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A clinicopathological study of C1q nephropathy: A single center experience

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Abstract

Background: C1q nephropathy also known as seronegative lupus nephritis, is a relatively rare form of glomerulonephritis which is less understood till now. With the advancement of immunofluorescence and electron microscopic histopathological examination more and more new cases are being diagnosed now a days. Previously it was considered as a diseases of children and young adults but in practical point of view a large number of adult patients are affected by these diseases. The aim of this study is to review the incidence, clinical features, histolopathological morphology of C1q nephropathy in adult Bangladeshi population in BSMMU.

Methods and Material: This is a retrospective study done in nephrology department of BSMMU. Out of 180 biopsy reports which were done in between 2020 to 2025, 10 reports of C1q nephropathy were retrieved.

Results: This study shows the incidence of C1q Nephropathy is 5.5%, mostly females are affected (80%). Mean age at presentation was 35.5 year. Most common presentation was hematuria with sub nephrotic range proteinuria(50%), Nephrotic range proteinurea was present in 20% cases, 2 patients presentd with isolated proteinuria(20%). 1 patient (10%) presented with renal impairments. Regarding histopathological findings all patients had mesangeal proliferation, 70% patients had dominant and 30 % patients had co-dominant deposition of C1q in the mesangium.

Conclusion: This study gives an idea regarding the clinicopathological findings of C1q nephropathy in Bangladeshi population.

Keywords: C1q nephropathy; Proteinurea; Hematuria

Introduction

In 1985, the medical researchers Jennette and Hipp made a significant contribution by first identifying C1q nephropathy as a distinct pathological entity [1]. This rare kidney disease is primarily characterized by the prominent deposition of C1q, a key component of the immune system, within the mesangium, the supportive tissue in the glomeruli of the kidneys. Unlike lupus nephritis, which shares similar histological characteristics, C1q nephropathy lacks the clinical manifestations and serological markers typically associated with lupus [2]. This distinction highlights the unique nature of C1q nephropathy.

Epidemiological studies indicate that the prevalence of C1q nephropathy in renal biopsies varies significantly, ranging from 0.2% to as high as 16%, with an increased incidence observed in pediatric populations [3]. Despite this variance, the underlying pathophysiology of C1q nephropathy remains

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poorly understood, posing challenges for effective diagnosis and treatment.

The heart of this pathology is C1q, which plays a critical role in the complement system—a vital part of the immune response responsible for activating the classical pathway. C1 is a complex protein composed of five subunits: two C1q, two C1r, and a single C1s component. When immune complexes form, they bind to the C1q part of the C1 molecules, triggering the activation of the complement cascade. The presence of C1q receptors in the glomerular mesangium leads to extensive activation of the complement system, which is primarily responsible for the resultant glomerular injuries observed in this condition. [4,5,6]

From a histopathological perspective, light microscopy findings categorize C1q nephropathy into two main groups: (1) Minimal Change Disease/Focal Segmental Glomerulosclerosis (MCD/FSGS) and (2) immune complex-mediated proliferative glomerulonephritis (GN). The immune complex-mediated GN group can further be classified into various types, such as focal or diffuse mesangial proliferative GN, membranous GN, and membranoproliferative GN [7].

Direct immunofluorescence microscopy (DIF) reveals striking findings, including the dominant or co-dominant deposition of C1q within the mesangium and along the capillary walls. Additionally, immunoglobulin deposits (IgG, IgM, and IgA) are often noted, and in some instances, a full-house deposition may be observed, characterized by the simultaneous presence of multiple immunoglobulins.

Electron microscopy provides further insights, showing electron-dense deposits in the mesangium and capillary walls, along with signs of podocytopathy and effacement of the foot processes, which are crucial for kidney filtration. Clinically, C1q nephropathy commonly presents with significant proteinuria and hematuria. In more severe cases, it can lead to renal impairment and may mimic rapidly progressive glomerulonephritis (RPGN).

Despite ongoing research, only a handful of large-scale studies have been conducted to deepen our understanding of this rare form of glomerulopathy. The literature showcases a variety of clinical presentations, but most studies emphasize either isolated proteinuria or nephrotic syndrome as the most prevalent manifestations [10]. It is noteworthy that patients with C1q nephropathy often exhibit resistance to steroid treatments, complicating management strategies [17]. In our study, we aim to share our experiences and findings regarding C1q nephropathy over the past five years, contributing to the growing body of knowledge about this intriguing and complex kidney disorder.

