e., serum creatinine less than 1.4 mg/dL, and proteinuria less than 400 mg in 24 hours; partial remission, i.e., more than 50% reduction in serum creatinine (if it is more than 2.3 mg/dL) and proteinuria.[7] Stable CKD was defined as GFR less than 60 mL/min and no change in creatinine during the last year of follow-up and advanced CKD was defined as GFR less than 60 mL/min and more than 50% reduction in GFR in the last follow-up compared to baseline GFR.

Data Analysis Method

Mean and standard deviation were used to present quantitative data with normal distribution. Median and interquartile rang (IQR) were used to present skewed data. Independent samples T- Test and U Mann-whitney were used for comparison of quantitative and Chi-square for comparison of qualitative data. Kaplan Meyer test was used for the evaluation of patient and kidney survival rates and Cox Regression for examination of the relationship between independent variables and the outcome. The receiver operating characteristic

(ROC) curve was plotted for quantitative variables to obtain a numerical cut-off for the effect of the variables on renal outcome, and the relative C-statistics were expressed.

We used SPSS version 16 for data anlysis.

Ethical Consideration

The Ethics Committee of Iran University of Medical Sciences approved the study (IR.IUMS.FMD.REC.1398.395). The informed consent to use the patient's information for research was taken from patients, at the time of admission. The information was recorded anonymously and by coding the patients.

RESULTS

One hundred twenty patients including 59 men and 61 women with pauci-immune crescentic GN were included in the study. The mean duration of follow-up was 44 ± 45.7 months. The mean age was 47 ± 17 years and the mean baseline proteinuria was 3690 ± 3552 mg in 24 hours. The median baseline GFR and mean hemoglobin levels were lower in patients with diffuse vs. focal crescentic GN (8 [8.96] vs. 18.9 [20.94] mL/min and 9.2 ± 1.7 vs. 10.4 ± 2 g/dL, respectively; $P < .001$ and .001, respectively) (Table 1).

Totally, ESKD occurred in 72 patients (60%). End-stage kidney disease occurred in 46 patients at the onset of diagnosis, in 18 patients within two years and only in 7 patients after two years.

Age and proteinuria had no significant association with the development of ESKD ($P = .969$ and .131, respectively). The median baseline GFR (measured in all) was 10.09 (15.02) mL/min and the mean GFR at 4 months (measured in 30 non- ESKD patients), was 41.91 ± 25.21 mL/min. The GFR values at baseline and at 4 months had a significant association with the development of ESKD ($P < .01$). Sixty-three patients (52.5%) underwent dialysis at admission. End-stage kidney disease occurred in 79% of the patients who needed dialysis at admission and in 38% of patients who did not need dialysis. Therefore, the need to dialysis at the disease onset had a significant association with the development of ESKD ($P < .001$). Sixty-two patients (51%) were ANCA positive, 47 (39%) were ANCA negative and in 11 patients (10%) ANCA was not measured. The rate of ESKD was 62.9% in ANCA positive and 55.3% in ANCA negative patients ($P = .424$), i.e., ANCA status showed no significant difference between patients who did or did not end up in ESKD (Table 2).

Pathologic characteristics of the patients are shown in Table 3. The mean total crescent percentage, glomerulosclerosis (GS) and interstitial fibrosis/tubular atrophy (IF/TA) were 45.8 ± 30, 25.4 ± 25.6 and 35.5 ± 23.2 percent, respectively.

Fifty-two patients had diffused and 68 patients had focal pauci-immune crescentic GN. In patients with diffuse pauci-immune crescentic GN, hemoglobin was significantly lower, and baseline serum creatinine, the need for dialysis at the onset of disease and ANCA positivity were significantly higher, compared to patients with focal pauci-immune crescentic GN (Table 1).

