ORIGINAL ARTICLE

# C3 glomerulonephritis in Cape Town, South Africa: a case series

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## ABSTRACT

**Background:** C3 glomerulonephritis (C3GN) is a rare disease of the alternative complement pathway and is associated with poor kidney and patient outcomes. To the best of our knowledge, there are no studies on this condition reported from sub-Saharan Africa. We aimed to identify the incidence, describe the clinical features, and report on the time to the composite outcome of CKD, ESKD or death following kidney biopsy.

**Methods:** A retrospective cohort study of all adult patients with a kidney biopsy-confirmed diagnosis of C3GN was performed at our tertiary centre in Cape Town, South Africa, over a 16-year period. C3GN was defined as exclusive C3 positivity or a C3 stain of two orders of magnitude greater than any other immune reactant on immunofluorescence. Kaplan–Meier survival analysis was performed for the composite outcome.

**Results:** A total of 19 patients with C3GN were identified with an estimated incidence rate of 0.9 per million population per year. The composite outcome occurred in 79% (n = 5) with a median survival 25 months. The median age was 31 (IQR 24–45) years, most were male (79%) and 58% were hypertensive. Three-quarters presented with nephritic-nephrotic syndrome. At the time of biopsy, the median creatinine was 212 (IQR 134–752) µmol/L, estimated glomerular filtration rate 33 (IQR 8–65) mL/min/1.73 $m^2$, proteinuria of 5.8 (IQR 5–10) g/day and low C3 in 53%.

**Conclusion:** This is the first description of C3GN from sub-Saharan Africa. Overall prognosis was very poor, which may be due to late presentation.

**Keywords:** membranoproliferative, complement, glomerulopathy, C3GN, sub-Saharan Africa.

## INTRODUCTION

Mesangiocapillary glomerulonephritis (MCGN), also known as membranoproliferative glomerulonephritis, is currently the most common pathological pattern of glomerular injury identified in our centre [1]. It was previously classified using electron microscopy findings [2]; however, recent advances in the understanding of the different pathogenic mechanisms underlying the MCGN subtypes have resulted in a new classification system. It is classified based on glomerular immune deposit staining on immunofluorescence (IF), both immunoglobulin and complement (immune-complex mediated MCGN), and those with predominant C3 staining (complement-mediated MCGN, or C3 glomerulopathy) and non-immunoglobulin or complement deposits [3].

C3 glomerulopathy is a disease comprising rare subtypes of glomerulonephritis (GN), including dense deposit disease (DDD), and C3 glomerulonephritis (C3GN). C3GN is characterised by C3 deposits that are found in the glomerular mesangium and capillary wall, in sub-endothelial and/or subepithelial areas. Discontinuous intramembranous deposits are also sometimes seen on electron microscopy (EM) [4].

Received 24 March 2023; accepted 30 July; published 25 August 2023.
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DOI: https://doi.org/10.21804/26-1-5810

A recent study, in Cape Town, that investigated all consecutive kidney biopsies performed over the last decade, reported that MCGN was the most common histopathological pattern of injury in this biopsy series [1]. Internationally, a few large-scale studies have investigated C3GN, but the condition has recently garnered attention with the improved understanding of its pathogenesis, which has led to the development of new drugs which target the alternative complement pathway.

A recent study from India reported a prevalence of C3GN of only 1.5% with a high rate of progression to end-stage kidney disease [5]. Similarly, a study in France reported poor outcomes with more than 50% of patients having substantial kidney dysfunction within 12 years of diagnosis [6], while others recorded a greater degree of kidney injury and higher mortality in patients with C3GN relative to controls [7]. Age, reduced kidney function, and the proportion of crescents on kidney biopsy were identified as risk factors of progression [8].

To the best of our knowledge, there are no epidemiological studies reported from sub-Saharan Africa (SSA). Therefore, we aimed to identify the incidence, clinical features, or outcome of C3GN at our centre.

