Original Article

Crescents in Kidney Biopsy – What Do They Imply? A Clinicopathologic Study of 40 Cases in a Tertiary Care Center

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Abstract

Introduction: Crescents in glomeruli mean proliferation of parietal epithelium of Bowman's capsule with the presence of macrophages, lymphocytes, neutrophils, fibrin, and collagen. When crescents are present in >50% of nonfibrosed glomeruli, it is called crescentic glomerulonephritis (CGN). The presence of crescents is indicative of poorer prognosis. CGN can be pauci immune (PI), immune complex mediated (ICM), and anti-glomerular basement membrane (anti-GBM) disease. **Aim:** The aim was to study the clinicopathological spectrum of CGN over a period of 10 years in our center. **Materials and Methods:** Forty kidney biopsies with the presence of crescents over a period of 5 years were retrieved retrospectively from the histopathology records of the department of pathology. The clinical history, laboratory parameters, histopathology report, and the direct immunofluorescence (DIF) findings were analyzed. **Results:** Totally 40 cases had crescents on light microscopy. Out of these, 17 cases qualified for CGN. The mean age of the patients was 20 years. Nephritic syndrome was the most common presentation in these 17 cases. The mean creatinine level was 3.55 mg/dL. PI (7/17, 41.1%) was the most common category, followed by ICM (6/17, 35.2%) and anti-GBM (4/17, 23.5%). Out of the ICM, two cases were of IgA nephropathy with crescents and one of lupus with crescents. **Conclusion:** PI is the most common type of CGN. DIF examination is essential for exact categorization of CGN. Kidney biopsy in these cases can guide management and benefit patients with timely initiation of aggressive therapy.

Keywords: Biopsy, crescents, kidney

Introduction

Crescents are formed due to increased glomerular permeability resulting from various types of glomerular insults. This increased permeability leads to influx of inflammatory cells. Along with this, there is also proliferation of the parietal layer of Bowman's capsule. The World Health Organization (WHO) describes crescents as two or more layers of cells partially or completely filling the Bowman's space.[1,2]

When crescents are present in >50% of glomeruli, it is called crescentic glomerulonephritis (CGN). However, crescents being the end result of variety of pathogenetically distinct glomerular diseases, therefore, they can be seen in a wide spectrum of glomerular disorders apart from CGN. When present, crescents give an indication of poor prognosis, and the clinical scenario in such cases is usually described as rapidly progressive glomerulonephritis (RPGN).[3]

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Hence, light microscopic diagnosis of CGN is not sufficient and further characterization is essential in order to give appropriate targeted treatment. Further categorization requires immunofluorescence, electron microscopy, and serology.

On literature search, we found previous studies on CGN.[4] However, there were no studies discussing kidney biopsies which had crescents in <50% of glomeruli. In our study, we have tried to analyze the clinicopathologic profile of the patients whose kidney biopsies showed the presence of crescents irrespective of the percentage of glomeruli showing crescents. Further, we also studied the categorization and spectrum of CGN cases that were received in our tertiary care center during the study period.

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Materials and Methods

All the kidney biopsies received in our department of pathology from 2009 to 2019 were reviewed retrospectively in the study. Out of all biopsies, 40 showing the presence of crescents on light microscopy were selected. Clinical information pertaining to these 40 cases was recorded in a predesigned format.

Two samples of renal biopsies were taken for each case. From the first biopsy, multiple thin sections were cut for light microscopy after fixation in 10% formalin processed to obtain paraffin sections and stained with special stains including periodic acid–Schiff, Gomori's methenamine silver stain, and Masson's trichrome. The second biopsy core was received in Michel's fluid for direct immunofluorescence (DIF). The tissue was embedded in the cryostat embedding medium, frozen, and cut at 3-micron thickness at −22°C. Sections were taken on poly-L-lysine-coated glass slides. Later, the slides were rinsed in phosphate-buffered saline (PBS) at pH 7.2 for 10 min. The sections were treated with fluorescein isothiocyanate-labeled and optimally diluted antisera – IgG, IgA, IgM, C3, C1q, and fibrinogen. The slides were incubated in wet chamber for 1 h in dark room, washed with PBS, and mounted with buffer and glycerine. The slides were observed under green filter of fluorescence microscope at 494-nm wavelength. DIF was reported based on nature and distribution of immune deposits, glomerular localization, intensity of staining, and pattern of immune complex deposits. After correlating clinical data with light microscopy and immunofluorescence finding, the final diagnosis was rendered.

Data were entered in a spreadsheet in a predesigned format and analyzed using Microsoft Excel software.

Results

Forty kidney biopsies were included in this study during the period from the years 2009–2019 which showed the presence of crescents. Out of which, 17 qualified for CGN.

