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Original Article

Clinical Presentation and Outcome of c1q Nephropathy - A Single-Centre Prospective Study

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Abstract

Background: C1q nephropathy is a rare glomerular disease with characteristic mesangial c1q deposition noted on immunofluorescence microscopy. It is histologically defined and poorly understood. Light microscopic features are heterogeneous and comprise minimal change disease, focal segmental glomerulosclerosis (FSGS), and proliferative glomerulonephritis (GN).

Aim: This study aims to study the clinical presentation, histopathological profile, and outcomes in patients with c1q nephropathy.

Methods: A total of 13 patients who satisfied the above criteria were studied. Clinical profile and laboratory parameters including urine analysis, urine spot protein-creatinine ratio, blood biochemistry, serum complement, and histopathological profile were analyzed. Creatinine clearance was estimated using Cockgraut Gault formula. They were followed up for the assessment of response to treatment.

Results: Among the 13 patients, 12 were female (92.3%). All (100%) were hypertensive at the time of presentation. Age ranged from 15 to 48 year with the mean of 34 years. Microscopic hematuria was found in all 13 patients (100%). Nephrotic proteinuria was found in 10 patients (77%), and 4 patients (30.7%) had GFR <60 mL/min. The kidney biopsy revealed diffuse proliferative glomerular nephritis (DPGN) in 12 patients (92.3%), one patient had FSGS (7.7%). Cellular crescents were found in 2 patients (15.3%). One patient was lost for follow-up. 3 patients (25%) improved with ACE inhibitors and statins. 9 patients (69.2%) were started on steroids, of which the four patients who had renal failure received cyclophosphamide in addition to steroids. Of the nine patients, complete remission was found in 2 patients (22%), partial remission in 2 patients (22%), and no response to immunosuppressive medication was seen in 5 patients (55.5%) (one patient had FSGS and four patients had DPGN).

Conclusion: Of the 13 cases with c1q nephropathy, all patients had hypertension and microscopic hematuria. Nephrotic proteinuria was seen in three-fourths of the patients. The most common histopathological presentation was diffuse proliferative GN. Half of the patients showed poor response to oral steroids.

Key words: Antinuclear antibodies, C1q nephropathy, C3, C4, Diffuse proliferative glomerulonephritis, Focal segmental glomerulosclerosis, Immunosuppressive medication, Minimal change disease, Nephrotic proteinuria

INTRODUCTION

C1q nephropathy, first described by Jennet and Hipp in 1985, as a pattern of glomerulonephritis (GN) characterized by predominant mesangial c1q deposition but with other histological features resembling lupus nephritis.[1] This is a variant of lupus nephritis called seronegative lupus nephritis, yet at the time of presentation of renal disease, there is no past or present clinical or serological evidence of systemic lupus erythematosus (SLE).[2,3] It is proposed that if the pattern has renal histology entirely consistent with lupus nephritis, a significant proportion of them will in due course develop overt SLE.[3] The prevalence of c1q is 0.2–16.0% and seems to be higher in children.[3] C1q nephropathy often manifests as steroid-resistant asymptomatic proteinuria or nephrotic

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syndrome. Light microscopic features are heterogeneous and comprise no glomerular lesion, focal segmental glomerulosclerosis (FSGS), and proliferative GN.[4-6] The clinical and microscopic presentations are quite varied, and the diagnosis is based on histopathology. Likewise, outcomes generally depend on clinical and histological factors. Patients presenting with lower level proteinuria, nephritic syndrome, and the histologic variant of minimal change disease (MCD) tend to have favorable outcomes, as opposed to those with nephrotic range proteinuria and FSGS variant having unfavorable outcomes.

Aim

This study aims to study the clinical presentation, histopathological profile, and outcomes in patients with c1q nephropathy.

MATERIALS AND METHODS

This is a retrospective case series analysis that was done in Kilpauk Medical College. Inclusion criteria are patients with renal biopsy showing dominant or codominant c1q immune deposits were analyzed for clinical, biochemical, and histopathological profile. Patients with clinical and serological evidence of lupus and hypocomplementemia were excluded from the case series. 13 patients who satisfied the criteria for c1q nephropathy were analyzed. All the patients were examined clinically for the presence of systemic hypertension, pedal edema, and extrarenal manifestations of lupus (malar rash, discoid rash, photosensitivity rash, recurrent oral ulcer, non-erosive arthritis, polyserositis, neuropsychiatric lupus, hemolytic anemia, and thrombocytopenia). Urine analyzed for red blood cells (RBCs) and urine spot protein-creatinine ratio (PCR). Serum creatinine, creatinine clearance (Cockcroft-Gault formula), antinuclear antibodies (ANA), C3, and C4 were done.