## METHODS

A retrospective cohort study of all adult patients with a kidney biopsy-confirmed diagnosis of MCGN was performed to describe the pattern of C3GN at our tertiary centre (Tygerberg Hospital) in Cape Town, South Africa, over a 16-year period from 2000 to 2016. All adult patients, 18 years old or more, were included. The incidence rate was calculated using an estimated adult population dependent on Tygerberg Hospital for tertiary renal healthcare services of 1.3 million.

Patient demographics, the clinical presentation, laboratory results, including kidney biopsy data, were extracted from electronic patient records. Clinical data included age and sex, duration of follow-up, indication for kidney biopsy and blood pressure at the time of biopsy. Laboratory results included serum albumin, serum cholesterol, serum creatinine and estimated glomerular filtration rate (eGFR), urine protein-to-creatinine ratio (UPCR) and complement levels (C3 and C4) at the time of biopsy.

The biopsies were reviewed by two experienced pathologists. Each kidney biopsy was studied using light microscopy, immunofluorescence, and electron microscopy techniques. Histological features on light microscopy included the number of glomeruli, proportion of globally sclerosed glomeruli, proportion of crescents, and the degree of interstitial fibrosis [mild (<25%), moderate (25–50%) and severe (>50%)]. Immunofluorescent staining for C3, IgG, IgA and IgM was performed and electron microscopy for electron-dense deposits in the mesangial, subepithelial and subendothelial locations was assessed. C3GN was defined as exclusive C3 positivity or a C3 stain of two orders of magnitude greater than any other immune reactant on immunofluorescence including IgG, IgM, and IgA. Secondary causes of MCGN including monoclonal gammopathies, infections such as hepatitis B, hepatitis C and HIV, and autoimmune disorders were excluded.

The outcome measures included the incidence of C3GN at our centre, a description of the clinical features at presentation, and report on patient and kidney consequences following kidney biopsy.

Analyses were performed using Stata® version 16.1. Descriptive statistics were presented as means and standard deviation if data were normally distributed, or median and interquartile ranges (IQR) if data were not normally distributed. We did not perform logistic regression analysis because of the small sample size. Kaplan–Meier survival analysis was performed for the composite outcome of chronic kidney disease (CKD) (eGFR <60 mL/min/1.73 $m^2$ for more than 3 months), end-stage kidney disease (ESKD) (eGFR <15 mL/min/1.73 $m^2$ for more than 3 months) or death, and was censored for CKD and ESKD at the time of biopsy.

### Ethical considerations

This study was approved by the Health Research Ethics Committee (HREC) of Stellenbosch University (HREC approval number: S20/10/289, project identification: 18920). As this was a retrospective study, a waiver of individual informed consent was granted.

## RESULTS

A total of 228 kidney biopsies with a histological pattern of MCGN were screened. Of these, 205 were excluded for not fulfilling our definition of C3GN, and four were excluded because of missing data. Therefore, 19 patients with C3GN were included. The estimated incidence rate was 0.9 cases per million population (pmp) per year.

A summary of the clinical characteristics at the time of biopsy is shown in Table 1. The median age at diagnosis was 31 (IQR 24–45) years and more than three-quarters of the patients were male. Hypertension was a common finding seen in more than half of the patients (58%).

At presentation, kidney function was impaired in 17 (89%) patients with a median creatinine of 211 (IQR 134–752) µmol/L. Nephrotic-range proteinuria was also present in all but one patient, with a median urine protein-to-creatinine

