

Rapidly Progressive Glomerulonephritis: A Single-Center Experience

Hızlı İlerleyen Glomerülonefritler: Tek Merkez Deneyimi

ABSTRACT

OBJECTIVE: Rapidly progressive glomerulonephritis is associated with rapid deterioration of kidney function. We aimed to evaluate patients followed-up with the diagnosis of rapidly progressive glomerulonephritis.

MATERIAL and METHODS: This retrospective study included 28 patients who were compared for remission status and baseline serum creatinine levels.

RESULTS: We evaluated 20 male and 8 female patients with a mean age of 46.68 ±15.94 years. Patients with higher baseline serum creatinine had significantly lower hemoglobin (p=0.01), platelet counts (p=0.01) and calculated e- GFR at last hospital visit (p=0.03) compared to patients with lower baseline serum creatinine. At discharge, the number of dialysis-dependent patients was significantly higher in the patients with higher baseline serum creatinine than the patients with lower baseline serum creatinine (p=0.01). Patients who had achieved remission had significantly lower percentage of cellular crescents (p= 0.009) and sclerotic glomeruli (p= 0.04) than patients who did not achieve remission. Dead patients were more likely to have a lymphocyte count of < 1000 cells/mm³ (p=0.009).

CONCLUSION: Patients with high baseline serum creatinine levels were more likely to have lower hemoglobin levels and platelet counts. High baseline serum creatinine level and high percentage of cellular crescents and sclerotic glomeruli were related to worse renal prognosis. Patients with lower lymphocyte counts had higher mortality rates.

KEY WORDS: Rapidly progressive glomerulonephritis, Crescentic glomerulonephritis, Remission, Lymphocyte count

ÖZ

AMAÇ: Hızlı ilerleyen glomerülonefritler böbrek fonksiyonlarının hızlı kaybı ile ilişkilidir. Hızlı ilerleyen glomerülonefrit tanısıyla takip edilen hastaları değerlendirmeyi amaçladık.

GEREÇ ve YÖNTEMLER: Bu retrospektif çalışma 28 hastayı kapsadı. Hastalar remisyon durumları ve başvuru bazal serum kreatinin seviyeleri açısından karşılaştırıldı.

BULGULAR: Ortalama yaşları 46,68±15,94 yıl olan yirmi erkek, sekiz kadın hasta değerlendirildi. Bazal serum kreatinin seviyesi yüksek olan hastaların hemoglobin seviyeleri (p=0,01) ve platelet sayıları (p=0,01) bazal serum kreatinin seviyesi düşük olan hastalara göre anlamlı olarak daha düşüktü. Bazal serum kreatinin seviyesi yüksek olan hastaların son hastane başvurusunda hesaplanan e- GFR değerleri, bazal serum kreatinin seviyesi düşük olan hastalara göre anlamlı olarak daha düşüktü (p=0,03). Taburculuk esnasında diyaliz bağımlı hasta sayısı, bazal serum kreatinin seviyesi yüksek olan hastalarda, bazal serum kreatinin düşük olan hastalara göre anlamlı olarak daha yüksekti (p=0,01). Remisyon sağlanan hastalarda remisyon sağlanamayanlara göre ortalama sellüler kresent yüzdesi (p=0,009) ve sklerotik glomerül yüzdesi (p=0,04) anlamlı olarak daha düşüktü. Ölen hastaların lenfosit sayılarının 1000 hücre/mm³ altında olma ihtimali daha yüksekti (p=0,009).

SONUÇ: Serimizde bazal serum kreatinin seviyesi yüksek olan hastalarda hemoglobin seviyesi, platelet sayısı düşük saptandı. Yüksek bazal serum kreatinin seviyesi, yüksek sellüler kresent ve sklerotik glomerül yüzdelere kötü renal prognoz ile ilişkili olduğu saptandı. Ölen hastaların daha düşük lenfosit sayısına sahip oldukları gösterildi.

