



ORIGINAL ARTICLE

Revisiting post-infectious glomerulonephritis in the emerging era of C3 glomerulopathy

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Abstract

Background: Post-infectious glomerulonephritis (PIGN) is an immune complex-mediated glomerular injury that typically resolves. Dominant C3 deposition is characteristic of PIGN, but with the emergence of C3 glomerulonephritis (C3GN) as a distinct entity, it is unclear how the pathologic similarities between PIGN and C3GN should be reconciled. Therefore, nephrologists and nephropathologists need additional guidance at the time of biopsy.

Methods: We studied 23 pediatric and young adult patients diagnosed with PIGN. Patients were divided into two groups, one with co-dominance between C3 and immunoglobulins and the other meeting proposed diagnostic criteria for C3GN. Clinical and pathological features were compared.

Results: No clinical and/or pathological features could distinguish between those with C3-co-dominant deposits and those with C3 dominance. Nearly all patients in both groups regained their baseline renal function without clinical intervention.

Conclusions: Although the identification of abnormalities of the alternative pathway of complement is characteristic of C3GN, testing is not widely available and the turnaround time often exceeds 1 month. Our study found that PIGN with either co-dominant or dominant C3 deposition in a cohort of young patients has excellent short-term outcomes. Close clinical observation for persistent abnormalities, such as hypocomplementemia, prolonged hematuria or proteinuria, is recommended to single out patients that may harbor intrinsic complement abnormalities.

Key words: alternative pathway, complement

Introduction

Post-infectious glomerulonephritis (PIGN) is an immune complex-mediated glomerular injury that can occur as a consequence of an infection. The clinical presentation of hematuria, proteinuria (usually sub-nephrotic) and low C3 complement levels typically resolves within weeks [1]. PIGN predominantly manifests as a proliferative glomerulonephritis (GN) with

frequent intracapillary neutrophils (exudative GN). Subepithelial 'humps' are often seen on ultrastructural examination [2]. Codeposition of immunoglobulin (Ig) G and C3 is commonly observed in PIGN, while C3-dominant glomerular deposition was previously considered to represent a later stage of PIGN. However, the emergence of C3 glomerulonephritis (C3GN) as a distinct entity requires a reassessment of this concept.

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C3 glomerulopathy, which is a term that encompasses both dense deposit disease and C3GN, has highlighted the importance of the alternative pathway (AP) of complement and resulted in a re-evaluation of the diagnostic criteria for membranoproliferative GN [3, 4]. However, distinguishing between PIGN and C3GN has become a diagnostic challenge for both nephrologists and nephropathologists. For a subset of cases with dominant C3 glomerular deposition, it is unclear how the differences and similarities between PIGN and C3GN should be reconciled. Although the identification of abnormalities of the AP of complement is characteristic of C3GN, these laboratory tests are not widely available, and the turnaround time for results often exceeds 1 month. Therefore, nephropathologists and nephrologists will need additional guidance at the time of kidney biopsy, so we conducted the following study to address this increasingly common dilemma.

Materials and methods

We reviewed the University of Chicago Department of Pathology archives from 2005 through 2013 and found 24 kidney biopsies diagnosed as PIGN from 23 patients under the age of 25 years. This arbitrary age cutoff was established due to the availability of extensive clinical and laboratory data at both presentation and follow-up. Nephrotic-range proteinuria was defined as >3.5 g of proteinuria based on 24-h urine collection or a urine protein-to-creatinine ratio of >3.5 g/g. Normal kidney function was defined as an estimated glomerular filtration rate (eGFR) of >90 mL/min/1.73 m², chronic kidney disease stage II as 60–89 mL/min/1.73 m², stage III as 30–59 mL/min/1.73 m², stage IV as 15–29 mL/min/1.73 m² and end-stage renal disease as <15 mL/min/1.73 m² [5]. eGFR was determined using the modified Schwartz formula and the Modification of Diet in Renal Disease (MDRD) study equation.

