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ORIGINAL ARTICLE

Post-infectious glomerulonephritis with crescents in adults: a retrospective study

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Abstract

Background: Crescent formation generally reflects severe glomerular injury. There is sparse literature on post-infectious glomerulonephritis (PIGN) with crescents in adults. This retrospective study looked at nine such cases to see if there is a correlation between the severity of presentation, steroid treatment, histological severity and outcome.

Methods: Biopsy reports of all the adults who underwent kidney biopsy from February 2010 to June 2014 in a tertiary care hospital were screened and all the cases with the diagnosis of PIGN with crescents were selected. Clinical presentation, laboratory data, histology, treatment and outcome were analysed.

Results: Six patients had evidence of recent/current infection, but all except two were non-streptococcal. The mean creatinine was 360.67 μmol/L (range 70.72–770.85) and the mean estimated glomerular filtration rate (MDRD eGFR) was 30.28 mL/min/1.73 m^2 (range 6.4–111.1) on presentation. All five patients who were treated with steroids had an excellent response. Among the four patients who did not receive steroids, two were left with significant renal impairment (mean MDRD eGFR 23.5 mL/min/1.73 m^2) at a mean follow-up of 15.5 months (range 10–21). The mean percentage of glomeruli with crescents was 36.13% (range 11.76–100) and except in one, there was no tubular atrophy or interstitial fibrosis and none had glomerulosclerosis. None of the patients progressed to end-stage renal disease.

Conclusion: Non-streptococcal infections are more common precipitants. There was no correlation between histological and clinical severity. Patients treated with steroids had better renal outcomes.

Key words: crescents, infection-related glomerulonephritis, post-infectious glomerulonephritis, steroids, vasculitis

Introduction

Post-streptococcal glomerulonephritis is the most common form of post-infectious glomerulonephritis (PIGN) in children. It is known to have a favourable prognosis. In adults, glomerulonephritis associated with other infections is more common. Especially in the elderly, staphylococcus is a common culprit. Other pathogens include viral, fungal, protozoal and parasitic infections. In contrast to post-streptococcal glomerulonephritis, most other bacterial

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pathogens cause glomerulonephritis when the infection is still active, hence the term infection-associated glomerulonephritis or infection-related glomerulonephritis (IRGN) has been proposed [1]. In patients with staphylococcus-associated glomerulonephritis, predisposing conditions like diabetes, alcoholism, cancer, malnutrition or intravenous drug addiction are often found [2].

Crescent formation generally reflects severe glomerular injury and it is seen in a variety of glomerulonephritides. Morphologically, crescents classically are defined as extracapillary hypercellularity with two or more layers of cells in the Bowman space [3]. Whether or not there is a direct correlation between the severity of renal disease and histological severity in this condition is debatable. Some studies showed a worse outcome in patients with crescents and some showed no correlation [4, 5].

The role of steroids in the treatment of PIGN/IRGN is controversial. There is anecdotal evidence supporting the use of steroids, but in some studies, no correlation was found between steroid use and outcome [4–6]. In this retrospective analysis, we studied nine cases of PIGN/IRGN with crescents in adults to see if there is a correlation between the severity of presentation, steroid treatment, histological severity and outcome.

Materials and Methods

This is a retrospective study. Biopsy reports of all the adults who underwent kidney biopsy from February 2010 to June 2014 in a tertiary care hospital were screened and all the cases with the diagnosis of IRGN/PIGN with crescents were selected. Biopsy reports of those <18 years of age were excluded. Other causes of crescentic glomerulonephritis and those with no glomeruli in immunofluorescence samples were also excluded.