ANAHTAR SÖZCÜKLER: Hızlı ilerleyen glomerülonefritler, Kresentrik glomerülonefritler, Remisyon, Lenfosit sayısı

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BACKGROUND

Rapidly progressive glomerulonephritis (RPGN) as a cause of acute kidney injury is associated with rapid deterioration of kidney function and poorer prognosis. Therefore, early diagnosis of RPGN is very essential for a rapid therapeutic intervention (1,2). RPGN and crescentic glomerulonephritis (CGN) are synonymous expressions. CGN is categorized based on the pattern of immunoglobulin deposition by immunohistochemistry and the categories are anti-glomerular basement membrane (anti-GBM) disease, pauci-immune CGN (usually anti-neutrophil cytoplasmic antibody (ANCA)-associated) and immune complex type CGN (3). Current treatments improve the prognosis of RPGN, but affected patients remain at a substantially higher risk of death and adverse outcomes (4,5).

Our purpose in this study was to evaluate patients presented with CGN, their clinical characteristics and histopathological features in a population from a tertiary nephrology center.

MATERIAL and METHOD

Patients

This is a retrospective study on patients diagnosed with CGN and followed up at a single nephrology center. From May 2010 till May 2015, CGN was diagnosed in 28 patients.

Diagnosis and follow-up

Kidney biopsies were performed in all patients with a normal kidney size who presented with active urinary sediment, proteinuria and decreased glomerular filtration rate (GFR). "Active urinary sediment" was defined by the presence dysmorphic red blood cells (80% of the erythrocytes) or erythrocyte casts (one or more red blood cell casts/50 lpf) in urine microscopy. The kidney biopsies were performed percutaneously using an automated gun guided by ultrasound.

The biopsy samples were processed using a light microscopy and immunofluorescence examination. The pathologic definition of CGN was established with the presence of crescents in > 50% of glomeruli, which were identified under light microscopy by the presence of at least two layers of cells in Bowman's space.

The patients' data collected include age, gender, duration of hospital stay, intensive care stay, mortality, time from the onset of symptoms to hospitalization, time from hospitalization to diagnosis, time from diagnosis to biopsy, time from biopsy to cyclophosphamide; laboratory parameters including hemogram, lipid profile, renal function tests, albumin, total protein, light microscopic findings; tubular atrophy, interstitial fibrosis, percentage of cellular crescent (ratio of cellular crescents to non-sclerotic glomeruli), percentage of sclerotic glomeruli (ratio of sclerotic glomeruli to total glomeruli) and number of patients with fibrotic glomeruli; immunofluorescence findings such as IgG, IgA, IgM, kappa, lambda, fibrinogen, C3 and C1q, serology

for human immunodeficiency virus and hepatitis C virus and hepatitis B surface antigen; an autoimmune panel including complement levels (C3/C4), anti nuclear antibody (ANA), double stranded DNA (dsDNA), anti-neutrophil cytoplasmic antibody (as Anti-MPO and Anti-PR3), and anti-GBM antibody.

Charlson Comorbidity Scores were calculated for the patients and they were grouped as 0-1-2 according to the resulting comorbidity scores (6)

Remission was defined as the level of serum creatinine <1.4 mg/dL and defined as proteinuria of < 0.3 g per 24 hours. Partial remission was defined as proteinuria >0.3 but <3.5 g per 24 hours or a decrease in proteinuria by at least 50% from the initial value and <3.5 g per 24 hours (7).

Statistical Analysis

Patients were compared regarding remission and baseline serum creatinine (the cut-off point 2.5 mg/dL). The statistical software R was used for statistical analysis. Descriptive statistical methods (mean, median, standard deviation, minimum, maximum, frequency, percentage) were used in order to evaluate study data. The Mann-Whitney U test was used in order to compare parameters without normal distribution. Chi-Square and Fisher's Exact tests were used in order to compare qualitative data. The Wilcoxon Signed Ranks test was used for intra-group comparisons of parameters with no normal distribution. A p-value of <0.05 was considered significant.

RESULTS

Among the 28 patients with CGN, 20 were male and 8 were female, with a mean age of 46.68 ± 15.94 years. The mean duration from the onset of symptoms to hospitalization and the mean follow-up time were 11.04 ± 12.16 days and 16.93 ± 14.52 months, respectively. The laboratory results at baseline and at the last hospital visit are shown in Table I.