In the diffuse form mean, the percentage of GS and IF/TA were 20.1 ± 26.7 and 44.8 ± 26,

Table 1. Demographic, Clinical and Laboratory Characteristics in Pauci-immune Crescentic GN

	Diffuse Pauci-immune Crescentic GN	Focal Pauci-immune Crescentic GN	*P*	Total
Number (%)	52 (43.3)	68 (56.7)		120 (100)
Age, y*	45.7 ± 15.9	48 ± 18.5	.484	47 ± 17
Sex (male / female)	25 / 27	34 / 34	.835	59 / 61
Hypertention ≥ 140/90 mmHg (%)	19 (36.5)	30 (44)	.335	49 (40.8)
Hemoglubin, g/dL*	8.9 ± 1.6	10.3 ± 1.9	< .001	9.7 ± 1.9
Baseline Creatinine, mg/dL**	6.95 (7.32)	4.25 (4.37)	< .001	5.35 (5.2)
Baseline GFR, mL/min**	6.95 (8.96)	12.65 (20.94)	< .001	10.09 (15.02)
GFR at 4 months, mL/min*	38.51 ± 24.1	43.6 ± 26.1	.61	41.9 ± 25.2
Baseline Proteinuria, mg/24h**	2147 (2870)	3145 (4326)	.055	2772 (3530)
Need for Dialysis at the Onset of Disease (%)	36 (69)	27 (39.7)	.001	63 (52)
ANCA Positive (%)	35 (67.3)	27 (39.7)	.011	62 (51.6)

*mean ± standard deviation
**median (interquartile rang)
Abbreviations: GN, glomerulonephritis; GFR, glomerular filtration rate; ANCA, anti neutrophil cytoplasmic antibody.

Table 2. Effect of Age, Laboratory and Pathologic Characteristics on ESKD in Pauci-immune Crescentic GN

	ESKD	NO ESKD	*P*
Number (%)	72 (60)	48 (40)	
Age (year)*	47 ± 19	47.1 ± 15	.969
Initial GFR (mL/min)**	8 (7.1)	18.9 (25.61)	< .001
GFR at 4 months (mL/min)*	22.5 ± 9.077	47.8 ± 25.703	< .001
Hemoglubin (g/dL)*	9.2 ± 1.7	10.4 ± 2	.001
Need for dialysis at admission (%)	69.4	27	< .001
Proteinuria (mg/24h)*	3597 ± 2639	3832 ± 4550	.131
Total crescent percentage (%)*	49.3 ± 29.8	40.5 ± 30.5	.075
Active crescent percentage (%)*	49.8 ± 31.4	41.4 ± 29.6	.076
Percentage of glomerulosclerosis (%)*	32.3 ± 27.2	14.4 ± 18.3	< .001
Percentage of IF/TA*	43.3 ± 22.9	23.6 ± 18.3	< .001
ANCA positive (%)	37 (51.3)	25 (52.2)	.424

*mean ± standard deviation
**median (interquartile rang)
Abbreviations: GN, glomerulonephritis; ESKD, end stage kidney disease; GFR, glomerular filtration rate; IF/TA, interstitial fibrosis/tubular atrophy; ANCA, anti neutrophil cytoplasmic antibody.

Table 3. Pathologic Characteristics in Pauci-immune Crescentic GN

	Diffuse Pauci-immune Crescentic GN	Focal Pauci-immune Crescentic GN	*P*	Total
Number (%)	52 (43.3)	68 (56.7)		120 (100)
Total Crescent Percentage*†	74.1 ± 18.6	24.1 ± 16.3	< .001	45.8 ± 30.3
Active Crescent Percentage*‡	66 ± 28.1	32.1 ± 25.1	< .001	47 ± 31.5
Percentage of Glomerulosclerosis*	20.1 ± 26.7	29.7 ± 24.1	.006	25.4 ± 25.6
Percentage of IF/TA*	44.8 ± 26.2	28.7 ± 18.2	.001	35.5 ± 23.2
Presence of Endocapillary Prolifration (%)	4 (7.6)	13 (19.1)	-	17 (14.1)
Presence of Mesangial Prolifration (%)	2 (3.8)	7 (10.2)	-	9 (7.5)
Presence of Capsular Rupture (%)	21 (40.3)	11 (16.1)	.003	32 (26.6)
Presence of Taft Necrosis (%)	15 (28.8)	15 (22)	.395	30 (25)

*mean ± standard deviation
†percentage of total crescent to total glomeruli
‡percentage of cellular and fibrocellular crescent to non-sclerotic glomeruli
Abbreviations: GN, glomerulonephritis; IF/TA, interstitial fibrosis/tubular atrophy.

respectively. These values were 29.7 ± 24 and 28.7 ± 18.2, in the focal form and with a statistically significant difference (P = .006, .001; respectively) (Table 3).