Standard processing of renal biopsies included light microscopy and immunofluorescence. Electron microscopy was not carried out in any of them. The diagnosis was established by clinicopathologic correlation, with clinical features favouring the diagnosis of IRGN/PIGN, biopsy revealing endocapillary proliferative and exudative glomerulonephritis on light microscopy and C3-dominant or co-dominant glomerular staining on immunofluorescence. The presence of at least one cellular or fibrocellular crescent was a prerequisite for inclusion in the study. For light microscopy, all cases were stained with haematoxylin and eosin, periodic acid-Schiff, Masson trichrome and Jones methenamine silver. Immunofluorescence (IF) staining had been performed on 3-μm cryostat sections using polyclonal fluorescein-isothiocyanate-conjugated antibodies to IgG, IgM, IgA, C3, C1q, C4, kappa, lambda, fibrinogen and albumin. The intensity of IF staining was graded on a scale of 0 to 3+.

The medical records of the patients were reviewed and clinical data including demographic details, presenting clinical and laboratory findings, type and source of infection, treatment and follow-up data were obtained. Estimated glomerular filtration rate (eGFR) was calculated by the six-variable Modification of Diet in Renal Disease (MDRD) Study equation. Decreased eGFR was defined as <60 mL/min/1.73 m^2. For outcome analysis, complete remission was defined as improvement in GFR >60 mL/min/1.73 m^2. Institutional ethical committee approval was obtained.

Results

Clinical features and laboratory characteristics are summarized in Table 1.

Age at diagnosis ranged from 37 to 77 years (mean 53 years; median 49 years). The male:female ratio was 4:5. Two were known hypertensives, one had a history of ischaemic heart disease and none had diabetes. One was an alcoholic. Five patients

Table 1. Clinical and laboratory characteristics at presentation

Patient no.	Age (years)	Sex	Fever	Haematuria	Oliguria	Peripheral oedema	Other comorbidities	sCr (on admission)	sCr (peak)	eGFR on admission	Alb (g/L)	Proteinuria (g/day)	C3
1	45	M	Y	Y	Y	Y	HTN	112.27	112.27	65.2	28	1.7	Normal
2	35	F	Y	Y	Y	Y	–	680.68	777.92	6.4	30	–	Normal
3	63	F	N	Y	N	N	–	327.08	554.27	13.2	–	2.3	–
4	65	F	Y	Y	N	Y	Bronchiectasis	247.52	724.88	18	30	1	Normal
5	45	M	N	Y	Y	Y	HTN, alcoholism	70.72	70.72	111.1	23	4.5	Normal
6	73	M	N	Y	N	Y	IHD, chronic eczema	770.85	770.85	6.4	32	2.5	Normal
7	35	F	N	Y	Y	N	–	466.75	539.24	9.8	-	3.6	Low
8	63	M	Y	Y	Y	Y	–	258.12	312.94	23.3	23	1.1	–
9	49	F	Y	Y	Y	Y	–	318.24	468.52	19.2	29	–	Low

Note: sCr is scaled in μmol/L; conversion factor for sCr in μmol/L to mg/dL, ÷ 88.4; eGFR (MDRD) is scaled in mL/min/1.73 m^2; haematuria indicates macro-/microhaematuria or both.
M, male; F, female; Y, yes; N, no; HTN, hypertension; IHD, ischaemic heart disease; sCr, serum creatinine; eGFR, estimated glomerular filtration rate (MDRD); Alb, (serum) albumin; g/L conversion factor to g/dL, ÷10; C3, complement 3.

had fever, all of them had microhaematuria, but only five had macrohaematuria. Proteinuria varied from 1 to 4.5 g/day. There was clinical evidence of active/recent infection in six patients (Table 2). The mean creatinine was 360.67 μmol/L (range 70.72–770.85) [4.08 mg/dL (range 0.8–8.72)] and the mean MDRD eGFR was 30.28 mL/min/1.73 m^2 (range 6.4–111.1) on presentation. Two patients had normal renal function and seven had severe renal impairment, of which four needed dialysis. C3 was low in two, normal in five and data were not available in two. ANA, anti-dsDNA and ANCA were negative in seven patients and data were not available in two. Hepatitis B and C and HIV serology were negative in all. All had normal-sized kidneys, with the majority (8/9) having grade I parenchymal changes. The time from onset of infection to biopsy varied between 4 and 11 days.

Kidney biopsy characteristics

Biopsy features are summarized in Table 3.

