C3-Glomerulonephritis in New Zealand – A Case Series

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Abstract

Background: C3-glomerulonephritis can lead to progressive renal impairment from complement-mediated glomerular injury. Incidence and outcomes of C3-glomerulonephritis are not known in the New Zealand population.

Methods: We reviewed all cases of C3-glomerulonephritis from the past 10 years at a tertiary referral centre in New Zealand. Descriptive information on baseline characteristics and clinical outcomes was collected.

Results: 26 patients were included (16 men; mean±SD age 44±25 years) with a median follow-up of 30 months. Disease incidence was 1.3 cases per million individuals, of which 42% were Pacific Islanders. Most patients presented with renal impairment, with a median (IQR) creatinine at diagnosis of 210 (146-300) μmol/L, and 11 (42%) patients presented with nephrotic syndrome. Seven (27%) patients progressed to end stage renal disease and 2 (8%) had died. End stage renal disease occurred in 20% of patients treated with immunosuppression and in 50% of those not treated. Complete remission was seen in 25% of patients treated with some form of immunosuppression and in 17% of those not treated.

Conclusions: Our results are consistent with previous descriptions of C3-glomerulonephritis. There was a suggestion of better clinical outcomes in patients treated with immunosuppression. There was a higher disease incidence in Pacific Islanders, which may indicate an underlying susceptibility to complement dysfunction in this population.

Background

C3-glomerulonephritis (C3GN) is a rare form of glomerulonephritis occurring in around 1–2 per million individuals.[1–4] The disease results from excessive activity of the C3-convertase in the alternative complement pathway, leading to downstream complement activation and glomerular injury from C3-deposition and the C5b-9 membrane attack complex (MAC).[5,6] Biopsies feature isolated C3 immunofluorescence in the absence of other immunoglobulins and can be distinguished from a related entity, dense deposit disease (DDD), based on the location of C3 deposits seen on electron microscopy. DDD features linear intramembranous deposits, whereas deposits in C3GN are mesangial, subendothelial or subepithelial deposits.[7]

The activity of the C3 convertase can be increased by several mechanisms. C3 nephritic factor (C3NeF) is an acquired autoantibody that stabilizes he C3 convertase. Functional factor H deficiency from an inherited mutation or acquired defect can result in loss of inhibition of the C3-convertase.[1,6] Other complement proteins such as factors B and I can also be targeted by antibodies, and complement factor H-related protein gene mutations (CFHR1, CFHR2 and CFHR5) can also interfere with the binding of factor H to tissue-bound complement fragments.[4,7,8]

C3GN patients have variable levels of proteinuria (which may be nephrotic-range) and microscopic or macroscopic hematuria.[9,10] Reduced serum C3 levels are often seen. Patients have variable rates of renal function decline, and some may present with a rapidly progressive glomerulonephritis.[8] However, most studies describe poor long term outcomes in patients with C3GN and frequent progression to end stage renal disease (ESRD).[11] There are no previous descriptions of C3GN in New Zealand patients and treatment is based on international studies. New Zealand has an ethnically diverse population, and it is unknown whether Maori and Pacific Island populations have higher incidence of C3GN. To investigate this disease in our population we reviewed all cases of C3GN over the past 10 years.

Methods

This retrospective observational case series reviewed all patients with renal biopsy-confirmed C3GN over the past ten years at Auckland City Hospital in Auckland, New Zealand. This is a tertiary referral centre providing renal pathology services to around 1.9 million patients in the Auckland and Northland regions of New Zealand.

A database of renal histopathology reports was used to identify cases of C3GN from January 1st, 2008 - December 31st, 2018. Biopsies described on light microscopy as a membranoproliferative lesion with isolated C3 staining on immunofluorescence (or > two orders of magnitude more intense than other immunoglobulins) were included. All age groups were included. Patients with possible postinfectious GN based on electron microscopy findings were excluded if the clinical picture was supportive of this. All cases were reviewed with a renal histopathologist.