The frequency of ESKD was 61.5% in patients with diffuse form and 58.8% in those with focal form (P = .764). The frequency of remission (complete or partial) was also not different between diffuse and focal forms (25 and 26%, respectively; P = .26) (Table 4).

According to the Berden classification,[4] in our study, 37 patients (30.8%) were in the focal, 38 patients (31.6%) in the crescentic, 20 patients (16.6%) in the mixed and 25 patients (20.8%) in

Table 4. Outcome of Patients with Pauci-immune Crescentic GN

	Diffuse pauci-immune crescentic GN	Focal pauci-immune crescentic GN	*P*	Total
Number (%)	52 (43.3)	68 (56.7)		120 (100)
Compelet Remision (%)	6 (11.5)	13 (19.1)	.26	19 (15.8)
Partial Remision (%)	7 (13.4)	5 (7.3)	.26	12 (10)
CKD Undependent to Dialysis (%)	5 (9.6)	7 (10.2)	.9	12 (10)
Kidney Transplant (%)	0 (0)	14 (18.6)	-	14 (11.6)
ESKD (Live and Die) (%)	32 (61.5)	40 (58.8)	.764	72 (60)
Death (%)	15 (28.8)	16 (23.5)	.51	31 (25.8)

Abbreviations: GN, glomerulonephritis; CKD, chronic kidney disease; ESKD, end stage kidney disease.

the sclerotic category. The rate of ESKD was 35.1, 60.5, 75 and 84%; in the 4 categories respectively (P = .001) (Table 5).

Only 28 patients (23.3%) had received at least 3 doses of intravenous cyclophosphamide or 3 months of oral cyclophosphamide, which has been defined as the minimum required cyclophosphamide dose in patients with diffuse crescentic GN.[6] We found that 70.7% of patients who did not receive any or the minimum required cyclophosphamide dose developed ESKD compared to 28.5% of patients who had received the minimum required cyclophosphamide dose (P < .001) (Table 6).

By plotting the ROC Curve, we noticed that patients with IF/TA ≥ 25% and total crescent percentage < 55% had been more likely not to receive cyclophosphamide (C-statistics: 0.635 and 0.652, respectively). But, in fact, even in patients with IF/TA ≥ 25%, the development of ESKD was more likely in patients who did not receive cyclophosphamide compared to those who received it (P = .002, OR = 9.33, 95% CI: 2.25 to 38.6). Also, in patients with total crescent percentage < 55%, ESKD was more likely to develop in patients who did not receive cyclophosphamide (P = .065, OR = 3.88, 95% CI: 0.918 to 16.4). From 28 patients who received at least 3 doses of cyclophosphamide, 10 patients had IF/TA 25 to 60% that 7 patients didn't develop ESKD.

One, three, five and ten-year kidney survival rates were 49, 38, 38 and 31%, respectively and the mean and median time of development of ESKD were 6.7 ± 9.7 years and 1 year (range: 0 to 18.4).

One, three, five and ten year patient survival rates were 83, 73, 69 and 67%, respectively. The mean patient survival was 11.4 ± 14.01 years and the median was 14 years (range: 0 to 18.4).

The effect of different parameters on kidney survival were evaluated in patients with pauci-immune crescentic GN, through cox regression analysis.

The need for dialysis at the onset of disease (P < .001, HR = 3.514, 95% CI: 2.071 to 5.962), low hemoglobin level (P = .003, HR = 0.819, 95% CI: 0.717 to 0.935), low baseline GFR (P < .001, HR = 0.963, 95% CI: 0.942 to 0.984), low GFR at 4 months (P = .036, HR = 0.933, 95% CI: 0.875 to 0.996), high percentage of GS (P = .001, HR = 1.015, 95% CI: 1.006 to 1.024), IF/TA ≥ 25% (P = .001, HR = 2.82, 95% CI: 1.55 to 5.11) and failure to receive the minimum required cyclophosphamide dose (P = .002, HR = 0.31, 95% CI: 0.148 to 0.65) were associated with lower kidney survival rates. The percentages of total and active crescents had no significant effect on kidney survival (P > .05). In multivariate analysis, failure to receive the minimum required cyclophosphamide dose, the need for dialysis at the onset of disease and low hemoglobin, were associated with lower kidney survival (HR = 0.290, 2.52, 0.836; respectively, P < .05) (Figure 1).