Light microscopy

All the biopsy specimens showed diffuse endocapillary proliferative and exudative glomerulonephritis. The majority of the glomeruli appeared solid with proliferative tufts comprised of neutrophils. Partial obliteration of the capillary lumen secondary to proliferation of endothelial cells, neutrophils and sparse mesangial cells was noted in all the cases. The mean number of glomeruli was 10.55 (range 4–20) per biopsy. The mean percentage of glomeruli with crescents was 36.13% (range 11.76–100). Three biopsies showed ≥50% crescents. The majority of them (7/9) showed circumferential active cellular crescents, one showed partial active cellular crescents and one showed circumferentially oriented fibrocellular crescents. Necrotising lesions or fibrinoid changes were not seen in any of the glomeruli. Only one glomerulus showed glomerulosclerosis. Tubules showed foci of red blood cells in the lumen in the majority (8/9). Mild tubular atrophy and interstitial fibrosis was noted in one, which also had minimal interstitial inflammation.

Immunofluorescence

All the biopsy specimens demonstrated diffuse and global, coarse granular deposits along the capillary walls and occasionally in the mesangium with C3 (2+ to 3+) and two showed IgG 2+. IgA, IgM and C1q were negative in all of them. Extraglomerular deposits were not seen in any of them.

Treatment and progress

Treatment and progress are summarized in Table 4. Follow-up data were available for all nine patients. Five patients were treated with steroids, of which two received intravenous methylprednisolone at 500 mg for 3 days followed by oral prednisolone at 1 mg/kg, whereas the rest received oral prednisolone at 1 mg/kg/day. The indication for starting steroids was a lack of spontaneous improvement in renal function with adequate treatment of infection. The duration between presentation and steroid initiation varied between 7 and 14 days. Of the four patients who did not receive steroid treatment, two did not receive steroids because of relatively preserved renal function {mean creatinine 91.94 μmol/L [range 70.72–112.27] [1.04 mg/dL (range 0.8–1.27)], mean MDRD eGFR 88.15 mL/min/1.73 m^2 [range 65.2–111.1]}. The other two did not receive steroids because of history of recurrent infections (bronchiectasis with recurrent respiratory tract infection in one and history of recurrent leg cellulitis in the other patient who was also frail and elderly). Those who were treated with steroids had their doses tapered and stopped once there was significant improvement in renal function but the duration was variable. All the five patients who were treated with steroids had excellent response {mean creatinine 85.75 μmol/L [range 61.88–114.92] [0.97 mg/dL (range 0.7–1.3)], mean MDRD eGFR 74 mL/min/1.73 m^2 [range 58–99]} at a mean follow-up of 22.65 months (range 3.5–41.75). Of the four who did not receive steroids, two had normal renal function {mean creatinine 96.36 μmol/L [range 73.37–120.22] [1.09 mg/dL (range 0.83–1.36), mean MDRD eGFR 83 mL/min/1.73 m^2 [range 60–106]} at a mean follow-up of 16.37 months (range 3.33–29.25) and two had significant renal impairment {mean creatinine 221.88 μmol/L [range 159.12–285.53] [2.51 mg/dL (range 1.8–3.23), mean MDRD eGFR 23.5 mL/min/1.73 m2 [range 19–28]} at a mean follow-up of 15.5 months (range 10–21). The mean percentage of glomeruli with crescents in patients needing dialysis was 20.3%

Table 2. Site of infection and infectious agent

Site of infection	Infectious agent
Urinary tract	*Citrobacter* (urine)
Acute gastroenteritis	–
Respiratory + urinary tract infection	*Klebsiella* (sputum and urine)
Leg cellulitis/skin	Positive ASO titre
Urinary tract	Alpha haemolytic streptococcus (urine)
Urinary tract	*Candida* (urine)

ASO, anti-streptolysin O.

