Research Article

Crescents in renal biopsies and crescentic glomerulonephritis - A 5 year study from South India

Ravikumar G.[1], Rout P.[2]

[1]Dr. Gayatri Ravikumar, Assistant Professor, Dr. Pritilata Rout, Professor and Head, both are affiliated with Department of Pathology, St. John's Medical College, Sarjapur Road, Koranmangala, Bangalore, India.

Address for Correspondence: Dr. Gayatri Ravikumar, Assistant Professor, Department of Pathology, St.John's Medical College. E-mail: gayatri.ravikumar@gmail.com

Abstract

Background: Crescents indicate active disease with rapidly deteriorating renal function. Many primary renal diseases can be associated with crescents, however only a few conditions presents as crescentic glomerulonephritis (CrGN). The incidence varies in different population. **Aims and objective:** The aim of the study was to know the incidence of CrGN and that of crescents in various glomerulopathies along with their clinicopathological associations. **Material and methods:** Renal core biopsies over 5 year period were collected retrospectively from pathology archives and reviewed for crescents and CrGN. Clinical, serological, Immunoflourescence and follow up details were collected. **Results:** A total of 1629 renal biopsies were received. Crescents were identified in 9.69% and 2.08% were CrGN. Males and females were equally distributed. Paediatric population constituted 24%. The most common presentation was nephritic syndrome. Cellular crescents were seen in 81 cases, fibro cellular/ fibrous in 55 cases and both in 22 cases. In immune complex(IC) mediated group, lupus nephritis (LN) showed crescents in 31.7%, followed by PIGN (29.67%) and IgAN (25.2%). Vasculitis group had 79% crescents. All cases of anti GBM disease and pauci immune ANCA negative renal limited vasculitis (PI-RLV) had crescents. The most common CrGNs were anti GBM disease (100%), followed by vasculitis (37%) and PI-RLV (33%) and least in IC group (5% in PIGN and IgAN and 3.5% in LN). Complete remission was seen in 32.2%. **Conclusion:** Crescents in renal biopsies are not rare. Although CrGN is more common in vasculitis and anti-GBM disease, the incidence of IC-GN is more in our population and a significant number may show crescents.

Key words: Crescents, Crescentic glomerulonephritis, immune complex mediated, pauci-immune ANCA negative vasculitis.

Introduction

Crescents in renal biopsy indicate an active disease. It is the most common biopsy diagnosis which clinically presents as rapidly progressive renal failure. Many of the glomerulonephritides harbour crescents. Crescentic glomerulonephritis (CrGN) is diagnosed only when more than fifty per cent of the glomeruli show crescents and can be broadly grouped into three categories:

Immune-complex mediated glomerulonephritis, pauci-immune glomerulonephritis and anti-glomerular basement membrane (GBM) disease [1]. Crescents indicate damage to the glomerular basement membrane with extravasation of inflammatory mediators into the Bowman's space [2], which leads to proliferation of the parietal epithelium. It is not a disease entity by itself and is a histopathological representation of acute glomerular injury. CrGN is a well-studied entity, however the clinicopathological spectrum of the glomerular disease associated with crescents in renal biopsies has not been presented in detail in the literature from India, with sparse data from South India.

With the awareness that population based differences in the disease patterns are known to exist, it is useful to have studies on different population groups to know the incidence and behaviour of the disease entity to tailor population specific treatment. This study was therefore undertaken to know the incidence of crescents and CrGN in the population served by our centre and to

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categorise the cause of crescents with the help of immuno-fluorescence and serology. The clinicopathological correlation and follow up wherever available was also studied.

Material and Methods

Study design: This was a retrospective observational descriptive study.

Setting and data source: Renal biopsies received for routine histopathological diagnosis were retrospectively collected from the archives of the Department of Pathology, St.John's Medical College, Bangalore. They were classified into various groups based on immunohistological criteria and are listed in Table1.

Table1: Classification of renal core biopsies based on immunohistological features.

I. Immune complex mediated
a. Lupus nephritis (LN)
b. IgA nephropathy (IgAN),
c. Post infectious glomerulonephritis (PIGN)
d. Membranoproliferative glomerulonephritis (MPGN)
e. Membranous glomerulopathy (MGN),
f. Thrombotic microangiopathy (TMA),
g. Henoch Schonlein purpura nephritis (HSP-N)
II. Vasculitis group
III. Anti-GBM disease
IV. Pauci-immune ANCA negative renal limited vasculitis

Inclusion and exclusion criteria: All the renal core biopsies over a 5 year period were included. Renal biopsies in cases of accelerated hypertension (HT) and diabetic nephropathy (DN) were also included. In cases where there was no definite histopathological diagnosis /descriptive/ inconclusive diagnosis the biopsies were grouped under no definite diagnosis (NDD). Renal core biopsies done for non-glomerular disease and transplant renal biopsies were recorded separately to get total numbers. There were no definite exclusion criteria.