Comparison of patients with high (creatinine >2.5 mg/dL) and low (creatinine \leq 2.5 mg/dL) baseline serum creatinine is shown in Table II. Patients with higher baseline serum creatinine levels had significantly lower hemoglobin levels ($p=0.01$) and platelet counts ($p=0.01$) compared to patients with lower baseline serum creatinine levels. The e-GFR at the last hospital visit was significantly lower in patients with higher baseline serum creatinine levels ($p=0.03$). In addition, the patients with higher baseline creatinine levels were more likely to be dialysis-dependent at hospital discharge after the first presentation ($p=0.01$). However, there was no statistically significant difference between age, gender, Charlson Comorbidity Score, baseline proteinuria, time to biopsy, time to cyclophosphamide, symptoms duration before hospitalization and pathological findings consisting of tubular atrophy, interstitial fibrosis, number of patients with fibrotic crescents, percentage of cellular crescents and percentage of sclerotic glomeruli.

Table I: Laboratory parameters at baseline and last hospital visit.

Parameters	Baseline	Last hospital visit	p
Creatinine (mg/dL)	3.71 ± 2.92	2.49 ± 2.16	0.04 ¹
e-GFR (ml/min/1.73 m ²)	39.65 ± 30.86	59.07 ± 33.07	0.08 ¹
Proteinuria (g/day)	8.96 ± 15.73	1.39 ± 1.57	0.00 ¹
White blood cell (/mm ³)	9557.31 ± 3617.16	10208 ± 4329.90	0.77 ¹
Hemoglobin (gr/dL)	10.82 ± 2.11	11.80 ± 2.27	0.10 ¹
Platelet count (/μL)	256238.46 ± 82267.21	267608 ± 143234.4	0.79 ¹
Total protein (g/ dL)	6.18 ± 0.94	6.56 ± 1.19	0.17 ¹
Albumin (g/ dL)	2.75 ± 0.79	3.62 ± 0.95	0.00 ¹
Total cholesterol (mg/ dL)	182.52 ± 64.75	215.5 ± 68.07	0.09 ¹
Low density lipoprotein (mg/ dL)	120.63 ± 56.43	131.67 ± 51.34	0.34 ¹
High density lipoprotein (mg/ dL)	34.57 ± 12.45	44.08 ± 16.09	0.04 ¹
Triglyceride (mg/ dL)	143.05 ± 63.84	208.55 ± 76.93	0.02 ¹
1: Mann-Whitney U Test for Dependent Samples			

e- GFR: estimated glomerular filtration rate.

Table II: Comparison of patients regarding baseline serum creatinine.

Parameters	Creatinine≤2.5 g/dL (n=11)	Creatinine>2.5 g/dL (n=15)	p
Age (years)	46.76 ± 15.96	51.0±17.05	0.47 ¹
Gender			
Male	13	5	0.76 ²
Female	4	3	
Time to cyclophosphamide (days)	20.27 ± 14.65	10.13 ± 6.01	0.12 ¹
Symptoms duration (days)	16.79 ± 12.40	13.5 ± 9.53	0.90 ¹
Baseline Proteinuria (g/dL)	4.30 ± 4.17	16.34 ± 25.57	0.36 ¹
Hemoglobin Level (Mean, SD)	12.01 ± 2.21	9.95 ± 1.59	0.01 ¹
Platelet Count (Mean, SD)	301909 ± 60417.64	222747 ± 81470.89	0.01 ¹
Dialysis Dependency [^]			
Absent	10	5	0.01 ²
Present	1	8	
e- GFR (ml/min/1.73 m ²)*	72.18 ± 29.10	48.98 ± 33.41	0.03 ¹
1: Mann-Whitney U Test, 2: Fisher's Exact Test,			

e- GFR: estimated glomerular filtration rate, ^: at discharge, *: at last hospital visit.

