CASE REPORT

C1q Nephropathy: A Rare Cause of Nephrotic Syndrome in Adults

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Abstract

C1q nephropathy first described in 1985 is a rare cause of glomerular diseases, especially in adults, but still not much is known about and lacks specific guidelines. The diagnosis is based on mesangial C1q deposition either dominant or codominant pattern in the absence of systemic lupus erythematosus (SLE). Here, we report a 28-year-old female who presented with anasarca, frank nephrotic syndrome, and hypertension. Also, antinuclear antibodies (ANA) was negative and renal biopsy revealed focal segmental glomerulosclerosis (FSGS) morphological pattern along with mesangial C1q predominant staining with primary podocytopathy and mesangial electron-dense immune deposits on electron microscopy. The diagnosis of C1q Nephropathy was made and oral steroids were started. The minimal change disease (MCD) pattern has better outcomes than FSGS. Focal segmental glomerulosclerosis might respond poorly or gets dependent on oral steroids and often requires second-line immunosuppressive therapy.

Keywords: C1q nephropathy, Focal segmental glomerulosclerosis, Nephrotic syndrome, Proteinuria, Systemic lupus erythematosus.

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Introduction

About three decades ago, a distinct glomerular disease entity C1q nephropathy was first proposed by Jennette and Hipp.[1] C1q nephropathy is a histoimmunological diagnosis and comprises of characteristic dominant or codominant deposition of C1q in renal mesangium in the absence of clinical as well as immunological features of systemic lupus erythematosus and type 1 membranoproliferative glomerulonephropathy.[1,2] Undeniably, the disease entity has increased recognition and is considered as an independent disease but still many aspects of pathogenesis, clinical profile, and treatment responsiveness are not clear.

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Case Description

A 28 year-old normotensive, afebrile female presented to us with decreased urine output and frothy urine from the last 3 months and facial puffiness, bilateral lower limb swelling, and abdominal distension from the last 2 months which was progressive in nature. No history of difficulty in breathing, palpitation, yellowish discoloration of eyes or body, itching, rash, photosensitivity, oral ulcers, hair loss, joint pain, fever, and altered talk or behavior. No history of hypertension, diabetes mellitus, tuberculosis, epilepsy, or jaundice. The patient is married and has three children. There is also a history of one elective abortion. She is a housewife, vegetarian, non-alcoholic, and non-smoker. On examination, the following results were found: Blood pressure (BP), 160/90 mm Hg; bilateral pitting edema; facial puffiness; and presence of fluid thrill. Fine crackles in bilateral infrascapular areas with vesicular breath sounds were auscultated. Laboratory studies revealed serum creatinine of 0.93 mg/dL with creatinine clearance of 90 mL/minute, total cholesterol 492.7 mg/dL, triglycerides 604.8 mg/dL, high-density lipoprotein (HDL) 32.4 mg/dL, and low-density lipoprotein (LDL) 234.9 mg/dL. Total serum protein was 3.00 mg/dL with albumin 0.22 mg/dL. Urine examination showed 4+ albumin, 3–4 red blood count (RBC), and 3–4 pus cells with spot urinary urine albumin to creatinine ratio (ACR), 3501.95 mg/gm; C-reactive protein (CRP), 0.2 mg/L; and erythrocyte sedimentation rate (ESR) 76 mm/hour. Ultrasonography abdomen showed normal-sized kidneys with a slight increase in cortical echogenicity and moderate ascites. Ascitic fluid analysis showed a serum ascites albumin gradient (SAAG) ratio of 0.1 gm/dL. Complete blood count (CBC), serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), alkaline phosphatase (ALP), prothrombin time (PTI), serum electrolytes, thyroid profile, and echocardiography were within normal limits. ANA to extranuclear antigen antibodies (ENA) profile, viral markers for human immunodeficiency virus infection (HIV), hepatitis B and C, urine culture, and blood culture were negative. The patient was evaluated on the lines of the nephrotic syndrome as well as connective tissue disorder and a renal biopsy was done. Renal biopsy revealed the following.

Light microscopy (Fig. 1) revealed focal and segmental tuft sclerosis 5/46 (10.8%) glomeruli with focal intraglomerular foam cell change, hyalinosis, and no evidence of crescent. It also showed broad scarred areas with few globally sclerosed areas. Direct immunofluorescence (DIF) showed predominant 3+ glomerular mesangial staining for C1q. The immunostaining

pattern is shown in Table 1. Ultrastructural electron microscopic studies showed diffuse effacement of foot processes of visceral epithelial cells, mesangial, and paramesangial electron-dense deposits without any definite substructure on high magnification (Fig. 2). So, after ruling out SLE and Type I Membranoproliferative glomerulonephritis (MPGN), a diagnosis of C1q Nephropathy with FSGS pattern was made. She was started on oral prednisolone 1 mg/kg body weight along with supportive care. The patient was doing good and under regular follow-up.