Baseline characteristics and outcomes were collected from electronic health records. Clinical outcomes included mortality, incidence of ESRD (defined as requirement for maintenance dialysis or transplantation), renal survival (defined as absence of ESRD during follow-up), progressive disease (defined as doubling of serum creatinine), stable disease (defined as no doubling of creatinine but without clinical remission) or clinical remission. Complete remission was defined by an estimated glomerular filtration rate (eGFR) of > 60 ml/min/1.73 m^2 (or a return to ± 15% of baseline values if baseline eGFR was < 60 ml/min/1.73 m^2) and proteinuria < 0.5 g/24hr (or equivalent protein/creatinine ratio).[12,13] Demographic data included age, gender, ethnicity and comorbidities. Laboratory data included initial creatinine, C3/C4 levels, other complement testing, proteinuria and hematuria. Nephrotic-range proteinuria was defined as a urine protein/creatinine ratio > 350 mg/mmol and microscopic hematuria was defined as > 5 red blood cells / high-power field. Treatment data included use of angiotensin converting enzyme (ACE) inhibitors, steroids and other immunosuppression. Histopathological findings included features on light microscopy (crescents, scarring, interstitial infiltrate and interstitial fibrosis), immunofluorescence (IgG, IgA, IgM, C3, C1q) and electron microscopy (location of deposits).

Results were reviewed by a biostatistician. Continuous variables were expressed as mean +/- SD or median with IQR. Only a small number of patients were included therefore multivariate logistic regression

was not performed. Study approval was obtained from the local ethics committees prior to study commencement.

Results

Baseline characteristics are shown in Table 1. A total of 26 patients were identified (16 males; mean ± SD age 44 ± 25 years) with a median follow-up of 30 months. There were 7 (27%) patients aged < 18 years. The most common ethnicity was Pacific Island (42%) followed by NZ European (31%) and NZ Maori (15%). The overall disease incidence was 1.3 cases per million individuals, 2.09 cases per million in NZ Maori and 5.6 cases per million in Pacific Island patients.

Table 1
Characteristics of patients at baseline and clinical presentation

Characteristic		All patients (n = 26)
Age at diagnosis, years (SD)		44 (25)
Median follow-up, months (IQR)		30 (19–46)
Gender, no. male (%)		16 (62)
Ethnicity, no. (%)	NZ European	8 (31)
	Maori	4 (15)
	Pacific Islander	11 (42)
	Asian	3 (12)
Comorbidities, no. (%)	Hypertension	14 (54)
	Type 2 diabetes	4 (15)
	Chronic kidney disease	4 (15)
Cr at diagnosis, umol/L (IQR)		210 (146–300)
Proteinuria, mg/mmol (IQR)		552 (293–983)
Dialysis at diagnosis, no. (%)		2 (8)
Hematuria, no. (%)	Microscopic	25 (96)
	Macroscopic	1 (4)
Complement levels, no. (%)	Normal	8 (31)
	Isolated low C3	12 (46)
	Low C3 and C4	5 (19)
	Not done	1 (4)
Complement screen, no. (%)	Not done	11 (42)
	C3NeF negative, Factor H normal	14 (54)
	Factor H deficiency	1 (4)
Monoclonal gammopathy, no. (%)	None	23 (88)
	MGUS	1 (4)
	Myeloma	2 (8)

*NZ: New Zealand; C3NeF: C3 nephritic factor; MGUS: monoclonal gammopathy of unknown significance

Most patients presented with renal impairment, with a median (IQR) creatinine at diagnosis of 210 (146–300) µmol/L, and nephrotic-range proteinuria (IQR) of 551.5 (293–983) mg/mmol (protein:creatinine ratio). 25 (96%) patients had microscopic hematuria. 12 (46%) had isolated low C3 and 5 (20%) had low C3 and C4. 15 (58%) patients had further complement screening but only one patient had an abnormality detected (Factor H deficiency). Monoclonal gammopathy was seen in 3 (12%) patients (2 with lambda light chain myeloma and 1 with MGUS).

The histopathological findings are summarized in Table 2. 17 (65%) of biopsies had some degree of interstitial infiltrate and median scarring (IQR) was only 7.5% (0–25). Deposits were seen in all locations on electron microscopy. Crescents were seen in 5 (19%) patients. No biopsies showed the typical dark, ribbon-like intramembranous deposits characteristics of DDD on electron microscopy.