By plotting the ROC curve to achieve a numerical cut off with the best sensitivity and specificity and with appropriate C Statistics, i.e. greater than 0.7

Table 5. Outcome of Kidney in Pauci-immune Crescentic GN According to Berden Classification

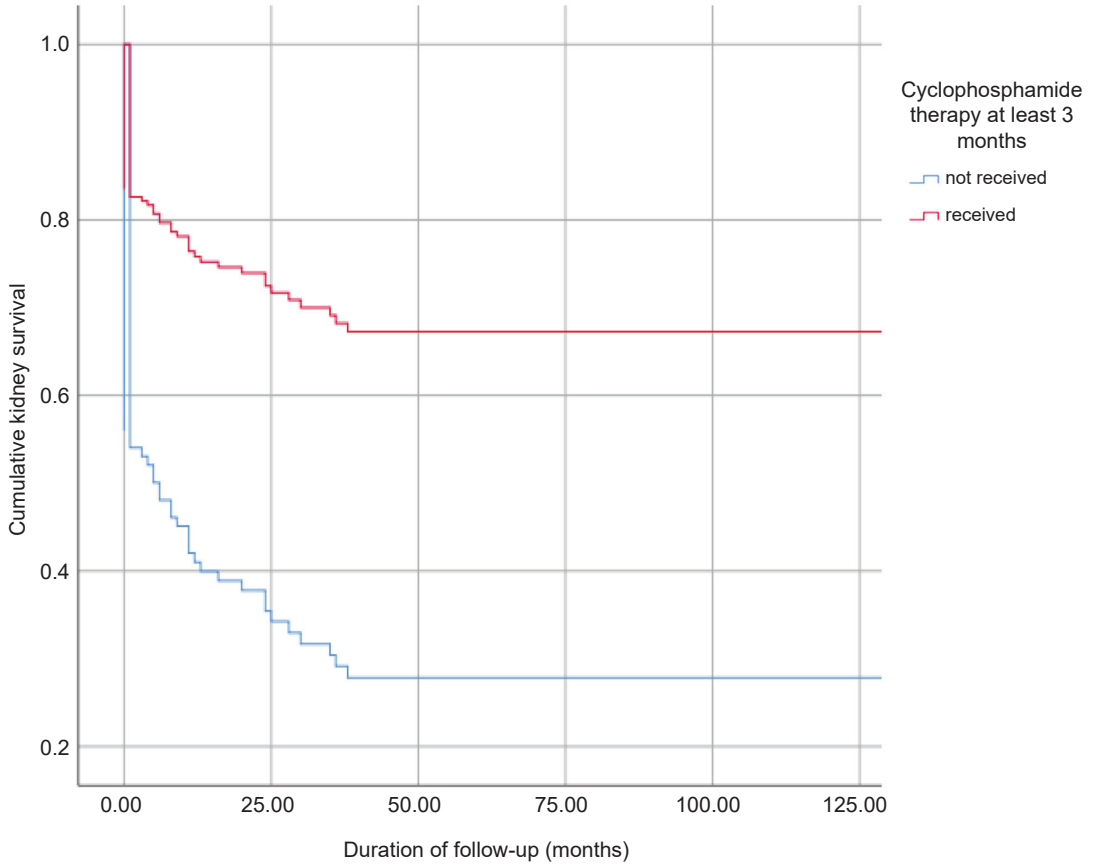
	Number	ESKD Cases (%)	*P*
Focal	37	13 (35.1)	
Crescentic	38	23 (60.5)	
Mixed	20	15 (75)	.001
Sclerotic	25	21 (84)	
Total	120	72 (60)	

Abbreviations: GN, glomerulonephritis; ESKD, end stage kidney disease.