**Table 1.** Clinical characteristics, laboratory results and composite outcome.

| Patient characteristics | All patients (n = 19) |
|---|---|
| Age (years), median (IQR) | 31 (24–45) |
| Male, n(%) | 15 (79) |
| Comorbidities, n(%) | |
| Hypertension | 11 (58) |
| Type 2 diabetes mellitus | 2 (11) |
| **Clinical presentation, n(%)** | |
| Nephritic-nephrotic syndrome* | 14 (75) |
| Acute kidney injury | 2 (11) |
| RPGN | 3 (15) |
| Mean arterial pressure, mean ± SD (mm Hg) | 113 ± 23.3 |
| **Laboratory results** | |
| Creatinine at biopsy (µmol/L), median (IQR) | 212 (134–752) |
| eGFR at biopsy (mL/min/1.73 m$^2$), median (IQR) | 33 (8–65) |
| Kidney impairment at biopsy, n(%) | 12 (63) |
| Proteinuria at biopsy (g/day), median (IQR) | 5.8 (5.0–10.0) |
| Creatinine at follow-up (µmol/L), median (IQR) | 425 (111–1236) |
| eGFR at follow-up (mL/min/1.73 m$^2$), median (IQR) | 19 (4–92) |
| Proteinuria at follow-up (g/day), median (IQR) | 2 (0.3–3.9) |
| Complement level tested, n(%) | 17 (89) |
| Low C3 | 9 (53) |
| **Follow-up (months), median (IQR)** | 15 (3–31) |
| **Treatment, n(%)** | |
| ACEi | 11 (58) |
| Glucocorticoids | 2 (10) |
| Glucocorticoids plus cyclophosphamide | 1 (5) |
| Received haemodialysis at presentation | 3 (16) |
| No treatment | 1 (5) |
| **Composite outcome, n(%)** | 15 (79) |
| CKD | 2 (11) |
| ESKD | 2 (11) |
| Died | 11 (58) |

Abbreviations: IQR, interquartile range; RPGN, rapidly progressive glomerulonephritis; eGFR, estimated glomerular filtration rate; ACEi, angiotensin-converting enzyme inhibitor; CKD, chronic kidney disease; ESKD, end-stage kidney disease. *The term nephritic-nephrotic syndrome refers to patients who presented with features of both syndromes and included: nephrotic-range proteinuria of >3.5 g per day, hypercholesterolaemia, hypoalbuminaemia, oedema, hypertension, haematuria and reduced kidney function.

**Table 2.** Histopathological characteristics.

| Kidney biopsy | All patients (n = 19) |
|---|---|
| **Median number of glomeruli, median (IQR)** | 36 (30–46) |
| **Interstitial fibrosis, n(%)** | |
| None | 1 (5) |
| Mild (<25%) | 6 (32) |
| Moderate (25–50%) | 8 (42) |
| Severe (>50%) | 4 (21) |
| **Proportion of sclerosed glomeruli, n(%)** | |
| None | 4 (21) |
| <50% | 8 (42) |
| >50% | 7 (37) |
| **Proportion of crescents, n(%)** | |
| None | 6 (32) |
| <50% | 9 (47) |
| >50% | 4 (21) |
| **Immunofluorescence staining, n(%)** | |
| **C3** | |
| 1+ | 7 (37) |
| 2+ | 6 (32) |
| 3+ | 6 (32) |
| **IgM** | |
| None | 15 (79) |
| 1+ | 4 (21) |
| **IgG** | |
| None | 15 (79) |
| 1+ | 4 (21) |
| **IgA** | |
| None | 15 (79) |
| 1+ | 4 (21) |
| **Electron microscopy deposits, n(%)** | |
| Subendothelial | 17 (89) |
| Subepithelial | 4 (21) |
| Mesangial | 8 (42) |
| Mesangial interposition | 17 (89) |
| Tubulo-reticular inclusion bodies | 4 (21) |

ratio of 5.8 (5–10) g per day. Three patients (16%) presented with acute kidney injury requiring acute kidney replacement therapy. The most frequent presentation was nephritic-nephrotic syndrome, accounting for three-quarters of the clinical presentation in our study cohort. Isolated low serum C3 concentrations occurred in half of the patients. Of note, none of the patients had concurrent low serum C3 and C4 concentrations.