Materials & Methods

This study focuses on kidney biopsies conducted at BSMMU between 2020 and 2025. We reviewed 180 biopsy reports to identify cases that met specific criteria. These criteria included: 1. The presence of mesangial dominant or codominant deposition of C1q in immunofluorescence microscopy, and 2. The absence of clinical and serological markers for systemic lupus erythematosus (SLE).

From this review, we successfully identified 10 cases that met these criteria for further evaluation. All biopsies were performed at our institution, where our dedicated team carried out the histopathological evaluations. After comprehensive assessments by nephrologists, we implemented sonographically guided percutaneous biopsies to ensure accuracy and patient safety.

Following proper preservation of the tissue samples, we proceeded with light and immunofluorescence microscopic examinations. For the light microscopy, we utilized various staining techniques, including Hematoxylin and Eosin (H&E), Periodic Acid-Schiff (PAS), silver stain, and Masson's trichrome stain. Each of these stains plays a crucial role in visualizing different components of kidney tissue. In the immunofluorescence analysis, we focused on identifying key markers such as immunoglobulins IgG, IgA, IgM, complement C3, C1q, fibrin, and light chains. While we were unable to conduct electron microscopy due to facility limitations. The extensive evaluations we performed have provided valuable insights into the renal conditions observed in the selected cases. This study highlights the importance of careful analysis and the role of thorough evaluations in understanding kidney pathology.

Operational definition:

C1q nephropathy is defined by the presence of mesangial immune deposits that stain dominantly or co-dominantly for C1q, accompanied by negative antinuclear antibodies (ANA) in the patient's serum, and the absence of clinical evidence for SLE2.

Nephrotic range proteinuria was defined as proteinuria with 3.5 g/day/1.73 m2 of body surface area or greater.

Sub-nephrotic range proteinuria is passage of protein 0.5-3.5 gm/day/1.73 m2 of body surface area

Isolated proteinuria: Isolated proteinuria is defined as non-nephrotic range proteinuria without abnormalities in the urinary sediment, including hematuria, as well as the absence of hypertension or diabetes14

Hematuria was defined as 3 or more erythrocytes per high-power field of urinary sediment.

Renal insufficiency was defined as calculated creatinine clearance below normal values for patient age and sex defined.

Mesangial hypercellularity was defined as 4 or more mesangial cells per mesangial area.

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Statistical Analyses:

The data were analyzed using the SPSS software program. Descriptive statistics of mean was used for continuous variables, and numbers (percentages) for categorical variables

Results

In this study, we evaluated a total of 10 biopsy findings of C1q nephropathy. All patients are adults. The mean age of the patient was 35.5 years. Younger patient was 19 years and the older one was 50 years Among the 10 patients, 8 patients are female (80%) and 2 patients are male (20%) (Table 1). Regarding clinical presentation, 9 patients presented with swelling (90%) and one patient presented with isolated hematuria without swelling (10%). Laboratory investigations show 9 patients had significant proteinuria among them 2 patients had nephrotic range proteinuria rest of the 7 patients had sub nephrotic range proteinuria. 7 patients presented with haematuria (70%). One patient had renal impairment. Others had normal renal function (Table 2). Regarding the serological marker, patients had normal C3, C4, ANA, Anti ds DNA, HbsAg, Anti HCV, P-ANCA, C-ANCA all were negative.

Table 1: Distribution of participants according to demographic variables

Demographic characteristics		Frequency	Percentage
Age	18-30	3	30%
	31-40	4	30%
	41-50	3	40%
	>50		
Gender	Male	2	20%
	female	8	80%

Follow up:

Among the 10 patients, 6 patients lost follow-up. 2 patients had spontaneous remission after one month. Other two patients respond to oral corticosteroids with normal renal function after one year of follow-up.

Discussion

Decades have passed since C1q nephropathy was first described. However, due to its rarity, there have been very few studies conducted in South Asian countries. Our study aimed to determine the clinicopathological correlation of C1q nephropathy in the Bangladeshi adult population. We retrospectively evaluated 180 biopsy findings, of which 10 met the criteria for C1q nephropathy in patients without clinical or serological evidence of systemic lupus erythematosus (SLE).