Table 3. Kidney biopsy characteristics

Patient no.	Total no. of glomeruli	Glomeruli with crescents (%)	No. of globally sclerosed glomeruli	Tubular atrophy and interstitial fibrosis	Interstitial inflammation	Immunofluorescence
1	13	11.76	0	Nil	Nil	C3 3+, IgG 2+
2	4	50	1	Nil	Nil	C3 3+
3	8	12.5	0	Nil	Nil	C3 3+
4	20	25	0	Nil	Nil	C3 3+, IgG 2+
5	12	33.33	0	Nil	Nil	C3 3+
6	8	25	0	Nil	Nil	C3 3+
7	5	100	0	Mild	Minimal	C3 3+
8	8	50	0	Nil	Nil	C3 3+
9	17	11.76	0	Nil	Nil	C3 3+

C, complement; Ig, immunoglobulin.

Table 4. Treatment and follow-up characteristics

Patient no.	Steroids (route)	Antibiotics	ACEI/ARB	sCr (at last follow-up)	eGFR (at last follow-up)	Follow-up duration (months)
1	–	Y	Y	114.92	60	3.33
2	O	Y	Y	61.88	99	41.75
3	O	N	N	68.95	79	3.5
4	–	Y	N	159.12	28	10
5	–	Y	Y	73.37	106	21.25
6	–	N	N	285.53	19	21
7	IV>>O	Y	Y	79.56	75	15
8	O	Y	Y	114.92	59	14.25
9	IV>>O	Y	Y	106.08	58	38.75

Note: sCr is scaled in μmol/L; conversion factor to mg/dL, ÷ 88.4; eGFR is scaled in mL/min/1.73 m^2.
O, oral prednisolone; IV, intravenous methylprednisolone; Y, yes; N, no; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; sCr, serum creatinine; eGFR, estimated glomerular filtration rate (MDRD).

(range 17.64–50), in contrast to 41.51% (range 11.76–100) in those who did not require dialysis. Two patients with crescents had normal renal function. One patient with 100% crescents did not require dialysis. Two patients with persistent renal dysfunction on last follow-up did not have any evidence of chronicity on biopsy. Of the nine patients, seven received appropriate antibiotics (empirical treatment with Piperacillin/tazobactam, which was then changed based on the culture and sensitivity). Two patients who were not treated with antibiotics did not have any clinical evidence of infection and had negative cultures. Six patients were treated with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Time taken for the proteinuria to resolve ranged from 2 months to 1 year and two patients had persistent proteinuria at the last follow-up. Of these two, one patient was lost to follow-up after 3.33 months [creatinine 114.92 μmol/L (1.3 mg/dL), MDRD eGFR 60 mL/min/1.73 m^2 at last follow-up] and another patient had persistent renal dysfunction [creatinine 159.12 μmol/L (1.8 mg/dL), MDRD eGFR 28 mL/min/1.73 m^2] at the last follow-up 10 months after initial presentation.

Discussion

This retrospective study analyses the clinical, pathological and outcome data of nine cases of PIGN/IRGN with crescents in adults. There were four males and five females and five of the patients were <50 years of age. The male preponderance that was seen in other studies was not observed in our study [4, 7, 8]. Two patients had nephrotic range proteinuria. In one study, this was observed in 60% patients with PIGN [9].

Six of the patients had evidence of active/recent infection, of which five had positive cultures (Table 2). Evidence of recent group A beta-hemolytic streptococcal infection was found in only one patient, who had ongoing active cellulitis of his leg at the time of presentation. Among the other five, the site of infection was urinary tract in two, urinary and respiratory tract in two and gastrointestinal tract in one, and all of them had had concurrent infection at the time of development of acute nephritis, justifying the term IRGN rather than PIGN. The finding of non-streptococcal infection predisposing to IRGN in the adult population is similar to the findings of the previous studies [4, 7]. Three patients who did not have clinical evidence of infection had their diagnosis made purely on a histological basis. One patient's urine culture grew *Candida*; to our knowledge, *Candida* causing PIGN/IRGN has never been reported before.