The mean age of the 17 CGN patients was 20 years, whereas the age ranged from 11 to 65 years. Six out of 17 (35.3%) patients were <18 years in age. Nephritic syndrome was the mode of presentation in 29.4% of CGN cases, with majority cases presenting with anasarca only. The mean creatinine level in CGN was 3.55 mg/dL. Pauci immune (PI; 7/17, 41.1%) was the most common category, followed by immune complex mediated (ICM; 6/17, 35.2%) and anti-glomerular basement membrane (anti-GBM) disease (4/17, 23.5%). Figure 1 shows the photomicrograph from a case of PI CGN: 1(a) is the H and E stain showing three glomeruli with fibrocellular crescents, 1(b) is the Masson's trichrome stain showing the three crescents highlighted, 1(c) is the silver methenamine stain of the crescents, and 1(d) H and E (×400) of the crescent.

In IC category, two cases were of crescentic IgA nephropathy and one of crescentic lupus nephritis. Table 1 shows the distribution and clinicopathologic profile of different types of CGN. Sixty-six percent (4/6) of PI cases were anti-neutrophil cytoplasmic autoantibody (ANCA) positive. The summary of these data is shown in Table 1.

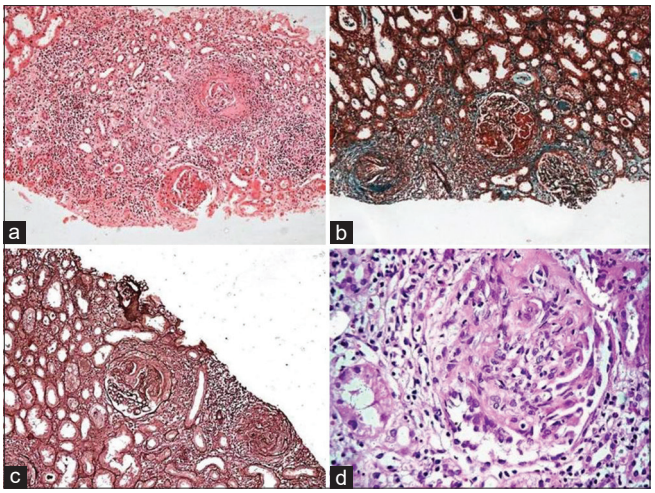

Figure 1: Photomicrograph from a case of pauci-immune crescentic glomerulonephritis: (a) H and E (×100) showing three glomeruli with fibrocellular crescents, (b) Masson's trichrome stain showing the three crescents (×100), (c) Silver methenamine of the crescents (×100), (d) H and E (×400) showing crescent

Figure 2a-c shows the DIF findings in a case of anti-GBM CGN: 2(a) is the IgG-stained slide showing 3+ linear positivity, 2(b) is the IgA stain showing no staining, and 2(c) is the C3 stain showing 2+ positivity. Figure 2d-f shows the DIF findings in a case of IC CGN: 2(d) shows 3+ granular positivity on IgG, 2(e) shows 1+ positivity on IgA, and 2(f) shows 1+ positivity on C3 immunostaining.

The clinicopathologic profile of the remaining 23 cases showed the presence of crescents, but they are not been qualified for CGN. Lupus nephritis was the most common cause of the presence of crescents in non-CGN cases being present in 69.5% (16/23) of cases. Next, in frequency, IgA nephropathy was seen in 21.7% (5/23) of cases. In one case, the possibility of both IgA nephropathy and lupus nephritis was given since her ANA levels were unknown and DIF showed positivity for IgG, IgM, IgA, and C3. There was one case where the possibility of C3 nephropathy was given because she had a membrane proliferative pattern along with the presence of crescents and DIF showed C3 positivity. However, its confirmation requires further study using electron microscopy. The summary of these data is shown in Table 2.

Discussion

Glomerular crescents have been described as early as 1886 by Purdy.[5] Initially, it was thought that the crescents were formed exclusively due to the proliferation of glomerular capsular epithelial cells. Later, studies, however, demonstrated that crescents are composed of a mixed population of glomerular epithelial cells and various inflammatory cells along with macrophages.[1] It is postulated that crescents result from increased glomerular capillary membrane permeability which

Table 1: Clinicopathological profile of the patients with different types of crescentic glomerulonephritis in kidney biopsy specimens