Variables: The histopathology reports of these biopsies were reviewed and those with crescents were recorded. Amongst these cases, those which had more than 50% crescents were classified as CrGN. The clinical investigations considered include proteinuria, hematuria, presence of hypertension and increasing serum creatinine levels. Urine protein creatinine ratio (PCR) and serum complement levels were also recorded and categorised as normal, increased or decreased. Immunoflourescence and serological findings (ANA, ANCA and dsDNA) were also noted. Follow up details were collected and classified into various categories as listed in Table 2. Patients who had relapse and patients who had undergone renal transplant were also recorded. The study has been approved by the Institutional ethics committee (IEC ref no. 106/2014).

Table-2: Classification of follow up details of the patients.

Follow up	Parameter for classification
Complete remission	Proteinuria <0.33g/dl and Serum creatinine < 1.4mg/dl
Partial remission	50% reduction in baseline proteinuria to <1.5g/dl and <25% increase in baseline creatinine
Chronic kidney disease	GFR <60ml/min/1.73m^2 for > 3months
Dialysis dependant	Patients required dialysis for maintenance of renal function
Poor prognosis	When renal replacement therapy was considered (when GFR is <10ml/min/1.73 m^2) or When there was worsening renal function
End stage renal disease	GFR is <15ml/min/1.73 m^2

Statistical analysis: The study being descriptive in nature, frequencies were calculated and no other statistical methods were employed.

Results

Characterisation of the cases: There were a total of 1629 renal core biopsies received over a five year period, excluding the repeat biopsies, therefore assuring true prevalence of the glomerular pathology. Crescents were identified in 158 patients (9.69%), of which 34 (2.08%) were classified as CrGN. Of the 158 patients, 38 (24%) were in the paediatric age group, i.e. age up to 18 years and the rest were adults (76%). There was a near equal distribution of male and female patients (78 and 80 respectively). The most common clinical presentation was nephritic syndrome and some patients were known cases of lupus nephritis (LN), thrombotic microangiopathy (TMA) etc. Table 3 summarises the various clinical presentations in this group of patients.

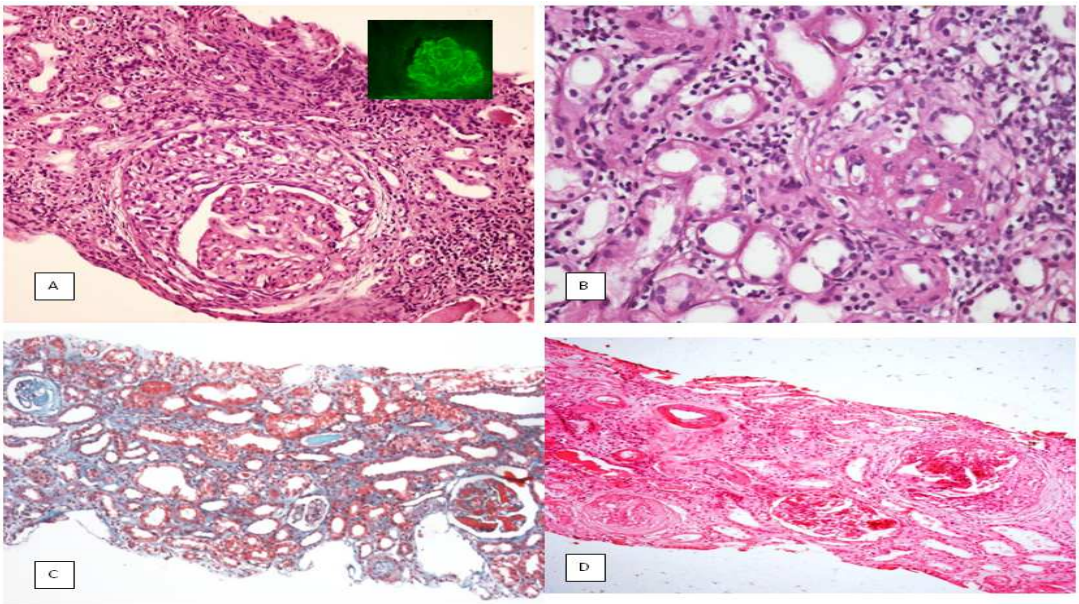

Figure-1(A-D): Photomicrographs showing crescents in A-Membranous nephropathy (H & E stain, original magnification, 20X), inset showing IgG positivity on immunoflourescence. B- HSP nephritis (H and E, original magnification, 40X). C- Thrombotic microangiopathy (Masson's trichrome stain, original magnification, 10X). D- Diabetic nephropathy (H&E stain, original magnification, 10X).