In our study, the incidence of C1q nephropathy was found to be 5.5%, which aligns with findings from Iskandar et al. and several Western studies [3]. Previous research indicated that this relatively uncommon glomerulonephritis is more common in younger individuals, with an average age of 17.8 years [8]. However, our study evaluated adult patients, revealing a mean age of presentation at 35.5 years. This suggests that C1q nephropathy can affect any age group, highlighting the need for a high level of clinical suspicion when dealing with suspected cases.

Among the 10 patients studied, 8 were female (80%). Other studies, such as the one by Markowitz et al., reported that 73% of adult C1q nephropathy patients were female [7], while Vizjak et al. found a higher prevalence in males [9]. In pediatric cases, the male-to-female ratio is nearly equal [12].

Of the 10 cases, 5 patients (50%) presented with hematuria along with sub-nephrotic range proteinuria, while only 2 patients (20%) presented with nephrotic range proteinuria.

Table 2: Clinical and laboratory data of patients with C1q nephropathy:

Patient	Clinical features	Haematuria	Proteinuria (gm/day)	S.creatinine (mg/dl)	Serological markers (C3,C4,ANA,Anti ds DNA, HBsAg, Anti HCV, P-ANCA, C-ANCA)	Remarks
1	Bilateral leg swelling	present	1	1.04	negative	
2	Recurrent leg swelling for 4 years	absent	6.5	0.58	negative	
3	Generalized swelling	absent	2.4	0.7	negative	
4	Generalized swelling,	present	4.1	0.9	negative	
5	Generalized swelling	present	1.2	0.9	negative	
6	Generalized swelling	present	3	0.6	negative	
7	Leg swelling	absent	1.6	1.4	negative	
8	Leg swelling	present	1	1.1	negative	
9	Isolated hematuria for 4 months	present	0.18	1.15	negative	resolved spontaneously
10	Leg swelling	present	1	0.9	negative	resolved spontaneously

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Figure 1: Distribution of clinical presentation of C1q nephropathy.