Table 6. Comparison of Characteristics and Outcome of Pauci-immune Crescentic GN Patients With or Without Cyclophosphamide Administration

	With Cyclophosphamide	Without Cyclophosphamide	*P*
Number (%)	28 (23.3)	92 (76.7)	-
ESKD (%)	8 (28.5)	65 (70.7)	< .001
Baseline Creatinin, mg/dL*	3.8 (4.07)	5.7 (5.5)	.187
Baseline GFR, mL/min*	14.63 (14.47)	9.6 (15.15)	.462
Percentage of Glomerolosclerosis*	13.5 (33.2)	26.7 (45.5)	.02
Percentage of IF/TA*	20 (36.25)	40 (40)	.037
Active Crescent Percentage*	57.7 (46)	40 (42)	.137
Total Crescent Percentage*	64.5 (45)	34 (44.75)	.015

*median (interquartile range)
Abbreviations: ESKD, end stage kidney disease; IF/TA, interstitial fibrosis/tubular atrophy; SD, standard deviation.



Kidney Survival in Patients With and Without Cyclophosphamide Therapy

for the factors affecting development of ESKD, IF/TA ≥ 25% (78% sensitivity and 62% specificity), baseline GFR ≤ 15.22 mL/min (60.4% sensitivity and 80.6% specificity) and serum creatinine ≥ 3.8 mg/dL (81% sensitivity and 64% specificity), were associated with the risk of ESKD development, with the C-statistics of 0.741, 0.72, and 0.748; respectively. Glomerulosclerosis ≥ 17% (66% sensitivity and 75% specificity), had an association with ESKD, with a C-statistic of 0.693.

In binary logistic analysis, cyclophosphamide administration was associated with reduced risk of development of ESKD in patients with baseline GFR ≤ 15.22 mL/min (OR = 6.3, 95% CI: 1.82 to 21.83, *P* = .004), serum creatinine ≥ 3.8 mg/dL (OR = 7.06, 95% CI: 2.01 to 24.8, *P* = .002), and GS ≥ 17% (OR = 8.2, 95% CI: 1.89 to 35.4, *P* = .005).

DISCUSSION

In this case series of patients with pauci-immune crescentic GN, 60 percent of patients developed ESKD. We found that the need for dialysis at the onset of disease, baseline GFR, GFR at 4 months, baseline hemoglobin, receiving the minimum required cyclophosphamide dose and percentage of GS and IF/TA in kidney biopsy had significant relationship with kidney survival.

In most studies, on pauci-immune crescentic GN, only patients with diffuse crescentic GN were enrolled.[8-12] We enrolled both patients with focal and diffuse pauci-immune crescentic GN and found no significant difference in development of ESKD between them. Since the main indication for offereing cyclophosphamide to patients with crescentic GN is the diagnosis of diffuse crescentic GN, this finding may indicate that without standard immunosuppresive therapeutic regimens, focal crescentic GN can also have a poor prognosis. High baseline creatinine and unfavorable outcome in these patients suggest that early biopsy and treatment of focal pauci-immune cases should be as aggressive as in diffuse pauci-immune cases.

In the study of Chen *et al.* on 136 cases with diffuse pauci-immune crescentic GN, 45% of patients

developed ESKD, which was lower than the rate of ESKD in our study (60%).[8] This difference may be due to late referral of our patients, who had high mean baseline serum creatinin and advanced chronicity at admission. In the Chen *et al.* study, the rate of GS, which was a crucial factor in the outcome of patients, was 15%, compared to 25% of our case series.[8] On the other hand, 76% of our patients did not receive the minimal necessary three months of cyclophosphamide as a standard therapy, either due to chronicity of disease at admission or low percentage of crescentic glomeruli. As mentioned earlier, administration of adequate doses of cyclophosphamide has a significant effect on kidney outcome.