Case Discussion

It is a rare glomerular disease diagnosed by immunofluorescence studies such as IgA and IgM nephropathy. It has a male preponderance. It is more common in children and young adults; however, Kanodia et al. reported bimodal presentation as 3 out of 11 C1q nephropathy patients were more than 70 years.[3] The prevalence of C1q nephropathy in renal biopsies varies from 0.2% to 2.5% in biopsies from children and adults; however, it is more prevalent in the pediatric population.[1] C1q is a key intermediate, initiator, and first component of the classical complement cascade which can be activated by many factors. It is formed extrahepatically by different cells like monocytes/macrophages, mesenchymal cells, and fibroblasts.[4] The exact mechanism for the selective affinity of immune complexes to renal mesangial cells is uncertain. The usual clinical manifestation ranges from mild asymptomatic proteinuria to frank nephrotic range proteinuria, hematuria, hypertension, and renal insufficiency and might progress to an end-stage renal disease (ESRD) requiring renal replacement therapy. With light microscopy, it is broadly categorized into the following two types: (1) MCG/FSGS and (2) Immune complex-mediated proliferative glomerulonephritis. Direct immunofluorescence uses antiserum against immunoglobulins or complement components or even proteins and then the pattern as well as the site of deposition is noted. There is staining for C1q in a dominant or codominant fashion in cases of C1q nephropathy. On electron microscopy, mesangial electron-dense deposits are characteristic; however, subendothelial or subepithelial can be present in addition.[4] There can be podocyte foot process effacement and cytoskeleton condensation.[5] It is more common in immune complex-mediated subtypes and rarely can have tubuloreticular cytoplasmic inclusions. Jennette and Hipp found C1q might be deposited in patients with proliferative lupus nephritis, membranous lupus nephritis, and type I MPGN which made the exclusion criteria for diagnosis of C1q nephropathy.[2] The biopsy in this patient was consistent with a primary podocytopathy and in additional mesangial electron-dense deposits, corresponding to the DIF findings, indicating mesangial immune complex deposition. These features are consistent and conclude the diagnosis of C1q nephropathy with a morphological pattern of FSGS. Lower proteinuria, minimal change variant, and nephritic variant have better outcomes as compared to those with nephrotic range proteinuria and FSGS.[1]

An Indian study reviewed 1,775 native renal biopsies collected over 3 years found 11 patients with C1qN with a prevalence of

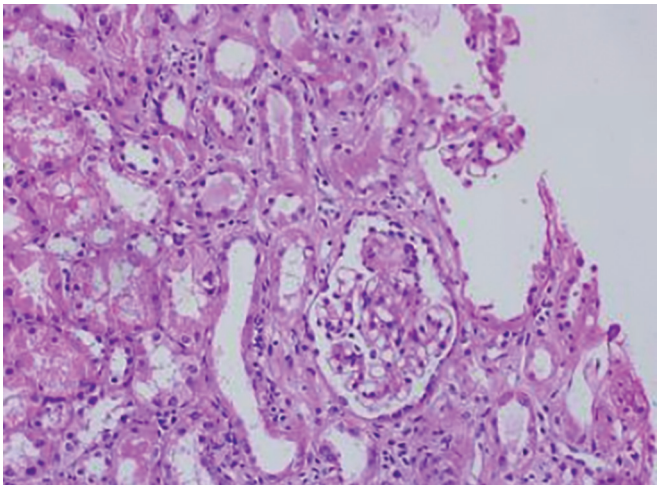
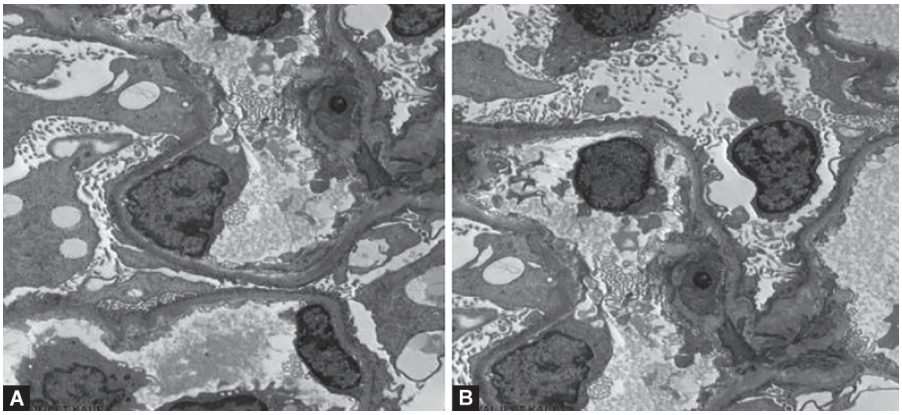


