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Clinico-Pathological Spectrum of Non Lupus Crescentic Glomerulonephritis in a tertiary care centre of eastern India

Atanu Pal^{1,*}, K. L. Karmakar², Anirban Sen¹ & Arabinda Das³

¹Department of Nephrology, Institute of Post Graduate Medical Education & Research, Kolkata – 700 020

²Department of Nephrology, R G Kar Medical College and Hospital, Kolkata – 700 004

³Department of Statistics, Acharya Prafulla Chandra College, Kolkata – 700 131

*Corresponding author: Atanu Pal, Assistant Professor, Department of Nephrology, Institute of Post Graduate Medical Education & Research, Kolkata – 700 020. Email: dratanupal@gmail.com

Abstract

CrGN is a medical emergency with catastrophic renal prognosis even with earliest aggressive therapy and magnitude of the problem (CrGN) is not available in the eastern part of India. In this study we have evaluated the clinical profile and histomorphological evolution of Crescentic glomerulonephritis of any cause except Lupus and outcome by using European League Against Rheumatism (EULAR) Protocol therapy among different age, sex population at the Department of Nephrology, IPGME&R and SSKM Hospital, Kolkata over a period of two years. Patients were evaluated for arthritis, serositis, oedema, manifestations of renal failure, oliguria, hematuria besides other clinical examination. Most common organ involved in CrGN is the kidneys, followed by lungs, while fever is the most common non specific symptom in our study. Among the renal manifestations, oliguria, rise in serum creatinine and sub-nephrotic range proteinuria were the most common symptoms. Oliguria was the commonest presentation in all the groups of CrGN. Renal dysfunction was present in the entire group.

Keywords: Glomerulonephritis , extracapillary proliferation

Introduction

Crescentic Glomerulonephritis (CrGN) is defined as crescents involving more than 50% of the glomeruli in biopsy specimens [1]. Histologically it is characterized by extracapillary proliferation and segmental Glomerular necrosis. CrGN is a Medical Renal Emergency with catastrophic renal prognosis even with earliest aggressive therapy. CrGN is not a specific disease but rather a morphologic expression of severe glomerular injury that can be caused by many different aetiologies and pathogenic mechanisms. ^[1] Magnitude of the problem (CrGN) is not available in the eastern part of India.

On the basis of immunopathologic findings, CrGN can be classified into five major categories: immune complex glomerulonephritis (ICGN), anti-Glomerular basement membrane antibody glomerulonephritis (AntiGBM) and pauci-immune glomerulonephritis (PiGN), combination of immune complex and pauci-immune GN and ANCA (Anti Neutrophil Cytoplasmic Antibody) negative renal limited vasculitis [1,2]. PiGN is the most common cause of crescentic pathology with Rapidly Progressive Glomerulonephritis (RPGN), followed in most series by Systemic Lupus Nephritis (SLE) and anti-GBM disease [3]. IgA disease is the most common primary GN in which we find crescents, but rarely presents clinically with RPGN [4]. This consideration prompted us to analyze our recent local experiences with CrGN. The prognosis of CrGN correlates directly with

the percentage of crescents, nature of crescents and degree of tubulo-interstitial fibrosis, however, the prognostic significance of a given percentage crescents is not the same in different categories [5].

In this present study, we have evaluated the clinical profile and histo-morphological evolution of CrGN of any cause except Lupus in all age groups in this part of our country.

Materials and Methods

This was a prospective observational single centre study over a period of two years conducted in the Department of Nephrology, IPGME&R and SSKM Hospital, Kolkata. Patients were evaluated at presentation regarding clinical data including age, sex, skin or throat infection, blood pressure, systemic manifestations such as skin rash, arthritis, serositis, oedema, manifestations of renal failure, oliguria, hematuria and history of medications. Laboratory parameters recorded were including urinalysis, serum creatinine, Urea, Sodium, Potassium Calcium, Phosphorus, Uric acid, complete blood count, plasma proteins, albumin, cholesterol, Anti Streptolysine O (ASO), Anti Nuclear Antibody (ANA), Complement 3 (C3), Anti Double Stranded Nuclear Antibody (anti ds-DNA) and 24 hour urinary protein excretion. ANCA and anti-GBM were done for all the patients. Informed and written consent were taken before doing the renal biopsy. Percutaneous renal biopsy was done by strict surgical aseptic procedure by ultrasonography (USG) guided methods. Biopsy was conducted by using Automated System Needle Biopsy (Bard Core-Biopsy Needle). Histopathological assessments (light and Immunofluorescence microscopy) of renal biopsy were done by one experienced histopathologist in the same institute.