More than half of the patients (58%) received an angiotensin-converting enzyme inhibitor (ACEi). A single patient was treated with oral cyclophosphamide on account of crescentic GN.

Collectively, moderate and severe interstitial fibrosis was seen in 63% of patients, with 37% already having >50% sclerosed glomeruli on biopsy (Table 2). Crescents >50% were present in 21%. C3 staining on immunofluorescence microscopy was 37%, 32% and 32% for 1+, 2+ and 3+ intensities, respectively. Both subendothelial deposits (89%) and mesangial interposition (89%) were the most common findings on electron microscopy.

The median follow-up was 15 (IQR 3–31) months. The composite outcome occurred in 79%. Most patients reached the composite outcome due to death. On Kaplan–Meier survival analysis (Figure 1), the median composite outcome was 25 months following kidney biopsy, censored for CKD and ESKD at the time of kidney biopsy.

## DISCUSSION

To the best of our knowledge, this is the first study to describe the incidence, clinical presentation, and outcomes of C3GN in SSA. We confirm that C3GN is a rare subtype of MCGN, with an incidence rate of 0.9 cases pmp. In the United States, an incidence of approximately 2–3 cases pmp has been reported, whereas lower rates were reported from Europe of 0.2–1.0 case pmp [9]. We suspect that our incidence rate may be an underestimate because many patients present with established ESKD at our centre and therefore are not biopsied, and there is lack of referral from primary healthcare facilities and limited access to healthcare services particularly for patients living in rural areas.

Our patients were relatively young, and most were male. A 10-year review at the Mayo Clinic found a mean age at diagnosis of 41.5 years with male predominance of 60% [10]. The reason for a male predominance is unclear. The most common clinical presentation of our cohort was nephritic-nephrotic syndrome with haematuria, nephrotic-range proteinuria and hypertension, and was consistent with the findings reported by others [9,10].

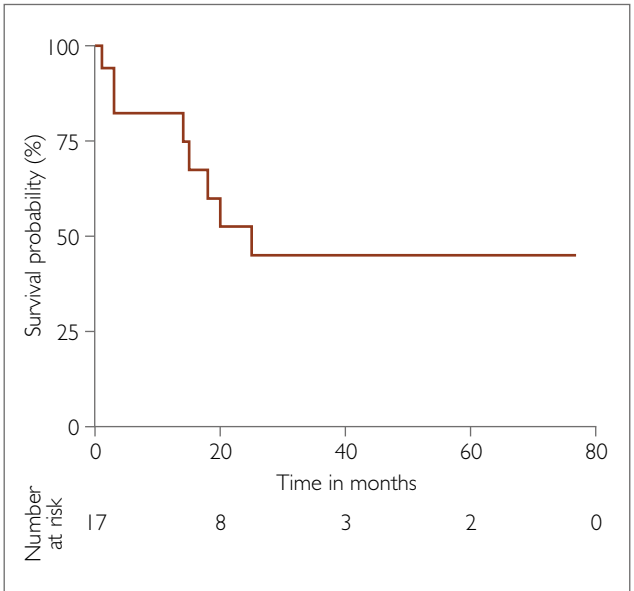


**Figure 1.** Kaplan–Meier survival analysis for the composite outcome censored for CKD and ESKD at the time of kidney biopsy.

Abbreviations: CKD, chronic kidney disease; ESKD, end-stage kidney disease.

Half of our patients reached the composite outcome by 25 months. Others have reported more favourable outcomes with only 30–50% progressing to ESKD over 10 years [10,11]. Possible factors for our poorer outcome include the late presentation, heavy proteinuria at the time of biopsy and the advanced histopathological changes on biopsy. This is supported by another study, which reported that an eGFR <45 mL/min/1.73 $m^2$, proteinuria >2 g per day, severe interstitial fibrosis and >25% crescents predicted the composite outcome doubling of serum creatinine or kidney failure [12]. Histologically, almost two-thirds of our patients had moderate to severe interstitial fibrosis, more than one third had >50% globally sclerosed glomeruli, and one in five patients had >50% crescents.