In our study, the mean kidney survival was 6.7 years and the median kidney survival was 1 year, indicating that most patients developed ESKD at the beginning of diagnosis, which may be due to late referral to nephrologist. The 5- year kidney survival in our study was 38%, in Chen *et al.* study was 44.3% and in Lin *et al.* study was about 40%.[8, 13] The one-year patient survival rate was 83% in our study and in the Heger study was 68%.[14] In our study, the 5-year patient survival rate was 69%, while in Syed *et al.* review article, it was 75%.[15]

Therefore, kidney and patient survival in our study was near to Lin *et al.* and Syed *et al.* studies, respectively.[13, 15] However, they enrolled only diffuse cases, but we evaluated both diffuse and focal cases.

In the Berden study, 35 of 100 patients with ANCA positive pauci-immune crescentic GN developed ESKD and according to Berden classification, focal, crescentic, mixed, and sclerotic groups had the best to worst prognosis, in odrer.[6] In the workshop of international validation study for the histopathological classification of ANCA-associated glomerulonephritis (AAGN) in 2017, a number of studies on pauci-immune crescentic GN which had classified the patients as Berden classification, were reviewed.[16] In Daalen *et al.* study, 1 and 5-year kidney survival were not significantly different in crescentic and mixed categories.[16] In Ogawa *et al.* and Endo *et al.* studies , tubular atrophy had significant effect on kidney survival, which is in contrast to the Berden study.[16] In our study, similar to Berden's, the lowest to highest ESKD rates were observed in focal, crescentic, mixed, and sclerotic groups, respectively.

Additionally, we showed that the percentage of IF/TA at admission, affects the kidney survival of patients with pauci-immune crescentic GN. In the study by Piyaphanee *et al*, IF/TA more than 20% was a risk factor of ESKD.[17] So, we recommend to include the deree of interstitial fibrosis and tubular atrophy in any prognostic pathologic classification of pauci-immune crescentic GN.

In our study, similar to Kantauskaite *et al.* study, positivity of ANCA did not have any effect on patients' outcome,.[18] But in Sharma *et al.* study, patients with a negative ANCA had worse prognosis.[19] These differences can be due to variability of laboratory kits or differences in race and genetic characteristics.

Regarding the poor prognostic factors in crescentic GN, Chen *et al,* showed oliguria, high serum creatinine, high percentage of GS, crescentic glomeruli and interstitial inflammation as baseline factors were associated with the development of ESKD.[8] In Syed *et al.*, a review article, high baseline creatinine and the need for dialysis at the onset of disease, correlated with poor prognosis.[15] In Berden's study, higher IF/TA had no effect on renal survival.[6] In other studies, crescent formation in more than 80% of glomeruli, creatinine more than 5.8 mg/dL, baseline oliguria, age over 60 years, high blood pressure, the need for hemodialysis at the onset of disease, high percentage of fibrous and fibrocellular crescents and circumferential crescents were associated with poor prognosis.[9, 10, 20- 22] Thus, high baseline creatinine, the need for hemodialysis at the onset of disease, high GS and IF/TA are common prognostic factors in our and most other studies.[9, 10, 20- 23]

In our study the percentages of GS and IF/TA, were higher than similar studies, that probably led to the inferior outcome of our patients.[9, 10, 22] Also, in a number of studies, the percentage of fibrocellular and fibrous crescents and not cellular crescents affected the kidney prognosis.[9, 10, 22] So, as histological point of view, it seems that in kidney biopsy, "chronicity" is the dominant prognostic factor in pauci-immune crescentic GN.

In our study, failure to receive cyclophosphamide had an assosciation with development of ESKD, in multivariate cox reggresion analysis. We found out that the total crescent percentage less than 55% and IF/TA more than 25% discouraged physicians from administrating cyclophosphamide. Our analysis

showed that in both settings of low crescent precentage and high IF/TA, cyclophosphamide administration may be still effective and have association with low incidence of ESKD (P = .002, OR = 9.33, for IF/TA ≥ 25% and; P = .065, OR = 3.88 for total crescents < 55%).

Therefore, in spite of the toxicity of cyclophosphamide that may make the physicians reluctant to administer cyclophosphamide in patients with focal crescentic GN or those with IF/TA ≥ 25%, we recommend to try at least 3 monthly doses of intravenous cyclophosphamide in these patients.