Table-3: Clinical Presentation of patients with crescents in renal biopsy.

Clinical presentation	Percentage of cases
Nephritic Syndrome	31.21
Rapidly worsening renal failure	28.02
Lupus nephritis	15.28
Nephritic Nephrotic syndrome	3.18
Nephrotic syndrome	2.54
Atypical Nephrotic syndrome	2.54
Hematuria	3.18
Edema	1.91
Acute interstitial Nephritis(AIN)	0.6
Acute interstitial Nephritis(AIN)+HIV	0.6
Thrombotic microangiopathy	0.6

The relevant biochemical investigations and serological findings are listed in Table 4. Hypertension was present in 72% of cases.

Table-4: Biochemical and serological investigations in patients with crescents.

Investigations	Percentage of cases
Proteinuria	99.21
Hematuria	82.94
Increasing creatinine	91.45
Higher urine PCR (n=67)	100
Decreased complement levels (n=85)	56.5
ANA positivity (n=123)	27.6
ANCA positivity (n=64)	14
ds DNA positivity (n=42)	57

Histopathological findings: The mean number of glomeruli was 12 (range 4-40). Cellular crescents were seen in 81 cases, fibro-cellular and fibrous crescents in 55 cases and 22 cases had both cellular and fibrous crescents. Segmental fibrinoid necrosis of the glomerular tufts was noted in 31 cases. Changes in the tubules were not significant other than casts and varying grades of tubular atrophy. An occasional case showed acute tubulointersitial nephritis. The interstitium showed periglomerular and perivascular granulomata in 2 cases of vasculitis and the rest had non- significant findings. Fibrinoid necrosis of the arterioles in the interstitium was seen in 9.49% cases.

The distribution of cases amongst the various histopathological diagnoses along with those showing crescents and CrGN are detailed in Table 5. The most common cause of crescents in the immune-complex (IC) mediated group was lupus nephritis, which showed crescents in 31.7% cases. The other common IC GNs with crescents were post-infectious glomerulonephritis (PIGN) (29.67%) followed by IgA nephropathy (25.2%). CrGN was relatively more common in the latter two than lupus nephritis. In the vasculitis group, 19 were ANCA related, of which 15 showed crescents and 7 were CrGN. There were 6 cases of pauci-immune ANCA negative renal limited vasculitis all of which showed crescents and 2 were CrGN. Anti-GBM disease was 100% CrGN. The rare findings in the present study include: a patient who was positive for ANCA and ANA and showed CrGN and 2 other patients who had connective tissue disorders other than lupus and both showed crescents with one being CrGN. Also there was one case each of Membranous nephropathy, thrombotic microangiopathy and diabetic nephropathy with crescents.

Table-5: Distribution of cases with crescents among renal biopsies for glomerular pathology and the total number in 5 years.

Histopathological diagnosis	Total number of cases (5 years)	Numbers with crescents including CrGN (%)	No. of CrGN {%}
Lupus Nephritis	142	45(31.7)	5(3.5)
IgAN	115	29(25.2)	6(5.21)
PIGN	91	27(29.7)	5(5.5)
MPGN	54	8(14.8)	1(1.9)
Vasculitis (ANCA mediated)	19	15(79)	7(37)
Pauciimmune ANCA negative, renal limited)	6	6 (100)	2(33)
Accelerated HT	35	4(11.4)	-
MN	122	1(0.8)	-
Anti GBM	4	4(100)	4(100)
TMA	6	1(16.7)	-
HSP	20	3(15)	1(5)
DN		1	-
No definite diagnosis	11	1(9)	1(9)

Follow up: Follow up details were available in 62.1% cases with a mean follow up period of 14 months. The patients received either one or a combination of the following treatment regimens based on clinical decision: pulse methylprednisolone, endoxan (cyclophosphamide) or wysolone. Some patients required dialysis and some had plasmapheresis. Complete and partial remission was seen in 32.2% and 2% cases respectively. In 11.39% there was chronic kidney disease and 6.96% required renal replacement therapy or had worsening renal failure. Five percent of patients were dialysis dependent. Relapse, post transplant status and ESRD was seen in 1.2% patients each.