All kidney biopsies were reviewed and separated into two groups based on diagnostic criteria for C3GN [4, 6]. One group (n = 13) consisted of dominant C3 deposition, which was defined as either staining for C3 only or C3 staining at least 2+ greater staining intensity than Ig (scale 0–4+) [4]. Those biopsies that did not satisfy the immunofluorescence (IF) criteria for the first group were assigned to the second group (n = 10) with co-dominant Ig [IgG (n = 9) or IgA (n = 1)] and C3 deposition. The IF staining pattern was categorized as predominantly mesangial, ‘starry-sky’ or ‘garland’. The ‘starry-sky’ pattern was defined as fine granular staining of mesangial and capillary walls, and the ‘garland’ pattern was defined as densely packed and occasionally confluent staining of primarily capillary walls [7].

The University of Chicago Medical Center and Lurie Children’s Hospital institutional review boards approved this study.

Results

Clinical and laboratory findings

Thirteen patient biopsies met the proposed diagnostic criteria for C3GN, while the remaining 10 patient biopsies demonstrated co-dominant C3 and Ig staining. The clinical data are summarized in Table 1. The median patient age was 9 years with an interquartile range (IQR) of 7 years.

C3-dominant group. Nine (69%) patients had evidence of a preceding infection in the form of a positive anti-streptolysin O (ASO) titer (n = 3), documented febrile illnesses (n = 5) or positive blood culture for *Staphylococcus aureus* (n = 1). The remaining four

patients had negative ASO titers and/or no documented infectious symptoms. Ten (77%) patients presented with an eGFR of <90 mL/min/1.73 m², and 8 (62%) had an eGFR of <60 mL/min/1.73 m². Hematuria and proteinuria were universally present with a median urine protein-to-creatinine ratio of 3.9 g/g (IQR: 6.1). Proteinuria was in the nephrotic range for six (55%) patients with available measurements. Eleven (85%) patients had low C3 levels at the time of diagnosis.

C3-co-dominant group. A preceding infection was identified in five (50%) patients, but the remaining five had negative ASO titers or no documented infectious symptoms. Seven (70%) patients presented with an eGFR of <90 mL/min/1.73 m², and six of them had an eGFR of <60 mL/min/1.73 m². All nine patients with available data had proteinuria with a median urine protein-to-creatinine ratio of 10 g/g (IQR: 16.3), which was in the nephrotic range for seven (78%) patients. Six (60%) patients had low C3 levels at the time of diagnosis.

Renal pathology

The light, IF and electron microscopic biopsy findings are summarized in Table 2.

C3-dominant group. By light microscopy, an exudative GN (intracapillary neutrophils) was present in 11 (85%) cases (Figure 1). Mesangial hypercellularity was present in seven (54%) biopsies, including one case without endocapillary proliferation, and ranged from mild in six cases to marked (>8 cells per mesangial area) in one case. A membranoproliferative pattern of injury was not present in any glomerulus. Cellular crescents were identified in seven (54%) biopsies, which involved >50% of glomeruli in three (23%) patients. One biopsy had focally prominent immune complex deposition in the form of ‘wire-loop’ deposits. Focal global glomerular sclerosis involved <5% of the glomeruli in three biopsies. One had diffuse (71%) global glomerular sclerosis, which

Table 1. Clinical features and follow-up

	C3 dominant	C3 co-dominant
Total patients	13	10
Female	6 (46%)	6 (60%)
Male	7 (54%)	4 (40%)
Median age (years)	10	7.5
Preceding infection and/or ASO+	8 (62%)	5 (50%)
eGFR <90 at presentation	10 (77%)	7 (70%)
C3 levels		
Low	11 (85%)	6 (60%)
Normal	2 (15%)	4 (40%)
Proteinuria	13 (100%)	10 (100%)
Nephrotic range	6 (55%)	7 (78%)
Hematuria	13 (100%)	10 (100%)
Follow-up kidney function		
Normal	11 (92%)	8 (89%)
CKD II	0	1 (11%)
CKD III	0	0
CKD IV	0	0
ESRD	1 (8%)	0
Proteinuria resolution	8 (67%)	8 (89%)
Time to resolution (mean)	7 months	6.5 months
Persistent hypocomplementemia	2 (22%)	0

ASO, anti-streptolysin O; eGFR, estimated glomerular filtration rate (unit: mL/min/1.73 m²); CKD, chronic kidney disease; ESRD, end-stage renal disease.