RESULTS

Total of 13 patients, among them 12 were female. Mean age group of our cohort was 34 years. Predominant age was between 20 and 40 years of age.

All 13 patients had systemic hypertension (100%) and pedal edema (100%). Nephrotic proteinuria was found in 10 patients (77%), other 3 patients (23%) had non-nephrotic proteinuria. Average urine spot PCR was 6.5. Microscopic hematuria was found in all patients (100%). Renal failure was found in 4 patients (33%). In all 13 patients, C3 and C4 were in normal range [Table 1].

In accordance with the selection criteria, all 13 cases had positive glomerular staining for c1q in the mesangium, in addition to that IgG, IgM, and IgA (full-house pattern) were also found in 12 patients with diffuse proliferative GN. Dense c1q deposit with the intensity of 3+ or 4+ was found in all 13 patients. In all cases, c1q was deposited in mesangial areas, and in some cases, c1q deposits found in peripheral areas of the glomerulus [Figure 1].

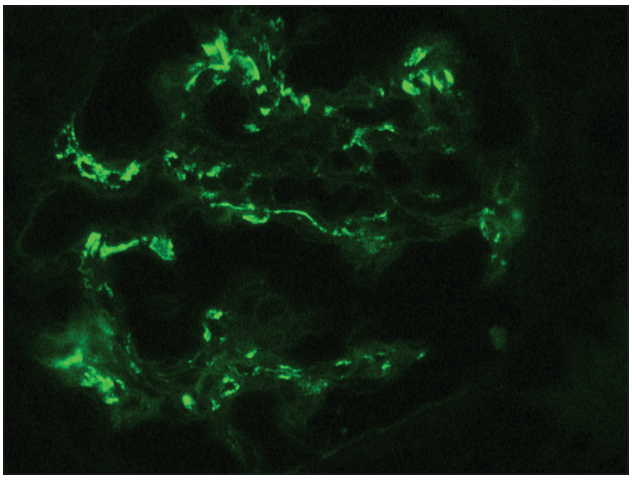

Figure 1: C1q deposits in mesangium

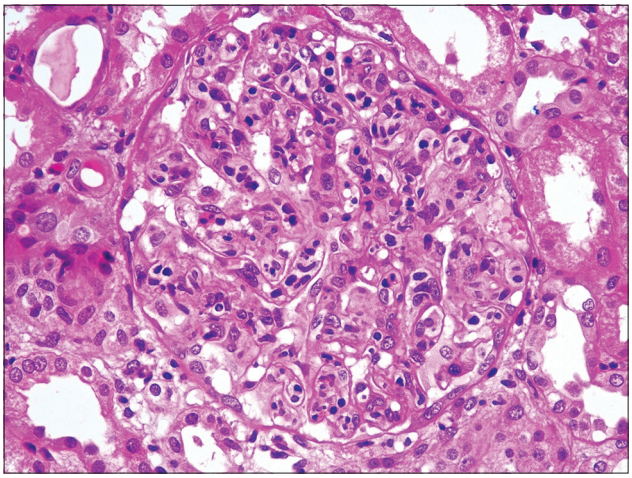

Figure 2: Diffuse endo capillary proliferation

Light microscopic examination showed 12 patients had features of diffuse proliferative glomerular nephritis (DPGN) (92.3%). Among them, two patients had fibrocellular crescents. 1 patient (7.7%) showed features of FSGS [Table 2 and Figure 2].

All patients received angiotensin-converting enzyme (ACEI) and statins (100%). 9 patients (69.2%) received immunosuppressive medications. 5 patients (55.5%) were treated with steroids alone. 4 patients (30.7%) with renal failure were treated intensively by following the National Institute of Health protocol of Class IV lupus nephritis. Cellular crescent was found in two patients.

Table 1: Distribution of clinical presentation

Date of admission	Age	Sex	BP	U. Alb	U. Dep RBC/hpf	U. Spot PCR	S. creatinine	CR. CL mL/min
12/07	29	F	160/100	3+	5–6	3.2	1.1	89
3/09	24	F	150/90	4+	8–10	2.8	3.1	24
3/09	29	F	160/100	2+	3–4	3.0	1.5	46
7/09	36	F	150/100	2+	6–7	1.5	1.1	74
7/09	48	F	170/100	4+	10–15	3.03	0.9	67
1/10	30	F	150/90	4+	9–10	12.45	0.8	85
2/10	20	M	170/100	3+	9–10	4.7	0.9	79
3/10	33	F	200/120	4+	4–5	6.2	2.7	28
4/10	26	F	160/100	4+	10–11	4.5	1.0	76
5/10	40	F	150/100	4+	4–5	15.4	1.5	59
6/10	14	F	140/100	4+	8–10	12.7	0.9	84
6/10	20	F	150/100	4+	15–18	11.0	1.2	74
10/10	45	F	160/100	4+	4–6	4.0	1.0	73