After hospitalization; the mean duration to renal biopsy was 5.07±6.99 days. The average number of glomeruli obtained per renal biopsy specimen was 15.13±7.27. The number of patients diagnosed with pauci-immune and immune complex CGN were 20 and 6; respectively. No patient with anti-GBM disease was

diagnosed. The mean percentage of sclerotic glomeruli, cellular crescents and the number of patients with fibrotic crescents were 15.39 ± 18.62, 63.15 ± 25.96 and 7, respectively. The percentages of glomeruli with mild (<25%), moderate (25%-50%) and severe (>50%) sclerosis were 32.1%, 17.9% and

3.6%, respectively. The proportions of mild, moderate and no interstitial fibrosis were 14.3%, 7.1% and 78.6%, respectively. The percentage of mild, moderate, severe and no tubular atrophy were 53.6%, 21.4%, 3.6% and 21.4%, respectively. Necrosis was seen in 60.7% of the biopsy samples. Complement 3 and immune complex depositions were seen in 32.1% and 32.1% of biopsy specimens, respectively.

The ANCA status of patients was also evaluated. No patients had c-ANCA positivity. However, 5 patients had p-ANCA positivity. One patient had both p-ANCA and anti-GBM antibody positivity. Only one patient had anti-GBM antibody positivity. Besides renal involvement, pulmonary (pulmonary hemorrhage and nodules), dermal (purpura and petechiae), cerebral (alteration of state of consciousness) and gastrointestinal (gastrointestinal hemorrhage) involvement with vasculitis were documented in 4, 3, 1 and 1 patients, respectively. Diabetes mellitus was the only treatment-related side effect; it was seen in one patient and managed with insulin.

The mean duration from hospitalization to cyclophosphamide treatment was 13.75 ± 13.53 days. Three patients had history of tuberculosis infection and primary isoniazid prophylaxis was commenced. Two patients underwent plasma exchange. Rituximab infusion (375 mg/m^2) was given to 2 patients for rescue treatment.

The mean duration from diagnosis to remission was 1.75 ± 3.75 months. Eight and six patients had complete and partial remission, respectively. Nine patients did not respond to the treatment. Two deaths were observed after the first presentation with CGN. Three patients' follow-up data were unavailable. Comparison of patients regarding remission status yielded no statistically significant difference between age, gender, leukocyte count, hemoglobin level, platelet count, lymphocyte count, Charlson Comorbidity Score, baseline serum creatinine and proteinuria, time to biopsy, time to cyclophosphamide, symptoms duration before hospitalization and pathological findings consisting of tubular atrophy, interstitial fibrosis the number of patients with fibrotic glomeruli. However, patients who had achieved remission had significantly lower percentage of cellular crescents ($p=0.009$) and sclerotic glomeruli ($p=0.04$) than patients who did not achieve remission. The percentage of cellular crescents in patients who achieved remission and those who did not achieve remission were 50.73 ± 21.96 and 80.08 ± 22.10 , respectively. The percentage of sclerotic glomeruli in patients who achieved remission and those who did not achieve remission were 6.38 ± 9.42 and 27.75 ± 23.71 , respectively.

Four patients were followed up in intensive care unit at their first presentation. Of these four patients, two patients died: one from pneumonia and the other from respiratory insufficiency which was a result of alveolar hemorrhage. Another patient died at the fifth month. Previous lymphocyte counts were evaluated with regard to mortality. The patients with the lowest number

of lymphocytes were those who died and with a lymphocyte counts of 430 cells/mm^3 and 440 cells/mm^3 . Measurement of lymphocyte counts in dead patients was more likely to be below 1000 cells/mm^3 ($p=0.009$) and these patients with lower lymphocyte counts were more likely to die (100 % versus 20%), but the difference was not statistically significant ($p=0.065$).

DISCUSSION

Considering the etiology of CGN, our study revealed that ANCA-associated CGN was the most common variety, followed by immune complex type CGN. The etiology of CGN may be influenced by geographic location (8). A study conducted in China showed that immune complex glomerulonephritis was more common than ANCA-associated CGN among patients diagnosed with diffuse CGN (9). In western countries, ANCA-associated CGN was found as the most common form (10). Our study results are therefore consistent with the results of western studies.