Table 2. Pathologic features of kidney biopsy at presentation

	C3 dominant	C3 co-dominant
LM		
Exudative GN	11 (85%)	10 (100%)
Mesangial hypercellularity	7 (54%)	7 (70%)
Crescents	7 (54%)	3 (30%)
<50%	4 (31%)	3 (30%)
>50%	3 (23%)	0
Global glomerulosclerosis		
None	9 (69%)	8 (80%)
<50%	3 (23%)	2 (20%)
>50%	1 (8%)	0
IF/TA		
None	9 (69%)	8 (80%)
Mild	3 (23%)	2 (20%)
Moderate	1 (8%)	0
Severe	0	0
IF		
Starry-sky	12 (92%)	5 (50%)
Garland	1 (8%)	5 (50%)
EM		
Subepithelial 'humps'	13 (100%)	10 (100%)
Intramembranous deposits	13 (100%)	6 (60%)

LM, light microscopy; GN, glomerulonephritis; IF/TA, interstitial fibrosis and tubular atrophy; IF, immunofluorescence; EM, electron microscopy.

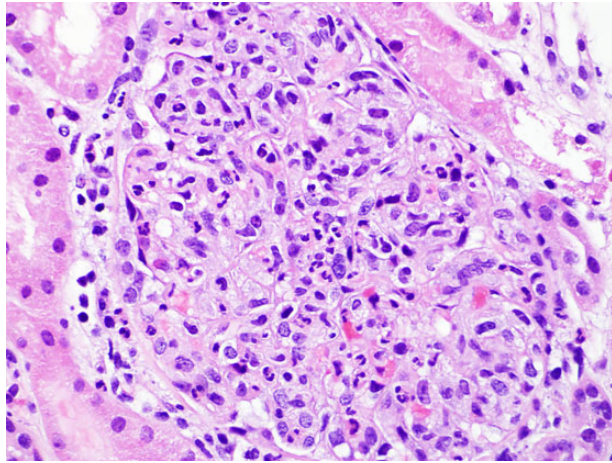


Fig. 1. A glomerulus from a patient with C3-dominant deposits shows an exudative glomerulonephritis with abundant intracapillary neutrophils (hematoxylin and eosin stain).

was accompanied by moderate interstitial fibrosis and tubular atrophy; however, the remaining 12 biopsies showed at most mild tubulointerstitial scarring. Ten (77%) cases had focally prominent active interstitial inflammation in non-scarred areas with focally prominent aggregates of neutrophils within the interstitial infiltrate in seven (54%) of these biopsies.

By definition, all 13 biopsies had either C3-only staining or least 2+ more C3 staining than Ig. Nine (69%) cases showed mesangial and capillary wall IF staining for C3 only without Ig, three (23%) showed <1+ IF intensity for IgG and one (8%) demonstrated 1+ IF staining for IgG. Twelve (92%) cases had a 'starry-sky' pattern (Figure 2A), while one demonstrated the 'garland' pattern (Figure 2B). No IF staining of the tubular basement membranes, interstitium or vessels was identified.

On ultrastructural examination, subepithelial 'humps' were identified in all cases (Figure 3A) and were limited to the mesangial 'notch' region of a glomerulus in one patient. All 13 cases showed intramembranous deposits that were frequently prominent. Many of these were osmiophilic in appearance, had an ovoid shape and were oriented perpendicular to the glomerular basement membrane (Figure 3B). Three cases also showed occasional elongated intramembranous deposits within the lamina densa that resembled dense deposit disease (Figure 3C). Extraglomerular deposits were not identified.

C3-co-dominant group. All 11 biopsies demonstrated an exudative GN. Mild mesangial hypercellularity was identified in seven (70%) biopsies. Glomerular basement membrane duplication was absent. Three (30%) patients had crescents that involved <11% of the glomeruli. For one of these patients, a second biopsy obtained 16 days later due to continued deterioration of kidney function revealed cellular to fibrocellular crescent formation involving 87% of glomeruli. Serologic testing for anti-neutrophil cytoplasmic antibodies was performed on this patient and was negative. Two (20%) biopsies showed focal global glomerular sclerosis, involving <10% of glomeruli. None of the biopsies showed significant interstitial fibrosis or tubular atrophy at the time of presentation. Six (60%) cases had at least focally prominent interstitial inflammation in non-scarred areas, and two of these had interstitial neutrophils.