Discussion

Crescents in renal biopsy are a result of insult to the glomerular capillary tufts due to the inflammatory mediators. As a result of the inflammatory insult, the parietal epithelial cells start proliferating and form crescents within the Bowman's space. The extent of crescent formation is an indicator of the disease severity. In the early stages crescents are cellular and progress to fibro-cellular crescents with passage of time. Finally the cellular crescents are replaced by collagen and lead to fibrous crescents which lead to a non-functioning glomerulus [3].

Crescents can be seen in the different forms of glomerulonephritis which can be broadly classified into three groups: immune-complex mediated glomerulonephritis, vasculitis and anti-GBM antibody disease [4]. Amongst the immune-complex mediated glomerulonephritis the most common ones associated with crescent formation are lupus nephritis, post–infectious GN, IgAN and membrano-proliferative glomerulonephritis.The recognition of crescents in renal biopsy is often associated with rapidly worsening renal function and rapidly progressive glomerulonephritis (RPGN) was the most commonly used terminology for any clinical condition with worsening renal failure.

Crescentic glomerulonephritis (CrGN) is diagnosed when more than 50% of the glomeruli show crescents. According to Steen Oslen, CrGN might constitute a final common pathway for several glomerular diseases which are severe etiologically and pathogenetically [5].

Although crescents can be diagnosed on light microscopy with utmost certainty, it is insufficient to know the underlying cause without the aid of immunoflourescence and serology, with addition of electron microscopy wherever available. The rapid and accurate diagnosis of CrGN is essential to initiate appropriate therapy for optimal patient outcome. Among the three broad categories of glomerulonephritis with crescents, CrGN is more common in pauci-immune ANCA mediated glomerulonephritis and anti-GBM disease than in immune complex mediated GN.

The incidence of crescents in renal biopsies in the present study is 9.69% and that of CrGN is 2.08%. In a 2 year study of CrGN from North Indian, Gupta *et al* reported an incidence of 2.65%, which is similar to the present study. Unlike our study, the highest incidence of CrGN (71.7%) was in the pauci-immune group, followed by IC-GN (28.3%) [6], whereas we found a higher incidence in the IC mediated group. Reports from China have also shown a higher incidence of CrGN among the IC group, constituting 68.6% of CrGN, followed by pauci-immune group with an incidence of 22.7%, similar to the present study. They also had 8.7% of CrGN related to anti-GBM disease whereas this did not feature in the study by Gupta *et al.* [6,7]. The incidence of CrGN varies across the world with studies from Western Europe and North America reporting an incidence of 2-10% and studies from South Africa reporting 3.8 % [8-11]. The IC CrGN is more common in young adults, whereas vasculitis related CrGN is common in elderly and anti-GBM is uncommon in any age. The paediatric cases constituted 24% of total renal biopsies with crescents and 20.58% of CrGN.

Choudhury *et al* reported an incidence of CrGN in 5.5% of their cases in a 3.5 year study from North India. They had predominantly adult patients with only 11.7% in the age group below 20 years [12]. Gupta *et al* had 26.08% CrGN in the paediatric group, but their age definition of paediatric was much younger (less than 14 years)[6]. Among the paediatric CrGN, the most common cause is IC GN as per evidence from the literature [13-15], whereas Sinha *et al* reported an equal incidence of both pauci-immune and IC CrGN in children, in their study on 36 children, under 18years, with CrGN from North India [16].

CrGN usually presents as rapidly worsening renal failure [7] which was the second most common presentation followed by nephritic symptoms in this study. CrGN is more common in anti-GBM disease followed by pauci-immune GN than ICGN as seen in the present study. Jennette and Thomson have reported

a similar finding in their study on 6000 native kidney biopsies [2]. The incidence of crescents and CrGN in their study is similar to the present study but for a minor differences within the IC GN group. LN showed a higher incidence of CrGN amongst the IC group, in both the studies and in the present study PIGN was slightly higher and there were fewer number of HSP compared to Jennette *et al* report [2]. The difference in percentage was marginal and it could probably represent a population based difference in the incidence of these ICGNs. Overall the percentage of CrGN was much lower in ICGN group indicating that ICGN is not as severe a form of GN compared to anti-GBM or pauci-immune group of GNs. As the study included all the renal biopsies with crescents and not exclusively CrGN, nearly half the cases had complete remission on follow up.

Conclusion

In conclusion, crescents in renal biopsies are not a rare occurrence and CrGN has an incidence of 2.08% of all renal biopsies. Although CrGN is more common in vasculitis and anti-GBM disease, the incidence of ICGN is more in our population and a significant number of them may show crescents. They progress rapidly and warrant urgent notification to the clinician. They are managed aggressively with steroids and cytotoxic agents and in patients who fail to respond to medical management the option of renal replacement therapy and transplant are considered.

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