CGN category	*n* (%)	Age (years)	Sex ratio (male:female)	Average creatinine at presentation	Clinical presentation (%)	Percentage of glomeruli with crescent
PI	7 (41.1)	36.4	1:0.4	5.1	4/7 (57%) anasarca 1/7 (14.3%) nephritic	78.8
ICN	6 (35.3)	20.8	1:1	2.6	4/6 (66%) anasarca 1/6 (16%) nephritic	69.5
Anti-GBM	4 (23.5)	26.5	1:3	5.3	2/4 (50%) nephritic 2/4 (50%) anasarca	66.7
Overall	17	20	1:0.9	4.7	5/17 (29.4%) nephritic syndrome	74.1

CGN: Crescentic glomerulonephritis, PI: Pauci immune, ICM: Immune complex mediated, GBM: Glomerular basement membrane

Table 2: Clinicopathologic profile of patients whose kidney biopsies had crescents (apart from crescentic glomerulonephritis cases)

Type of glomerular disease	Number of cases, *n* (%)	Mean age (years)	Sex (male:female)	Average creatinine at presentation	Clinical presentation (%)	Percentage of glomeruli with crescent
Lupus nephritis	16/23 (69.5)	24.81	1:15	3.25	9/16 (56.25) anasarca	23.7
IgA	5/23 (21.7)	27.5	1:1.5	7.7	All (100) anasarca 2/5 (40) nephritic	29.6
Possibility of IgA and lupus	1	16	Female	5.7	Anasarca	33.3
Possibility of C3	1	16	Female	1.3	Anasarca	30.7

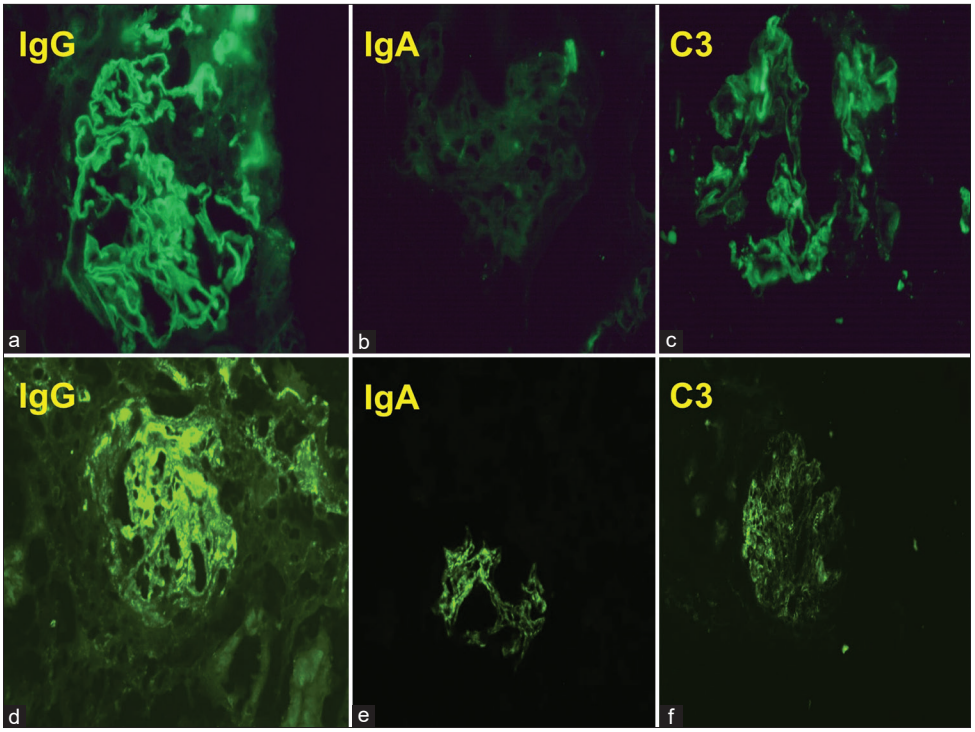

Figure 2: Direct immunofluorescence findings in a case of anti-glomerular basement membrane disease crescentic glomerulonephritis (×400): (a) IgG-3+ linear, (b) IgA negative, (c) C3-2+. Direct immunofluorescence findings in a case of immune complex crescentic glomerulonephritis (×400): (d) IgG-3+ granular, (e) IgA-1+, (f) C3-1+

results in influx of inflammatory cells, fibrin, and other plasma proteins to enter Bowman's space and induce cell proliferation to produce cellular crescents. Active crescents are invariably associated with fibrin positivity on immunofluorescence. Rupture of GBM can be demonstrated on silver-stained histologic sections or on transmission electron microscopy.

As the disease progresses, cellular crescents are transformed into fibrocellular crescents which later become completely fibrous crescents.