Statistical Analysis

Results are presented as means with standard deviation (SD) for normally distributed data, or medians with IQR for non-normal distributions. Normally distributed continuous variables are compared using t-test. Categorical variables are compared using chi-square tests. All statistical tests were two-sided, with a p-value <0.05 taken to indicate statistical significance.

Results

A total of 1023 patients with different renal diseases were biopsied during this one and half year period in Department of Nephrology, SSKM hospital. Among 1023 renal biopsied 8.99% (92) patients had a histological diagnosis of glomerulonephritis with crescent and out of this, CrGN was 4.40% (45).

Among 45 patients of CrGN, ten patients (0.98%) were due to lupus and remaining thirty five patients (3.42%) were other than lupus. So a total of thirty five patients (100%) of CrGN were studied. Among Pauci-immune groups 68.75% (24) were ANCA positive and 31.25% (11) were ANCA negative. Again among CrGN patients, eleven (31.43%) were male and twenty four (68.57%) were female. Out of twenty four female, seventeen patients had either p (ten patients: 58.83%) or c (seven patients: 41.17%) ANCA positivity (48.57% of total CrGN), one had antiGBM disease and the rest were ANCA negative CrGN. Thirty two (91%) of thirty five CrGN were PiGN which accounts for the majority. In contrast, two groups of patients that were found in this study include Anti-GBM and IgA nephropathy which comprises two (6%) and one (3%) patients respectively of all CrGN. Most of the patients (24) of PiGN were between the age of 21 years and 60 years (75%). CrGN was found in five patients (14.28%) and three patients (8.57%) before the age of 20 years and after the age of 60 years respectively. Mean age was 33.50±4.95 years and 38.41±14.834 years in the Anti-GBM group and the pauci-immune group respectively, whereas it was 17 years in IgAN. Male to female ratio in the Anti-GBM group was 1:1 and in the pauci-immune group it was 1:2.2. Average baseline serum creatinine was 12.94±2.475

mg/dl in the Anti-GBM group, 5.08 ± 3.664 mg/dl in the pauci-immune group and 8.62 mg/dl in IgAN. Daily Proteinuria was higher in the pauci-immune group which was 2.84 ± 1.614 g/day whereas 0.98 ± 0.489 g/day in the Anti-GBM group and 1.35 g/day in IgAN. The basic profile of the patients is given in the following table:

In this study females were more than males in all the sub groups of CrGN. Average age of patients were similar in Anti-GBM and ANCA positive patients whereas ANCA negative patients were a little bit of a higher age group and the differences were not statistically significant. The striking feature is the onset of symptoms and diagnosis which were significantly delayed in all the subgroups. The average delay in diagnosis was 3.51 ± 0.701 weeks in the Anti-GBM group, 4.14 ± 1.49 weeks in the ANCA positive group, and 3.90 ± 1.79 weeks in the ANCA negative group and 8 weeks in IgAN. Oliguria was the commonest presentation in all the groups of CrGN. Other clinical features like fever, seizures, encephalopathy, rash, arthralgias, and hypertension were present in varying degrees in different groups of CrGN. Renal dysfunction was present in the entire group and average baseline serum creatinine was 12.94 ± 2.47 mg/dl in AGBM group, 4.51 ± 2.53 mg/dl in ANCA positive group, 6.32 ± 5.55 mg/dl in ANCA negative group and 8.62 mg/dl in IgAN group. Sub nephrotic proteinuria is not a common presentation in CrGN but it was seen in both ANCA positive and ANCA negative groups at diagnosis.