In a study in Lithuania by Kantauskaite *et al.*, in 86 crescentic GN patients that all recieved immunosuppressive therapy, GFR less than 15 mL/min and sclerotic category had a significant adverse effect on renal survival, and the authors concluded that conservative treatment might be associated with better prognosis and fewer treatment complications.[18] In our study baseline GFR less than 15.22 mL/min, IF/TA more than 25%, GS more than 17% and baseline creatinine more than 3.8 mg/dL, were associated with ESKD and predicted poor prognosis. However, patients who have these poor prognostic factors should not be deprived from invasive treatment and cyclophosphamide administration.

Limitations

A number of patients had been followed in other centers and were not

accessible for outcome evaluation. The induction immunosuporessive regimen was limited to cyclophosphamide and prednisolone and the effect of rituximab could not be compared with cyclophosphamide, due to non- inclusion of this drug in the therapeutic guidleines of pauci-immune crescentic GN during the study period.

CONCLUSIONS

In our study, the need for dialysis at the beginning of presentation, low initial hemoglobin and high serum creatinine levels, percentage of glomerulosclerosis and interstitial fibrosis and tubular atrophy, and failure to receive cyclophosphamide were associated with development of ESKD.

We believe that the unfavorable prognosis of our patients has been mainly due to late referral and advanced chronicity in a number of patients, in addition to unwillingness of the physicians to deliver standard cyclophosphamide regimen to patients with low number of crescents, and believing that adverse effects may overcome the benefits.

Early referral of suspected patients and timely administration of cyclophosphamide, even in patients with low percentage of crescentic glomeruli or an IF/TA percentage of 25 to 60% are recommended, to improve the prognosis of pauci-immune crescentic GN.

CONFLICT OF INTEREST

The authors have no conflict of interest related to this study.

REFERENCES

1. Appel GB, Kaplan AA. Overview of the classification and treatment of rapidly progressive (crescentic) glomerulonephritis.2019. Available at: https://www.uptodate.com/contents/overview-of-the-classification-and-treatment-of-rapidLy-progressive-crescentic-glomerulonephritis. [Accessed 4/24/2021]
2. Ossareh S, Asgari M, Abdi E, et al. Renal biopsy findings in Iran: case series report from a referral kidney center. Int Urol Nephrol. 2010;42(4):1031-1040. doi:10.1007/s11255-009-9684-0
3. Pettersson EE, Sundelin B, Heigl Z. Incidence and outcome of pauci-immune necrotizing and crescentic glomerulonephritis in adults. Clin Nephrol. 1995;43(3):141-149.
4. Pendergraft WF, Nachman PH, Jennette JC, Falk RJ. Primary glomerular disease. Brenner & Rector`s the kidney. 10th ed. Elsevier: Jeffrey Patterson. 2016. P: 1072 & 1086.
5. Crescentic glomerulonephritis (proliferative extracapillary). Available at: https://www.kidneypathology.com/English_version/Crescentic_GN.html. [Accessed 4/24/2021]
6. Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol. 2010;21(10):1628-1636. doi:10.1681/ASN.2010050477
7. Choudhury TA, Singh RG; Usha, et al. Clinicopathologic spectrum of crescentic glomerulonephritis: a hospital-based study. Saudi J Kidney Dis Transpl. 2014;25(3):689-696. doi:10.4103/1319-2442.132241
8. Chen S, Tang Z, Xiang H, et al. Etiology and Outcome of Crescentic Glomerulonephritis From a Single Center in China: A 10-Year Review. Am J Kidney Dis. 2016;67(3):376-383. doi:10.1053/j.ajkd.2015.07.034
9. Nagaraju SP, Laxminarayana SLK, Kosuru S, et al. Clinicopathological Characteristics and Outcomes of Diffuse Crescentic Glomerulonephritis - A Single Center Experience from Southern India. J Clin Diagn Res. 2017;11(9):OC21-OC24. doi:10.7860/JCDR/2017/28307.10621