All 10 patients had diffuse and strong (3–4+) staining for both Igs and C3. Nine showed dominant IgG deposits and one patient demonstrated dominant IgA deposits. One half of the biopsies had a 'starry-sky' pattern of staining, while the other half showed the 'garland' pattern.

All patients had subepithelial 'humps' on ultrastructural examination, and two of these revealed a segmental distribution. Six patients demonstrated intramembranous deposits by electron microscopy, which all correlated with low C3 complement levels. In contrast, the remaining four patients without intramembranous deposits had normal serum C3 levels. Extraglomerular deposits were not identified by either IF or electron microscopy.

Treatment and clinical follow-up data

C3-dominant group. Follow-up data were available for all patients with a median length of 16 months (IQR: 36). Twelve (92%) patients had normal serum creatinine and/or eGFR at the time of last follow-up. One patient with crescentic GN was treated with corticosteroids and required short-term hemodialysis (three sessions). No other patients received immunosuppressive therapy. Of the 10 patients who presented with renal insufficiency, the average time to normalization was 2.3 months (range: 0.5–4 months). Proteinuria resolved in 8 (62%) of 13 patients with an average time to resolution of 7 months (range: 2–14), but persisted in 4 patients (one nephrotic range and three sub-nephrotic range at 5, 7 and 39 months). One patient was lost to follow-up after 1 month, and repeat urinalysis was not available. C3 complement levels returned to normal for seven (78%) of nine patients with available data, while depressed C3 levels persisted for two patients at 7 and 30 months. The patient with diffuse global glomerular sclerosis had persistent nephrotic-range proteinuria, and a second kidney biopsy performed at another institution 39 months later by report showed persistent GN with C3-dominant deposits, and mesangial electron-dense deposits and subepithelial 'humps' by electron microscopy, but a membranoproliferative pattern of glomerular injury was not identified. He went on to develop

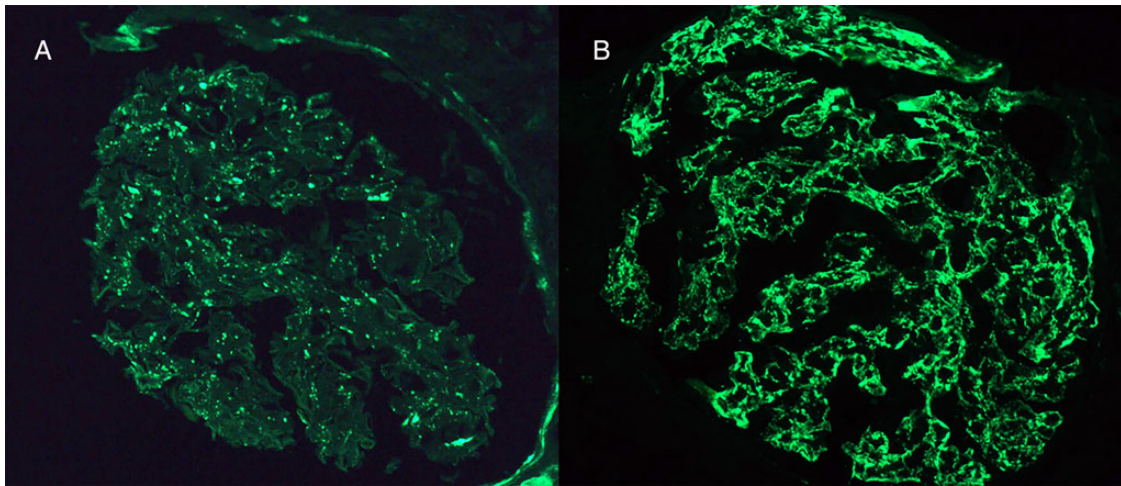


Fig. 2. (A) The 'starry-sky' IF pattern shows distinct granular staining of mesangial areas and capillary walls (C3 IF). (B) The 'garland' pattern of staining shows densely packed deposits with frequent confluent staining around capillary loops (C3 IF).