Fig. 1: Focal and segmental tuft sclerosis

Table 1: Direct immunofluorescence (DIF)

Parameter	*Result*
C1q	3+ mesangial; granular
C3	Trace mesangial; granular
Kappa light chains	1+/2+ mesangial
Lambda light chains	1+/2+ mesangial
IgG	2+ mesangial; granular
IgM	Negative
IgA negative	Negative

IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin G



Figs 2A and B: Electron microscopy showing diffuse effacement of foot processes of visceral epithelial cells with mesangial and paramesangial electron-dense deposits, (A) Diffuse effacement of foot processes; (B) Mesangial and paramesangial electron-dense deposits

0.61% with a mean age of 36.6 years, more common in males (8 males and 3 females). The most common pattern was mesangial proliferative glomerulonephritis (MePGN), then FSGS, and might have podocytopathy or non-podocytopathy. The codominant deposits were IgM, C3, etc. Follow-up was possible in only 7 patients out of which 3 had received steroids plus cyclosporine, 2 steroids plus mycophenolate mofetil, and 2 received steroids alone. Mesangial proliferative glomerulonephritis had a better prognosis than others.[3]

Another Indian study which studied 113 kidney biopsies conducted in children with steroid-dependent or steroid-resistant nephrotic syndrome done between August 2015 and October 2020 found 16 patients (14.33%) with C1q nephropathy, with 12 males and 4 females with a mean age of 44 months. Eight had minimal change nephrotic syndrome, seven had FSGS and one had diffused mesangial hypercellularity. Follow-up was possible in only 13, out of which eight (61.5%) were steroid dependent and 4 (30.7%) were steroid-resistant. Nine of these achieved remissions with calcineurin inhibitors (CNI), one with mycophenolate but two were non-responders and one partial responder. They concluded that C1q nephropathy should be suspected and ruled out in difficult nephrotic syndrome pts. Calcineurin inhibitors are most beneficial and suggested their early institution along with prednisolone.[6]

Kim et al. reviewed 6413 adult patients who underwent kidney biopsy from 2000 to 2018 at 3 centers in Korea and compared 23 patients with C1q nephropathy with those of matched MCD or FSGS. After a follow-up of 92 months, 4 C1q nephropathies had ESRD and 7 of the FSGS developed ESRD. Renal outcomes of C1Qn are comparable to FSGS, not MCD.[7]

Zhao et al. reported a successful remission of C1q nephropathy in 77-year-old female with intravenous (IV) methylprednisolone and cyclophosphamide along with supportive care hemodialysis and then oral prednisolone for the next 4 months.[8] Ito et al. described the role of LDL plasma apheresis with corticosteroids/cyclosporine in a case report.[9] Rituximab has been shown to introduce remission in a 13-year-old girl with steroid-resistant nephrotic syndrome for the last 6 years.[10] Similar improvement was shown in a case report by Sinha et al. in 11-year-old boy with rituximab (375 mg/m^2 weekly for 4 weeks).[11]

Even though the disease entity is known for more than three decades but still it poses a great management challenge. There are no definite prognostic or clinical markers to estimate risk and identify the population who will be steroid-resistant or progress to end-stage renal disease. The current recommendation is to treat according to the light microscopic lesion. First-line treatment is in the form of oral corticosteroids 1mg/kg body weight; however, these patients are often steroid-resistant or dependent and might achieve partial remission or no remission. Pulse methylprednisolone, CNI like cyclosporine, tacrolimus, mycophenolate mofetil, azathioprine, and even rituximab, are used sequentially or in combination but there is no specific preferred drug or definite clinical trials favoring one over the other. In adults, C1qN is more associated with FSGS and shows poor outcomes on follow-up requiring long-term immunosuppression to achieve and maintain remission.[12] A national registry should be done to estimate the exact prevalence, clinical profile, and outcomes and plan future research.

Take-home Message

- C1q nephropathy means characteristic dominant or codominant C1q mesangial deposits in absence of SLE.
- It is a distinctive immunopathological diagnosis with variable morphological patterns, clinical features, and outcomes.
- It should be suspected and ruled out in difficult nephrotic syndrome patients.
- As of now C1q deposits *per se* is not the main prognostic markers but require further research.
- Oral steroids are first-line but often require steroid-sparing or second-line immunosuppressant therapy like CNI. Focal segmental glomerulosclerosis and frank nephrotic syndrome have an unfavorable outcome as compared to the MCD variant.

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