PCR: Protein-creatinine ratio, RBCs: Red blood cells

Table 2: Distribution of renal histopathology

Age	Sex	ANA	C3	C4	LM	IF
29	F	−Ve	132	42.5	Segmental sclerosis-FSGS	C1q4+M
24	F	−Ve	138	31.90	DPGN - partial fibrocellular crescent	C1q4+M
29	F	−Ve	142	25.3	DPGN	C1q4+PM
36	F	−Ve	133	20.1	DPGN	C1q4+PMD
48	F	−Ve	173	21.5	DPGN - ?FSGS	C1q4+M
30	F	−Ve	113	43.4	DPGN	C1q4+PM
20	M	−Ve	136	33.3	DPGN	C1q4+PMD
33	F	−Ve	142	23.6	DPGN - fibrocellular crescent	C1q4+PM
26	F	−Ve	102	28.5	DPGN	C1q4+PMD
40	F	−Ve	155	45.2	DPGN	C1q4+PM
14	F	−Ve	137	38.9	DPGN	C1q4+PMD
20	F	−Ve	129	40.4	DPGN	C1q4+PMD
45	F	−Ve	150	44.7	DPGN	C1q4+PMD

FSGS: Focal segmental glomerulosclerosis, ANA: Antinuclear antibodies, DPGN: Diffuse proliferative glomerulonephritis

2 patients (22%) with crescents and 1 patient (11.1%) with massive proteinuria and renal failure received three daily pulses of injection. Methylprednisolone and 6 monthly pulses of injections Cyclophosphamide and followed with oral prednisolone. 1 patient (11.1%) with renal failure was treated with three daily doses of injections. Methylprednisolone and mycophenolate mofetil and oral prednisolone [Table 3].

One patient with diffuse proliferative GN lost the follow-up. Other 12 patients are on regular follow-up. Mean duration of follow-up was 14.4 months. Apart from ACEI and statins, nine patients who received immunosuppressive medication are on low-dose prednisolone now. Three patients are receiving azathioprine in addition to oral steroids.

Complete remission was defined as urine spot PCR <0.5, absence of microscopic hematuria, and normal glomerular filtration rate. Partial remission was defined as urine spot PCR between 1.0 and < 3.0, with or without RBC in urine and normal glomerular filtration rate.

3 patients (28%) were remitted with ACEI and statins. Remission with oral steroids was found in 2 patients (22%). Partial remission was found in 2 patients (22%), among them one had fibrocellular crescent, and renal failure was treated with three doses injection Methylprednisolone and 6 monthly pulses of injections Cyclophosphamide. 5 patients (55.5%) showed resistant to immunosuppressive medication, of which on histopathology one had FSGS and four had DPGN. Among the five patients, three had renal failure and one among them had partial fibrocellular crescent. These three patients were treated with injections. Methylprednisolone, injection Cyclophosphamide, and oral prednisolone. None of the patients progressed to chronic kidney disease Stage V.

DISCUSSION

C1q nephropathy is a controversial and uncommon form of GN characterized by mesangial Ig and complement deposits predominantly c1q with no evidence of SLE. It is a distinct clinicopathological entity of steroid-resistant nephrotic syndrome1.

Diagnostic Criteria for C1q Nephropathy[1,2]

1. Dominant or codominant c1q staining in kidney biopsy
2. Mesangial electron dense deposits
3. No clinical or serological evidence of SLE.

Two predominant clinicopathological subsets of c1q nephropathy are as follows:

1. Podocytopathy with a minimal change lesion or FSGS which typically presents with nephrotic syndrome
2. The typical immune complex glomerular disease that varies from no glomerular lesion to diffuse form of glomerular lesion.

Table 3: Distribution of treatment and follow-up

Age	Sex	Immunosuppressive medication	Duration of follow-up (months)	S. Cr	U. Alb	U. spot PCR	Response
29	F	Oral steroids	30	1.2	4+	4.0	NR
24	F	MP - three doses, cyclo six doses, PDN+AZA	22	1.3	3+	2.0	PR
29	F	MP - three doses MMF+PDN	18	1.5	3+	3.0	NR
36	F	ACEI+Statins	14	0.8	+	0.3	SR
48	F	ACEI+Statins	14	0.9	Nil	0.2	SR
30	F	Oral steroids - 4 months	12	1.0	Nil	0.4	R
20	M	No follow-up					
33	F	MP - three doses, four doses of CYCLO Low-dose PDN+AZA	9	2.5	4+	3.5	NR
26	F	ACEI+Statins	9	0.8	Trace	Nil	SR
40	F	MP 3 doses+6 doses of cyclo low-dose PDN	8	1.6	4+	3.0	NR
14	F	Oral steroids	8	0.8	4+	3.5	NR
20	F	Oral steroids+AZA	4	1.1	Nil	1.0	PR
43	F	Oral steroids	3	0.9	Nil	0.2	R