10. Faye M, Lemrabott AT, Fall Kh, et al. Crescentic Glomerulonephritis in a Sub-Saharan Country: Clinical Presentation, Etiological and Evolutive Profile. Nephro-Urol Mon. 2017; 9(6):e60365. DOI : 10.5812/numonthly.60365
11. Wu T, Jiajia Peng J, Meng T, et al. Clinicopathological features and prognostic analysis of 49 cases with crescentic glomerulonephritis. Exp Ther Med. 2019;Nov; 18(5): 3984–3990. DOI: 10.3892/etm.2019.8023.
12. Prakash J, Patel PS, Prakash S, et al. Etiopathological Study of Crescentic Glomerulonephritis and its Outcome: A Retrospective Analysis. Journal of The Association of Physicians of India. 2019;67(11): 18-21. PMID: 31793263
13. Lin W, Chen M, Cui Z, Zhao H. The Immunopathological Spectrum of Crescentic Glomerulonephritis: A Survey of 106 Patients in a Single Chinese Center. Nephron Clinical Practice. 2010;116(1): 65-74. DOI: 10.1159/000314665
14. Hedger N, Stevens J, Drey N, Walker S, Roderick P. Incidence and outcome of pauci-immune rapidLy progressive glomerulonephritis in Wessex, UK: a 10-year retrospective study. Nephrol Dial Transplant. 2000;15: 1593–1599. DOI:10.1093/ndt/15.10.1593
15. Syed R, Rehman A, Valecha G, Sayegh SE. Pauci-Immune Crescentic Glomerulonephritis: An ANCA-Associated Vasculitis. Review Article. BioMed Research International. Volume 2015. DOI: 10.1155/2015/402826
16. Van Daalen EE, Ferrario F, Noel LH, et al. WS9_1 International Validation Study for the Histopathological Classification of ANCA-Associated Glomerulonephritis (AAGN), Rheumatology. 2017;Volume 56, Issue suppl_3, March, Pages iii37–iii39. DOI: 10.1093/rheumatology/kex123
17. Piyaphanee N, Ananboontarick C, Supavekin S, Sumboonnanonda A. Renal outcomes and risk factors for ESRD in children with rapidly progressive glomerulonephritis. Pediatr Int. 2017;59(3): 334-341. DOI:10.1111/ped.13140
18. Kantauskaitė M, Laučytė-Cibulskienė A, Miglinas M. Histopathological Classification-A Prognostic Tool for RapidLy Progressive Glomerulonephritis. Medicina (Kaunas). 2018;54(2):17. DOI:10.3390/medicina54020017
19. Sharma A, Nada R, Naidu GS, et al. Pauci-immune glomerulonephritis: does negativity of anti-neutrophilic cytoplasmic antibodies matters?. Int J Rheum Dis. 2016;19(1):74-81. DOI: 10.1111/1756-185X.12729
20. Parmar MS, Bashir K. Crescentric Glomerulonephritis. [Updated 2019 Mar 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Jan. Available at: https://www.ncbi.nlm.nih.gov/books/NBK430727. [Accessed 4/24/2021]
21. Roy RR, Arju J, Sultana J, et al. Clinicopathological Spectrum and Treatment Outcome of Clinically Suspected RapidLy Progressive Glomerulonephritis: An Analysis of 35 Cases in a Tertiary Care Center, Bangladesh. J Ped Nephrol. 2019;7(3): 1-8. DOI: 10.22037/jpn.v7i3.26366
22. Rampelli SK, Rajesh NG, Srinivas BH, et al. Clinical spectrum and outcomes of crescentic glomerulonephritis: A single center experience. Indian J Nephrol. 2016;26(4): 252–256. DOI:10.4103/0971-4065.158574
23. Gigantei A, Salvianp C, Giannakakis K, et al. 2012. Letter To The Editor, Clinical and Histological Outcome Predictors In Renal Limited Pauci-Immune Crescentic Glomerulonephritis: A Single Centre Experience. Int. J. Immunopathol. Pharmacol. 2012;25(1): 287-292. DOI: 10.1177/039463201202500133

Correspondence to:
Sharzad Ossareh, MD
Professor of Medicine, Director of Nephrology and Fellowship Program, Hasheminejad Kidney Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
ORCID ID:0000-0003-3020-9465
Address: Vanak sq., Tehran 1969714713-Iran
Tel: 0098 21 8864 4420
Fax: 0098 21 8864 4441
E-mail : ossareh_s@hotmail.com

Received August 2023
Revised September 2023
Accepted November 2023