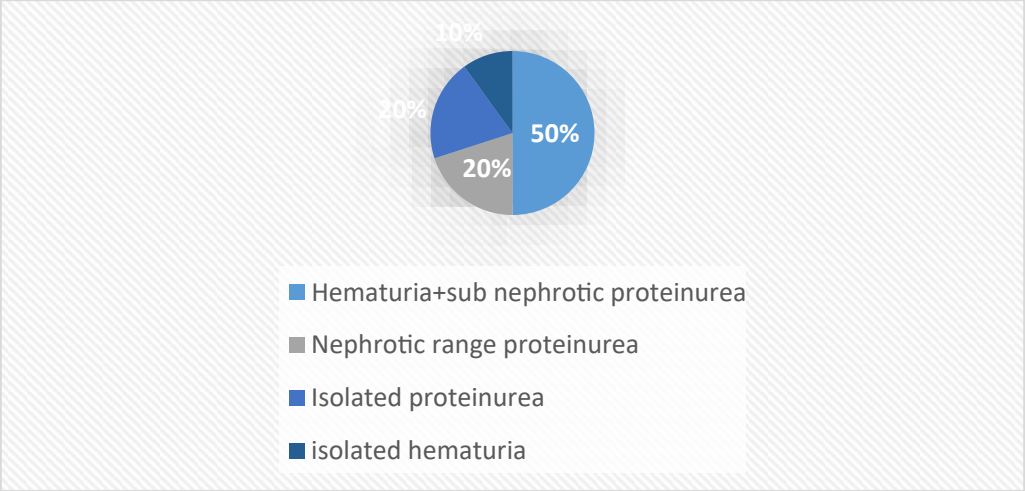

Table 3: Histopathological findings of C1q nephropathy

Patients	Light microscopy				DIF
	cellularity	matrix	GBM	Sclerosis	
1	increased	increased	thick	absent	C1q :3+, IgG 2+, Mesangial deposition
2	increased	increased	Not thick	absent	C1q :3+, IgG 1+,IgM1+,IgA1+,Kappa 1+, lambda: trace Mesangial deposition
3	increased	increased	Not thick	1/10	C1q :3+, IgG 1+,IgM1+,IgA1+,Kappa 1+, lambda : trace Mesangial deposition
4	increased	increased	thick	5/21	C1q :3+, IgG 2+,IgM1+,IgA1+,Kappa 3+, C3 1+ Mesangial + GBM deposition
5	increased	increased	Not thick	absent	C1q :3+, IgG 2+ Mesangial deposition
6	increased	increased	thick	absent	C1q :2+ Mesangial deposition
7	increased	increased	thick	absent	C1q :3+, IgG 2+, IgM 1+, IgA 1+, C3 1+, Kappa 2+ Mesangial deposition
8	increased	increased	Not thick	absent	C1q :2+ Mesangial deposition
9	increased	increased	Not thick	2/13	C1q :3+,IgG 2+, IgA3+, Kappa1+ Mesangial deposition
10	increased	increased	thick	absent	C1q : 2+ ,C3 : 1+ Mesangial deposition

One patient exhibited mild renal impairment at presentation. Hitasho et al. reported that asymptomatic hematuria and/or proteinuria were the most prevalent clinical findings, observed in 36 (59%) of his patients [15]. Similarly, Nishida et al. described 4 pediatric cases of C1q nephropathy, three of which had asymptomatic urine abnormalities and a relatively favorable clinical course [13]. Our findings support the notion that C1q nephropathy can present with a range of features, including hematuria, sub-nephrotic range proteinuria, nephrotic range proteinuria, and isolated hematuria.

All patients in our study were negative for ANA and anti-ds-DNA, and C3 and C4 levels were normal. Histopathological examinations revealed that all patients exhibited mesangial proliferation. Six patients had thickened basement membranes, and five patients showed varying degrees of glomerular sclerosis. In a study by Jennette and Hipp, 800 renal biopsies were evaluated, and 15 were identified as having C1q nephropathy. Vizjak et al., with the largest cohort of 72 cases, noted that the most common histological patterns were minimal change disease (MCD, 27 cases), followed by focal segmental glomerulosclerosis (FSGS, 11 cases) and proliferative glomerulonephritis (20 cases) [9]. A study conducted in Saudi Arabia from 2001 to 2011 identified 11 patients with C1q nephropathy, with 9 biopsies showing variable degrees of mesangial hypercellularity and 2 cases exhibiting FSGS [16].

The results from our study and the existing literature indicate that this multifaceted condition can present with various histopathological patterns [11]. In our findings, 70% of patients had predominant deposition of C1q, while 30% had co-dominant deposition, and proliferative glomerulonephritis was seen in 20 (28%). The clinical course of C1q nephropathy appears to depend on histological findings and clinical presentation. Both MCD and the mesangial proliferative

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glomerulonephritis variant are associated with relatively good prognoses, whereas FSGS is linked to worse outcomes [10].

Due to the lack of electron microscopy facilities, we could not adequately evaluate podocyte injury. Consequently, ultimate clinical outcomes could not be determined since 6 patients (60%) lost to follow-up. However, 2 patients responded well to steroid treatment, and after one year of follow-up, their renal function returned to normal. Notably, two patients presented with isolated hematuria; one also had sub-nephrotic range proteinuria. Remarkably, both patients achieved spontaneous remission without any immunosuppressive medication.

Limitation:

The study population involved in this research was relatively small, which may limit the comprehensiveness of our findings. To truly capture the clinicopathological features of C1q nephropathy in Bangladesh, it is essential to conduct a multicenter study that encompasses a larger group of participants. Unfortunately, we were unable to assess the electron microscopic features of the condition due to the absence of these specialized facilities within our country at present. Furthermore, the accuracy of our observations regarding clinical features and their correlation with histopathological findings would be significantly enhanced if we had the opportunity to conduct follow-ups with all 10 patients involved in the study. Such follow-ups would provide a more nuanced understanding of the disease's progression and its clinical implications.

Conclusion

In this report, we aim to provide a comprehensive overview of our experiences with C1q nephropathy over the past five years. This rare form of kidney disease presents differently depending on the geographical location, leading to significant variations in its clinical features, progression, and outcomes across different countries. Despite ongoing research, the precise pathophysiology of C1q nephropathy remains largely elusive, as multiple studies have highlighted a range of clinical manifestations and laboratory results that differ markedly from one another. To enhance our understanding of this complex glomerulonephritis, we believe it is crucial to conduct a well-structured, multicenter study that can incorporate diverse patient populations and establish a clearer picture of the disease's underlying mechanisms and treatment strategies.

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