On electron microscopy, subendothelial deposits were the most common site followed by mesangial and subepithelial deposits. Another study reported more frequent mesangial deposits followed by subendothelial deposits [13]. This study also reported that 61% had subepithelial deposits. This is three times greater than our findings. We suspect that our lower frequency of subepithelial deposits may be due to the exclusion of patients with suspected post-infectious glomerulonephritis based on high serological markers including anti-streptolysin O and anti-DNAse B antibodies. Currently, in SSA, the availability of definitive testing for acquired or genetic abnormalities of the alternative complement pathway, which could lead to a more accurate diagnosis of C3GN, is limited by its high cost and lack of routine accessibility.

At present, there is no established definitive treatment for C3GN. KDIGO guidelines recommend supportive measures, along with renin–angiotensin–aldosterone inhibitor therapy as first-line treatment to reduce proteinuria and control blood pressure [14]. In our cohort, the most common supportive therapy was ACEis without any additional immunosuppression; however, 42% did not receive ACEi therapy due to the development of hyperkalaemia. Three patients supported with dialysis died within 3–12 months.

Agreement on the efficacy of immunosuppressive therapy for C3GN is controversial because of a lack of randomised controlled trials [15]. The revised 2021 KDIGO guidelines recommend that mycophenolate mofetil (MMF) along with steroids be used as first-line therapy for moderate to severe C3GN [14]. This is based on a small retrospective study that reported better outcomes in patients who received MMF compared to other immunosuppressive regimens [16]. In cases of failure to respond to first-line therapy, the KDIGO guideline recommends eculizumab, a monoclonal antibody directed towards complement C5. Therapies that have been tried include plasmapheresis,

steroids, rituximab, cyclophosphamide, and mycophenolate mofetil (MMF). Apart from MMF and steroids [16], data supporting the use of the other immunosuppressives have been disappointing [13,16]. Rabasco et al. reported that none of the patients treated with MMF plus corticosteroids doubled serum creatinine or progressed to ESKD during 44 months of follow-up [16]. At presentation, kidney function was mildly reduced with a median serum creatinine of 115 µmol/L and with an eGFR of 67 mL/min/1.73 $m^2$; none of the patients had >50% glomerulosclerosis or severe interstitial fibrosis. Only a single patient in our cohort received treatment with cyclophosphamide because of crescentic glomerulonephritis and who died at 14 months. Although there was a good response with improvement in kidney function, he died of complications related to treatment. There are currently no KDIGO guidelines regarding the treatment of C3GN complicated by crescentic glomerulonephritis. In cases of poor response to MMF, eculizumab should be considered. We do not have access to this drug because of the cost. Current clinical trials are exploring other drugs which target the alternate complement pathway and include danicopan (NCT03369236), CDX-1135 (NCT01791686), pegcetacopan (NCT05067127) and avacopan (NCT03301467).

A strength of this study was the long review period; however, there were some limitations. This was a small, retrospective, single-centre study. Missing data may have introduced bias. As a result of the small sample size, we could not perform a multivariable logistic regression analysis to identify predictors of the composite outcome. Although pronase-digested tissue was inaccessible, preventing us from ruling out any concealed light chain deposits, it is worth noting that only one patient in our study was over 50 years of age. According to the current KDIGO guidelines, conducting this assessment is recommended for patients over 50 [10]. Also, we were unable to quantify or perform genetic testing for existing mutations of alternative complement regulatory proteins known to be involved in the pathogenesis, due to a lack of access.

## CONCLUSION

This is the first study to estimate the incidence and describe the clinical presentation and outcome of C3GN in cases from SSA. Although we found an incidence rate similar to others, we speculate that this may be an underestimate. The overall prognosis was very poor mainly due to late presentation and lack of access to novel therapies.

### Conflict of interest

The authors have no conflict of interest to declare.

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