MMF: Mycophenolate mofetil, PCR: Protein-creatinine ratio, ACEI: Angiotensin-converting enzyme

C1q, the first component of the complement cascade, is a pentamer compound consists of single c1q, two c1r, and two c1s. The complement cascade begins with the CH2 domain of IgG molecule binding to c1q, leads to conformational changes that sequentially activate c1r and c1s, and initiates a cascade of downstream events. C1q is a large calcium-dependent glycoprotein had Ig-binding site and controlled triple helical collagen-like domain. C1q results from complement activation by IgG. Hence, IgG is a codeposit along with c1q. C1q fixes the Ig that may become trapped non-specifically in the mesangium due to increased mesangial trafficking and defective clearance of plasma proteins. Ultrastructurally, c1q is located in the paramesangial area. Paramesangial area is a site where small electron dense deposits are not uncommonly seen. In MCD/FSGS, non-specific deposit of IgM and/or C3 can be seen in the paramesangial area. In the absence of the history of autoimmune disease, it is unlikely that the deposits of IgG and c1q can be found in the paramesangial area.[7-10]

When c1q nephropathy presented as proliferative GN, it shares some features with IgA nephropathy in renal biopsy. Overlapping with IgA nephropathy can be differentiated by more intense staining of c3 than c1q in IgAN.[8] In contrast to lupus nephritis, tubular reticular inclusions and antibody against c1q are usually negative in c1q nephropathy.[9]

Iskandar *et al.* reported that a series of 15 children with c1q nephropathy, in their experience c1q nephropathy, appear to fit within the morphology of MCD/FSGS, and the most common presentation is nephrotic or non-nephrotic proteinuria.[6]

Markowitz *et al.* reported that the largest series of c1q nephropathy, histologically falls within MCD/FSGS continuum and appears to exhibit the full spectrum of the histological variant of FSGS. Their cohort of 19 patients was predominately African-American females, and the cohort age group falls between 10 and 30 years of age. Their cohort had full nephrotic range proteinuria in 50% and renal insufficiency in 27.8%. The light microscopic evaluation showed MCD (two cases), FSGS NOS (nine cases), collapsing FSGS (six cases), and cellular FSGS (two cases). The outcome was generally good with 7 of 13 patients entering into partial or complete remission over a mean follow-up of 27.1 months.[5]

Davenport *et al.* reported four adult patients with c1q nephropathy, the pattern of glomerular disease was MPGN Type III, DPGN, FSGS, and membranous nephropathy. All had nephrotic proteinuria and renal insufficiency. Hypocomplementemia was reported in three patients, three patients underwent spontaneous remission, and one patient with FSGS had complete remission with steroids and cyclosporine.[11]

Sharman *et al.* reported nine cases with c1q nephropathy with the different light microscopic picture of diffuse proliferative GN (three cases) FSGS (two cases), combined membranous and mesangial proliferation (three cases), and crescentic GN (one case). All nine patients had c1q deposit in the mesangial and paramesangial region. In this series, more patients had asymptomatic proteinuria with the fewer nephrotic syndrome when compared with other studies. Ultrastructural evidence of tubule reticular inclusion was absent in all patients. Poor response to corticosteroids with the renal survival of 85% at 3 years was reported.[10]

In our cohort, we had predominately female patients (12 of 13 patients), all satisfied the diagnostic criteria of c1q nephropathy as suggested by Jennet and Hipp. In our cohort, DPGN was the dominant histopathological finding with the partial cellular crescent in two patients, nephrotic proteinuria in 10 patients, and renal failure was found in four patients. Steroid unresponsiveness was found in five patients (one FSGS and four DPGN) and none of them

showed the progression of renal failure. In concordance with Davenport *et al.* reported in NDT 1992 and Sharman *et al.* reported in NDT 2004, our cohort was predominantly DPGN. Reanalysis of ANA, C3, and C4 was negative and normal levels, respectively. Our cohort did not undergo assay of anti-c1q antibody and electron microscopy examination for tubuloreticular inclusions.

CONCLUSION

All of our patients had hypertension and microscopic hematuria. Nephrotic proteinuria was found in three-fourths of the patients. The most frequent histopathological presentation was diffuse proliferative GN. Inadequate response to immunosuppressive medication was found in more than half of the patients.

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