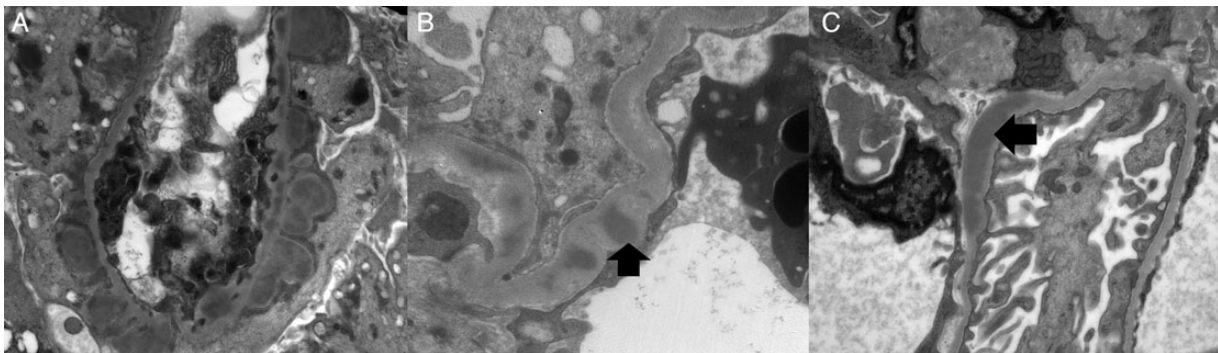


Fig. 3. (A) By electron microscopy, all cases showed at least focal subepithelial 'hump'-shaped deposits. (B) Intramembranous deposits were frequently identified, most of which were ovoid in shape and oriented perpendicular to the glomerular basement membrane (arrow). (C) A minority of cases in the C3-dominant group showed segmental elongated intramembranous deposits (arrow), reminiscent of dense deposit disease.

end-stage renal disease ~4.5 years after the initial diagnosis and underwent kidney transplantation.

One patient had persistent sub-nephrotic range proteinuria and hypocomplementemia with normal serum creatinine 30 months after his original diagnosis. He underwent AP of complement testing, revealing a slightly low AP of complement functional assay, which measures the amount of newly generated terminal complement component (C5b-9), and a borderline positive (1+ on a scale of 0-3+) C3 convertase stabilizing assay with properdin, which is a direct C3 nephritic factor assay. Genetic testing showed heterozygous deletion of CFHR3-CFHR1 and two copies of risk alleles in CFH (p.Val62 and p.His402) and C3 (p.Gly102 and p.Leu314), which are associated with an increased risk of developing C3 glomerulopathy.

C3-co-dominant group. Follow-up data were available for 9 of 10 patients with a median length of 35 months (IQR: 29.5). Eight (89%) patients had normal serum creatinine and/or eGFR at the time of last follow-up. Two patients were treated with corticosteroids, and one of them also required short-term hemodialysis (three sessions). Of the patients who presented with renal insufficiency, the average time to normalization of function was 2.5 months (range: 1-6). The patient with diffuse crescentic GN did not receive renal replacement therapy or immunosuppressive therapy

and maintained an eGFR of 80 mL/min/1.73 m² 5 years after her diagnosis. Resolution of proteinuria was seen in eight (89%) of nine patients in an average of 6.5 months (range: 1-16). Follow-up complement levels were obtained in two patients, which both returned to normal.

Discussion

The first C3 glomerulopathy meeting was recently convened, and one objective was to establish a definition of this new entity [6]. In particular, the consensus paper briefly acknowledged the substantial number of similarities between PIGN and C3GN and the difficulty in making this distinction based on morphology alone. The recommendation put forward was to label such cases as 'glomerulonephritis with dominant C3 (infection related)' and allow the clinical course and laboratory follow-up to dictate further differentiation. The relationship between PIGN and C3GN has been previously noted in the medical literature. Two decades ago, Frémeaux-Bacchi *et al.* reported three children with the classical presentation of PIGN who had transient C3 nephritic factor (C3Nef). All three patients rapidly recovered their renal function and complement levels normalized within 4 months, which corresponded to the disappearance of C3Nef. One of the three patients underwent a kidney biopsy, which showed PIGN with