Table 2
Histopathology characteristics on renal biopsy

Biopsy characteristic		**All patients (n = 26)**
Presence of EM deposits, no. (%)	Subepithelial	17 (65)
	Subendothelial	16 (62)
	Mesangial	22 (85)
	Intramembranous	9 (35)
Interstitial infiltrate, no. (%)		17 (65)
Intimal fibrosis, no. (%)		7 (27)
Scarring, median % (IQR)		7.5 (0–25)
Crescents, no. (%)		5 (19)
*EM: electron microscopy		

Treatment and clinical outcomes are shown in Table 3. Two patients required dialysis at initial presentation, and 8 (31%) progressed to ESRD and 2 (8%) had died after a median follow-up of 30 months. 16 (62%) patients were treated with an ACE-inhibitor. 12 patients were treated with prednisone and mycophenolate (MMF), 3 with prednisone and cyclophosphamide (of which one was also treated with plasma exchange), 3 with prednisone alone, and 6 patients received no immunosuppression. The two patients with myeloma were treated with a cyclophosphamide-bortezomib-dexamethasone (CyBorDex) regimen.

Table 3
Overall clinical outcomes

Treatment and outcome		All patients (n = 26)
Occurrence of ESRD, no. (%)		8 (31)
Mortality, no. (%)		2 (8)
Renal survival, no. (%)		18 (69)
Stable disease, no. (%)		11 (42%)
Complete remission, no. (%)		6 (23)
Treatment and outcome, no. (%)	ACE inhibitor	16 (62%)
	Prednisone only	3 (12)
	Prednisone and MMF	12 (46)
	Other immunosuppression	5 (19)
	Not treated	6 (23)
* ESRD: end-stage renal disease; ACE: angiotensin converting enzyme		

Clinical outcomes for each treatment subgroup are shown in Table 4. Of the 12 patients treated with prednisone and MMF, 2 had complete remission, 6 had stable disease and 4 progressed to ESRD. Of the 8 patients treated with other immunosuppression 3 had complete remission, 3 had stable disease, 1 had progressive disease and 1 progressed to ESRD. Of the 6 patients not treated with immunosuppression 1 had complete remission, 2 had stable disease (1 died) and 3 progressed to ESRD (1 died).

Table 4
Clinical outcomes by treatment subgroup

Outcome	No treatment (n = 6)	Prednisone and MMF (n = 12)	Other immunosuppression (n = 8)
Complete remission, no. (%)	1 (170)	2 (17)	3 (38)
Stable disease, no. (%)	2 (33)	6 (50)	3 (38)
Progressive disease, no.(%)	0 (0)	0 (0)	1 (13)
Occurrence of ESRD, no. (%)	3 (50)	4 (33)	1 (13)
Renal survival, no. (%)	3 (50)	8 (67)	7 (88)
* ESRD: end-stage renal disease; MMF: mycophenolate mofetil			

ESRD occurred in 25% of patients treated with some form of immunosuppression, and in 50% of those not treated. Complete remission was seen in 25% of patients treated with some form of immunosuppression and in 17% of those not treated. Renal survival occurred in 75% of those treated with some form of immunosuppression and in 50% of those not treated.

Of the 11 Pacific Island patients, 9 (82%) were treated with some form of immunosuppression. Of those, 1 (9%) had complete remission, 4 (36%) had stable disease, 1 (9%) had progressive disease and 3 (27%) progressed to ESRD. These results were similar to the overall cohort.

Discussion

This study describes the characteristics of 26 patients with C3GN in the New Zealand population, with a median follow-up of 30 months. Characteristics of C3GN have not been previously described in this population. Cases were spread across all age groups and were more likely to be of Pacific Island ethnicity. Most patients presented with elevated creatinine and nephrotic range proteinuria. An isolated low C3 was the most common finding on complement testing, although 20% had both low C3 and C4. Crescents were seen on biopsy in 19% of patients. After a median observation time of 30 months, around a third of patients had progressed to ESRD, similar to previous descriptions.[8] ESRD occurred in 25% of patients treated with some form of immunosuppression, and in 50% of those not treated. Complete remission was seen in 25% of patients treated with some form of immunosuppression and in 17% of those not treated.