Renal involvement was a hallmark of CrGN. In all the groups of CrGN extra-renal involvements were also seen in different magnitudes and often extrarenal manifestations were the forerunners in renal involvement. Common non-specific symptoms in our study were fever, otic and nasal discharge which were noted in 62-70% cases. Others systemic which were also involved include pulmonary, upper respiratory tract, musculoskeletal system, neurology, gastrointestinal, cutaneous, and ocular. Among all these systems pulmonary and cutaneous system involvements were the most common. The organ involvement in CrGN is summarised in Table 2.

More than 50% crescents were present in all the groups of CrGN. Maximum numbers of crescents were noted in c-ANCA positive than other groups of patients. 70% of p-ANCA positive and 75% of c-ANCA positive patients showed glomerular necrosis at the time of diagnosis but none in Anti-GBM and IgAN. Average age of involvement was similar in all the groups. Male and female ratio in the p-ANCA positive group was 1:4 whereas in c-ANCA positive group 1:1.4. Serum creatinine was similar in the entire group. (Table 3)

Wide histopathological variability was seen in renal biopsy. Histologically five different types of crescentic glomerulonephritis were detected in this study, among which focal necrotizing comprises maximum numbers (48.57%) followed by only crescentic (34.29%), diffuse necrotizing (5.72%), necrotizing vasculitis (5.72%) and granulomatous inflammation (5.72%) were equal frequencies (5.72%).

Table 1: Clinical profile of different Crescentic glomerulonephritis

Characteristic	AGBM	ANCA+	ANCA-	IgAN	p-value
Male	1(%)	7(%)	3(%)	0(%)	0.852
Female	1(%)	15(%)	7(%)	1(%)	
Age	33.50±4.95	36.05±14.62	43.6±14.68	17±0	0.263
Duration of symptoms, weeks	3.50±0.71	4.14±1.49	3.9±1.79	8±0.0	0.106
Oliguria	2 (100%)	17(77%)	8(80%)	1(100%)	0.837
Gross Hematuria	0	1(5%)	0	0	0.895
Fever	1 (50%)	17(77%)	6(60%)	1(100%)	0.602
Seizures, Encephalopathy	2 (100%)	2(9%)	0	0	0.001
Rash	0	5(23%)	1(10%)	0	0.691
Arthalgias	1 (50%)	2(9%)	1(10%)	0	0.361
Hypertension	0	4(18%)	2(20%)	0	0.874
Creatinine, mg/dl	12.94±2.47	4.507 ± 2.53	6.324± 5.55	8.62	0.263
Proteinuria(no.)	0 ± 0	0.23 ± 0.249	0.29 ± 0.296	0 ± 0	0.429

Table 2: Organ involvement in different Crescentic glomerulonephritis

Organ System Involvement	Number of Patients (%) (N=35)	AGBM (%) (N=2)	ANCA+ (%) (N=22)	ANCA- (%) (N=10)	IgAN (%) (N=1)
Renal	35 (100)	2 (100)	22 (100)	10 (100)	1 (100)
Pulmonary	12 (34.3)	2(100)	5(22.7)	4(40)	1(100)
Upper Respiratory Tract	6 (17.1)	2(100)	1(4.5)	2(20)	1(100)
Musculoskeletal	4(11.4)	1(50)	2(9.1)	1(10)	0
Neurologic	4 (11.4)	2(100)	2(9.1)	0	0
Gastrointestinal	2 (5.7)	0	1(4.5)	0	1(100)
Cutaneous	6 (17.1)	0	5(22.7)	1(10)	0
Ocular	1 (2.8)	0	1(4.5)	0	0
Fever	25 (71.4)	2(100)	17(77.3)	5(50)	1(100)
Otic	23 (65.7)	2(100)	14(63.6)	6(60)	1(100)
Nasal	22 (62.8)	2(100)	13(59.1))	6(60)	1(100)