The definition of glomerular crescent as given by the WHO is, two or more layers of cells partially or completely filling the glomerular space.[1] Diffuse crescents when present usually imply a poorer prognosis, however, focal crescents may be reversed if the disease is detected early and could be adequately treated.[6] The presence of diffuse crescents in >50% of the nonsclerosed glomeruli in the renal biopsy is termed as CGN. Crescents in <50% of glomeruli should be stated in the report as proportion of glomeruli showing crescents because of their prognostic importance.[7] CGN since associated with rapid renal dysfunction is termed as RPGN or sometimes rapidly progressive CGN. These cases have to be managed actively by corticosteroids and cytotoxic drugs or plasmapheresis.

Severity of renal insufficiency and tubulointerstitial damage along with activity and chronicity of glomerular crescents determine the prognosis.[8]

CGN can be seen in all age groups.[1] In our study also, the age ranged from the second to the seventh decade. Other researchers reported that it is uncommon in pediatric age group.[9] However, in our study, 35.3% of patients were <18 years in age. Similar findings were observed by Gupta *et al*.[4] PI is more common in males, whereas anti-GBM is more common in females.[2] Severity of renal insufficiency and tubulointerstitial damage along with activity and chronicity of glomerular crescents determine the prognosis. Patients with PI present with higher mean creatinine levels.[10] In our study, PI and anti-GBM GN had higher serum creatinine levels at presentation as compared to ICM.

CGN is the final outcome of a variety of pathologically diverse glomerular diseases. On light microscopy, many of these entities share overlapping features. Clinical history, DIF, and electron microscopy can help to delineate the exact diagnosis so as to aid appropriate clinical management. However, light microscopy helps to define the activity of crescents and chronicity of glomerular and tubulointerstitial damage which, in turn, affect prognosis.[2,11]

CGN is classically divided into three types, namely PI, ICM, and anti-GBM. PI is defined as CGN with ≤2+ immunostaining of glomeruli for any Ig by DIF. Anti-GBM CGN is the one with ≥2+ linear IgG positivity on DIF. ICM is defined as ≥2+ nonlinear glomerular positivity for any IgG on DIF. Crescentic membranoproliferative GN has substantial staining for C3, but little or no staining for immunoglobulin is also included in the immune complex category.[10]

Apart from these three distinct entities of CGN, crescents can be seen in lupus nephritis, C3 glomerulopathy (including dense deposit disease), IgA nephropathy, postinfectious glomerulonephritis, Henoch-Schönlein purpura glomerulonephritis, Type 1 membranoproliferative glomerulonephritis, and rarely in thrombotic microangiopathy, monoclonal immunoglobulin deposition disease, and diabetic glomerulosclerosis. Whenever crescents are seen in a disease not normally associated with crescents, the possibility of a coexistent ANCA-associated disease should be considered.

In this study, PI was found to be the most common category of all the types of CGN. This finding is consistent with the other studies.[2,4] More than 90% of PI patients have circulating ANCA.[1] In our study, 66% (4/6) of PI cases were ANCA positive. PI also showed the highest proportion of glomeruli involved by crescents (78.8% of cases).

Anti-GBM CGN was found to be the most uncommon category comprising 15% of CGN cases.[1,10] It cannot be diagnosed by LM alone, and definitive diagnosis is made on immunofluorescence. One of the most important positive prognostic factors is the timely initiation of immunosuppressive therapy in anti-GBM cases, so such cases should be reported and informed on priority basis and availability of immunofluorescence to ensure early diagnosis.[12]

ICM CGN includes a wide variety of glomerular disorders. It is seen more commonly in younger patients, as seen in our as well as in other studies.[4,13]

Crescents in <50% glomeruli should be stated in the report as proportion of glomeruli showing crescents because of their prognostic importance.[14]

Apart from CGN, crescents are mostly seen in lupus nephritis which is 15 times more common in females. In a recent study, crescents in IgA nephropathy were not found to be statistically associated with increased probability of progression to end-stage renal disease.[15]

Whenever crescents are seen in a disease not normally associated with crescents, the possibility of coexistent ANCA-associated disease should be considered. Crescents may unusually be associated with multibacillary leprosy, lymphoblastic leukemia (ANCA associated), and idiopathic MPGN.[4]

Although light microscopic examination may give a presumptive diagnosis, final diagnosis requires categorization by immunofluorescence. Accurate and early diagnosis is especially important for anti-GBM and ANCA-associated PI as plasmapheresis gives rapid improvement. Electron microscopy may be required in rare cases.

Conclusion

CGN is the final outcome of a variety of pathologically diverse glomerular diseases. On light microscopy, many of these entities share overlapping features. Clinical history, DIF, and electron microscopy can help to delineate the exact diagnosis so as to aid appropriate clinical management with timely initiation of aggressive therapy, especially in RPGN.

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Conflicts of interest
There are no conflicts of interest.

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