In a 2015 UK study of 80 patients with C3-glomerulopathy, 29% of patients progressed to ESRD after a median period of 28 months.[10] Other studies have found most patients eventually progress to ESRD within a decade of diagnosis.[8,14] Studies by Medjeral-Thomas et al. and Sevais et al. found that immunosuppression failed to prevent C3GN from progressing to ESRD.[8,10]

In a 2015 Spanish retrospective observational study, 60 patients with C3 glomerulopathy were assessed for response to immunosuppression over a median period of 47 months.[12] 20 patients did not receive immunosuppression, 22 received steroids and MMF, and 18 received other immunosuppression (steroids and cyclophosphamide or steroids alone). The incidence of ESRD was lower in treated versus untreated patients (3 out of 40 versus 7 out of 20). No patients in the steroids and MMF group had doubling of serum creatinine or developed ESRD. In patients who received steroids and MMF, renal survival was 100% at 5 years compared with 80% for those who received other immunosuppression and 72% in those not treated. The rates of clinical remission were also higher in patients who received steroids and MMF.

There are no randomized trials to guide treatment decisions. Other treatments, such as plasma exchange, eculizumab and rituximab have only been discussed in case reports.[15,16] As a result, patients being considered for immunosuppression for treatment of C3GN in New Zealand usually receive prednisone and MMF. Prospective randomized trials would be useful to confirm the optimal treatment regimen.

Interestingly, we found only one underlying complement abnormality, although comprehensive complement testing was not performed in many cases. This patient had factor H deficiency and was treated with prednisone and MMF and had stable disease at follow-up. Initial screening available in New Zealand includes testing for C3NeF and Factor H deficiency - previous reports state that up to 50% of cases of C3GN are caused by the presence of C3NeF.[8] Testing for underlying complement pathway abnormalities may have particularly utility in those being considered for future renal transplant.[17] Three of our cases had underlying monoclonal gammopathy, which has a well-established association with C3GN.[18] It is unknown whether Pacific Island patients have an underlying susceptibility to complement dysfunction which may account for the higher disease incidence in this population, or whether other novel mechanisms exist. Pacific Island patients have higher rates of diabetes, hypertension and obesity which result in higher rates of ESRD. [19] Aside from post-streptococcal glomerulonephritis, it is unknown whether Pacific Island patients are more susceptible to other forms of glomerulonephritis.[20] Pacific Island patients in our cohort did not appear to have significant differences in treatment or clinical outcomes.

The main limitation of this study is the small number of patients, however our data set represents all cases in the Auckland and Northland regions of New Zealand over the past ten years. Our histopathology laboratory serves all major hospitals in these regions (~ 1.9 million patients) giving an estimated annual incidence of 1.3 per million, similar to that documented elsewhere.[1] We were not able to collect a sufficient number of patients to allow multivariate logistic regression to detect important predictors of renal outcome. As a result, any inferences of treatment efficacy are limited. Patients with more severe disease may have been more likely to receive immunosuppression. As noted, limited complement testing was available at our centre.

Conclusion

This case series describes the clinical presentation of C3GN in New Zealand. Overall incidence appears to be similar to that reported in international literature though Pacific Island patients had slightly higher preponderance. Treatment with immunosuppression may reduce progression to ESRD in patients with C3GN.

Abbreviations

C3GN
C3 glomerulonephritis
DDD
Dense deposit disease
MAC
Membrane attack complex
C3NeF
C3 nephritic factor

ESRD
End stage renal disease
eGFR
Estimated glomerular filtration rate
MMF
Mycophenolate mofetil
NZ
New Zealand

Declarations

Ethics approval and consent to participate: Study approval was obtained from Counties Manukau Health Research Office and Health and Disability Ethics Committees (HDEC) prior to study commencement. Ethics Reference Number: 18/STH/210; Research Registration Number: 798

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests: None

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Authors' Contributions: Research idea and study design: HT; data acquisition: LS; Manuscript preparation: LS, HT. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors have read and approved the manuscript.

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