C3-dominant glomerular deposits [8]. More recently, Sethi et al. found abnormalities in the AP of complement, including acquired autoantibodies (such as C3NeF) and genetic mutations in 11 PIGN patients with persistent abnormal renal findings, which they designated as 'atypical' PIGN [9]. However, in light of the data, many of these patients could be re-classified as C3GN. This study begs the question of whether abnormalities in the AP of complement could account for most instances of 'atypical' PIGN [9, 10].

The overlap of clinical and pathologic features between PIGN and C3GN is striking. Infections are well-known stimuli for PIGN but also can precede C3 glomerulopathy. C3GN can be closely preceded by bacterial infections [11–18], including streptococcal infection as 57% of C3GN patients have elevated ASO titers [19]. Patients with either PIGN or C3GN can present with hematuria and proteinuria. Endocapillary proliferation or an exudative glomerular injury has been described in up to 20% of C3GN patients, and subepithelial 'hump'-shaped deposits have been reported in as many as 41%, which are all common features of PIGN [19]. PIGN usually has a self-limiting course, which is similar to the outcome that has also been observed in some cases of C3GN [20].

In this study, we found no significant clinical or pathological difference between the group of PIGN patients with co-dominant Ig and C3 deposits compared with those that met the diagnostic criteria for C3GN. Although our cohort size is small with short-term follow-up, our data suggest that in young patients with an exudative GN and C3-dominant deposits, short-term outcomes are excellent and further differentiation between PIGN and C3GN is unlikely to be clinically useful at the time of biopsy. However, in patients with a PIGN pattern of glomerular injury, particularly with C3-dominant deposits, continued clinical follow-up is recommended with repeat serum complement testing and urinalysis. In cases where laboratory abnormalities persist, including the presence of hypocomplementemia >8 weeks after presentation, progressive decline in kidney function and/or persistence of significant proteinuria (>500 mg/day) 1 year after presentation, further investigation of the AP of complement and re-designation as C3 glomerulopathy may be indicated.

In our experience, nephrologists often do not pursue additional investigation to identify abnormalities of the AP of complement, even when this course of action is recommended based on the pathological findings. This reluctance could be due to many factors, including the cost of the additional testing, slow turnaround time for results and the lack of guidelines regarding the clinical management of C3GN. The observations from our cohort may provide some guidance in the interim until additional studies can clarify this clinical dilemma.

Our study is limited by the absence of data regarding the status of the AP of complement in all except one of our patients. This patient had prolonged proteinuria and hypocomplementemia and indeed harbored a genetic alteration in AP of complement. The prevalence of AP of complement abnormalities in typical cases of PIGN is unknown, representing a major gap in our knowledge and understanding of its possible relationship to other complement-mediated glomerular diseases. The C3-dominant group in our study would in the present day raise the diagnostic consideration of C3GN at the time of biopsy, but knowledge of AP of complement status may not be necessary in many of these cases given that the renal function and complement levels of the vast majority of patients in our cohort returned to normal.

In summary, the distinction between PIGN and C3GN at the time of biopsy is extremely difficult using only clinical and/or pathologic parameters, and the status of the AP of complement may be the only way to stratify these two similar entities. This is especially true in cases where there is significant pathological overlap, such as those with exudative GN and subepithelial 'humps', which are common in both disorders. Fortunately, nearly all of the patients in our cohort regained their baseline kidney function with resolution of hematuria, proteinuria and hypocomplementemia within a short time period even without therapeutic intervention. Although C3GN was not a distinct entity when most of our biopsy diagnoses were established, this diagnostic consideration would be raised in over half of our cohort. Our data support the recommendations put forth by the C3 glomerulopathy consensus report, and we advise close clinical follow-up to determine whether further testing and designation as a C3 glomerulopathy is warranted.

Conflict of interest statement

None declared. This study was previously presented in abstract form at the 2014 annual meeting of the US and Canadian Academy of Pathology, which was held in San Diego, CA, and has not otherwise been published.

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