Staphylococcal infection was not found in any of our patients. Staphylococcus-associated glomerulonephritis (previously called post-staphylococcal glomerulonephritis) primarily occurs in older individuals and those with predisposing factors for staphylococcal infections [8]. Examples include diabetes, cancer, alcoholism and IV drug addiction. Our patients were relatively younger, and apart from one with a history of alcoholism, none had the above predisposing factors. This can also explain the absence of a dominant or co-dominant deposition of IgA on immunofluorescence in any of our patients. *Staphylococcus* is the most common organism associated with IgA-dominant PIGN, justifying the alternative designation 'IgA-dominant acute post-staphylococcal glomerulonephritis' [10]. Nasr *et al.* [10] reviewed 49 reported cases of this condition. *Staphylococcus aureus* was the infectious agent in 35 of the 37 patients in whom an organism was identified.

There are variable data on the correlation between histological and clinical severity in rapidly progressive glomerulonephritis (RPGN). There are studies that have shown a poorer prognosis with more extensive crescent formation in the setting of RPGN in general [11–13] and PIGN in particular in children and adults [14, 15]. On the other hand, there are studies that have shown no correlation between crescent formation and outcome [4]. In the current study there was no correlation between clinical and histological severity. Two patients with persistent renal dysfunction at the last follow-up did not have any evidence of chronicity on biopsy, including tubular atrophy, interstitial fibrosis and glomerulosclerosis, suggesting that the initial biopsy features are unlikely to be helpful in predicting long-term outcome.

Previous studies did not favour the use of immunosuppressive therapy in PIGN in children or adults, even in the setting of rapidly progressive crescentic disease [4, 6–8, 16]. In the elderly, a study showed no correlation between glucocorticoid therapy and renal outcome [17]. In staphylococcus-associated glomerulonephritis, immunosuppressive therapy is thought to do more harm than good, especially given the ongoing active infection in this condition and the association with immunosuppressive states. But the patients treated with steroids in our series did remarkably well compared with those who did not receive steroids. The younger age group and the lack of associated immunosuppressive conditions in our series may be factors that lead to better outcomes. This raises the question of whether steroids should be considered in the setting of aggressive disease in selected individuals. Further prospective studies are needed to make that recommendation, given the small number of patients in this retrospective analysis.

C3 glomerulopathy is a relatively new entity comprised of dense deposit disease (DDD) and C3 glomerulonephritis, both resulting from abnormal regulation of the alternative complement

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pathway and causing glomerulonephritis in children and young adults [18, 19]. It is an important differential diagnosis, especially in the two patients who had persistent renal dysfunction, as the prognosis of C3 glomerulopathy tends to be poor, especially DDD [20]. Twelve per cent of the patients with C3 glomerulopathy may have acute proliferative and exudative glomerulonephritis according to one study [21]. C3 was low in only two of seven patients in the current study among the patients with available data, and previous studies have quoted variable rates of 35–80% [4, 7, 8, 17]. C3 was normal in both the patients who had persistent renal dysfunction, but that does not help us to distinguish between PIGN/IRGN and C3 glomerulopathy, as a substantial number of adult patients with C3 glomerulopathy can have normal C3 [22]. Electron microscopy would have been helpful in making this distinction, which was not done in these patients. This can be considered a drawback of the current study.

To conclude, PIGN/IRGN with crescents usually presents as aggressive disease in adults and the associated organisms are usually non-streptococcal. There was no association between histological and clinical severity in our study. As far as steroid treatment is concerned, the findings in this study may have therapeutic relevance, because steroid treatment may have a role in a subset of younger and immunocompetent individuals. Further prospective studies are needed to confirm the significance of the findings of this study.

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Conflict of interest statement

None declared.