In our study, the patients with higher baseline serum creatinine levels had lower hemoglobin levels and platelet counts compared to patients with lower baseline serum creatinine levels. A study by Ozturk et al. compared patients who presented with baseline serum creatinine level of $\leq 4.2 \text{ mg/dL}$ and serum creatinine level of $> 4.2 \text{ mg/dL}$ (11). In this study, the hemoglobin level was statistically lower in patients with a serum creatinine level of $> 4.2 \text{ mg/dL}$. However, no result for platelet count was documented in their study.

In our study, patients with higher baseline serum creatinine level at presentation were more likely to have lower e-GFR at last hospital visit and they were also more likely to be dialysis-dependent at hospital discharge. The relation between higher baseline serum creatinine levels and poor renal prognosis was also reported by several studies (12-14). In the study by Ozturk et al. the percentage of dialysis-dependent patients at the time of diagnosis was 95.5% in the group with a baseline serum creatinine level of $> 4.2 \text{ mg/dL}$. Our patients' renal condition was better than the patients in the study of Ozturk et al. and our result at the time of diagnosis in the group with baseline serum creatinine level of $> 2.5 \text{ mg/dL}$ was 62% for dialysis dependency. One-year kidney survival rate was 51% in the study of Ozturk et al. In our series the percentage of patients with complete or partial remission at last hospital visit was 61% and the mean follow up time was 16.93 ± 14.52 months.

High baseline serum creatinine level was documented as a poor prognostic factor for survival in vasculitis patients (15,16). The sample size of our study was small and intrahospital mortality was observed in two patients after presentation with CGN (two and one months after diagnosis; respectively). In another patient, mortality was observed five months after the diagnosis. Thus, it was statistically impossible to determine a significant relationship between mortality and e-GFR at the last hospital visit. However, we evaluated whether any relationship

exists between mortality and lymphocyte count. A study by Izaks et al. evaluated 436 community-dwelling residents older than 85 years and found increased mortality in patients with lower lymphocyte counts (17). In our study, it has been also demonstrated that there were lower lymphocyte counts in patients who died.

The previously mentioned study by Hogan et al. (12) underlines the importance of early initiation of therapy in order to decrease glomerular inflammation and renal insufficiency. The study by Ozturk et al. demonstrated significantly longer duration from hospitalization to diagnosis in those who developed ESRD, compared to those who did not develop ESRD. In our study, we evaluated three time periods in order to evaluate whether any relationship exists between early or late initiation of treatment and remission. However, we found no statistically significant difference for symptom duration before hospitalization, time to biopsy and time to cyclophosphamide in terms of remission status.

In our study, the patients who did not achieve remission had higher percentage of cellular crescents and sclerotic glomeruli compared to those who achieved remission. Franssen et al. showed that glomerular sclerosis did not differ between patients with favorable renal outcome and those who developed chronic renal failure (18). Another study by Hogan et al. showed that glomerular crescents and glomerular sclerosis has no effect on renal survival (12). On the another hand, Ozturk et al. demonstrated that patients who developed end stage renal failure had higher percentage of crescents than those who did not develop end stage renal failure (11).

The mean baseline proteinuria of our patients was 8.96 ± 15.73 g/day which is higher than expected for CGN. The proteinuria results of three patients (52.7 g/day, 16.29 g/day, 61.74 g/day) might contribute to this high degree of proteinuria. The mean serum total protein was higher than the mean serum albumin. Taking into account the decreased albumin/globulin ratio, all patients with decreased albumin/globulin ratio and suspicion of paraproteinemia were evaluated for paraproteinemia but no patient was found to have paraproteinemia.

The limitations of our study include the small sample size and retrospective nature. The findings should be considered in the context of these limitations.

In conclusion, patients with higher baseline serum creatinine level were more likely to have lower hemoglobin levels and lower platelet counts in our series. Patients with lower lymphocyte counts had higher mortality rates. The relation between higher baseline serum creatinine level and poor renal prognosis was documented. There was also a relation between remission status and percentage of cellular crescents or sclerotic glomeruli.

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