Table 3: Comparative clinic-pathologic features of different Crescentic glomerulonephritis at the time of diagnosis

	p-ANCA+ anti-GBM- (N=10)	c-ANCA+ anti-GBM- (N=12)	ANCA+ anti-GBM+ (N=1)	ANCA- anti-GBM+ (N=1)	IgAN (N=1)
>50% crescents,%	100%	100%	100%	100%	100%
Mean % crescents	55.25±38.97	73.22±29.64	<10	86.66	<10
Glomerular necrosis	7(70%)	9(75%)	0	0	0
Glomerular sclerosis	7(70%)	5(41.67%)	1(100%)	0	1(100%)
Age	39.70±16.55	33.00±12.72	30	37	17
Male: female	1:4	1:1.4	1	1	1
Creatinine	4.04±1.87	4.90±2.71	14.69	11.19	8.62
Anti-GBM titer	12.20±2.66	13.75±2.80	256	317	11
ANCA titer	223.30±76.53	329.33±155.46	89	20	27

Discussions

This is a retrospective study of 34 patients of CSGN, where the incidence of CSGN was 4.4% of kidney biopsies, among which 3.42% were non lupus. The incidence of CSGN varies with geographic location and policies of kidney biopsies. The incidence of CSGN was 1.75% in a study from China [6]. However, studies from Western Europe and North America (2-10%) and South Africa (3.8%) showed a near-similar incidence [7,8,9,10]. Gupta et al. found an incidence of 2.65% of kidney biopsies, but the study included both pediatric and adult patients [1]. The difference with the present study may be due to the differing patient cohorts and policies of kidney biopsies. CSGN occurs in all ages. The mean age of presentation in our study was 33.50±4.95 years in the anti GBM group and in the pauci-immune group 38.41±14.834 years, whereas it was 17 years in IgAN 32.44±15.9 years, with a predominance of female. Gupta et al from India also observed younger age of presentation of CSGN (27.6±17.1 years) [1]. However, the study population included 26% of the pediatric group. There was a female predominance in immune complex-mediated CSGN [1]. The female predominance is due to the higher prevalence of immune complex diseases.

While considering the etiology of non-lupus CrGN, the present study revealed that ANCA associated vasculitis (68.75%) is the most common variety, followed by ANCA-negative idiopathic vasculitis (22.25%), anti GBM (6%) and IgA nephropathy (3%). Vasculitis and lupus nephritis are the two most important causes of CrGN [1,2]. Vasculitis is the most common form in western countries whereas, lupus is common in developed countries like India [11]. Data from a study in China demonstrated that lupus nephritis was the most common etiology, followed by IgA nephropathy and vasculitis [6]. Since in our study we have already excluded the lupus associated CrGN, hence our data corroborates with the existing literature.

Among the histopathological features, the proportion of crescents has been reported to be higher in PI CrGN. In his study, Jennette JC showed that about 90% of patients had crescents with approximately half of the cases showing crescents in $\geq 50\%$ of glomeruli. On the other hand, $\geq 50\%$ glomerular crescents were less frequently seen in the IC-mediated group [12]. Glomerular necrosis was more frequent in ANCA-associated CrGN and lupus nephritis. In this study only patients with $\geq 50\%$ glomerular crescents (as a standard defining feature of CrGN) were included. The mean percentage of crescents in this study among pANCA, cANCA, and anti-GBM positive patients were 55.25 ± 38.97 , 73.22 ± 29.64 , and 86.66 respectively. The frequencies of glomerular necrosis was 70%, 75% and 0 in pANCA, cANCA, and anti-GBM positive while the frequencies of glomerular sclerosis were 70%, 41.6% and 100% among the same groups respectively. These findings were in concordance with the existing literature.

In the present study, most common organ involved in CrGN is the kidneys, followed by lungs, while Fever is the most common non specific symptom. Among the renal manifestations, oliguria, rise in serum creatinine and sub-nephrotic range proteinuria were the most common symptoms. Other studies have shown, RPGN, nephrotic syndrome and chronic renal failure to be associated with CrGN. CrGN presenting with RPGN has better outcome. This is related to the early diagnosis and early initiation of immunosuppression therapy whereas delay in diagnosis is associated with poor prognosis.

Conclusion

Crescentic glomerulonephritis is one of the important causes of acute renal failure. Immunofluorescence examination is mandatory to differentiate between the various groups. Though further studies are required, histological features do not appear to provide important prognostic information in cases of crescentic glomerulonephritis.

Compliance with ethical standards

Conflict of interest: The authors declare no conflict of interest, as this research was undertaken solely for scientific purposes.

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