References

1. Nadasdy T, Hebert LA. Infection-related glomerulonephritis: understanding mechanisms. *Semin Nephrol* 2011; 31: 369–375
2. Nasr SH, Radhakrishnan J, D'Agati VD. Bacterial infection-related glomerulonephritis in adults. *Kidney Int* 2013; 83: 792–803
3. D'Agati VD, Jennette JC, Silva FG. *Non-Neoplastic Kidney Diseases*. Washington, DC: American Registry of Pathology, 2005
4. Nasr SH, Markowitz GS, Stokes MB *et al*. Acute postinfectious glomerulonephritis in the modern era: experience with 86 adults and review of the literature. *Medicine (Baltimore)* 2008; 87: 21–32
5. Zent R, Van Zyl Smit R, Duffield M *et al*. Crescentic nephritis at Groote Schuur Hospital, South Africa—not a benign disease. *Clin Nephrol* 1994; 42: 22–29
6. Raff A, Hebert T, Pullman J *et al*. Crescentic post-streptococcal glomerulonephritis with nephrotic syndrome in the adult: is aggressive therapy warranted? *Clin Nephrol* 2005; 63: 375–380
7. Montseny JJ, Meyrier A, Kleinknecht D *et al*. The current spectrum of infectious glomerulonephritis. Experience with 76 patients and review of the literature. *Medicine (Baltimore)* 1995; 74: 63–73
8. Moroni G, Pozzi C, Quaglini S *et al*. Long-term prognosis of diffuse proliferative glomerulonephritis associated with infection in adults. *Nephrol Dial Transplant* 2002; 17: 1204–1211
9. Natarajan G, Ramanathan S, Jeyachandran D *et al*. Follow-up study of post-infectious glomerulonephritis in adults: analysis of predictors of poor outcome. *Saudi J Kidney Dis Transpl* 2014; 25: 1210–1216
10. Nasr SH, D'Agati VD. IgA-dominant postinfectious glomerulonephritis: a new twist on an old disease. *Nephron Clin Pract* 2011; 119: c18–c25
11. Cunningham RJ III, Gilfoil M, Cavallo T *et al*. Rapidly progressive glomerulonephritis in children: a report of thirteen cases and a review of the literature. *Pediatr Res* 1980; 14: 128–132
12. Neild GH, Cameron JS, Ogg CS *et al*. Rapidly progressive glomerulonephritis with extensive crescent formation. *Q J Med* 1983; 52: 395–416
13. Baldwin DS, Neugarten J, Feiner HD *et al*. The existence of a protracted course in crescentic glomerulonephritis. *Kidney Int* 1987; 31: 790–794
14. Clark G, White RHR, Glasgow EF *et al*. Post streptococcal glomerulonephritis in children: clinicopathological correlation and long-term prognosis. *Pediatr Nephrol* 1988; 2: 381–388
15. El-Husseini AA, Sheashaa HA, Sabry AA *et al*. Acute postinfectious crescentic glomerulonephritis: clinicopathologic presentation and risk factors. *Int Urol Nephrol* 2005; 37: 603–609
16. Roy S III, Murphy WM, Arant BS Jr. Poststreptococcal crescentic glomerulonephritis in children: comparison of quintuple therapy versus supportive care. *J Paediatr* 1981; 98: 403–410
17. Nasr SH, Fidler ME, Valeri AM *et al*. Postinfectious glomerulonephritis in the elderly. *J Am Soc Nephrol* 2011; 22: 187–195
18. Fakhouri F, Frémeaux-Bacchi V, Noël LH *et al*. C3 glomerulopathy: a new classification. *Nat Rev Nephrol* 2010; 6: 494–499
19. Bomback AS, Appel GB. Pathogenesis of the C3 glomerulopathies and reclassification of MPGN. *Nat Rev Nephrol* 2012; 8: 634–642
20. Medjeral-Thomas NR, O'Shaughnessy MM, O'Regan JA *et al*. C3 glomerulopathy: clinicopathologic features and predictors of outcome. *Clin J Am Soc Nephrol* 2014; 9: 46–53
21. Walker PD, Ferrario F, Joh K *et al*. Dense deposit disease is not a membranoproliferative glomerulonephritis. *Mod Pathol* 2007; 20: 605–616
22. Nasr SH, Valeri AM, Appel GB *et al*. Dense deposit disease: clinicopathologic study of 32 pediatric and adult patients. *Clin J Am Soc Nephrol* 2009; 4: 22–32