

C1q Nephropathy - An Immunologic Epiphenomenon

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Abstract: C1q nephropathy is defined as the presence of mesangial C1q staining either dominant or codominant with the absence of clinical or serological findings of systemic lupus erythematosus (SLE)¹. It was first described by Jennette and Hipp in 1985¹. It has varied light microscopic features including minimal change nephropathy, focal segmental glomerulosclerosis (FSGS), and crescentic glomerulopathy. It may or may not present with nephrotic syndrome.

1. Case Report

A 45-year-old married female presented with complaints of swelling over lower limbs, face, and abdomen since 7-8 months, along with breathlessness on exertion for last 15 days.

There was history of hypothyroidism since 1 year on T Thyroxine 100mcg once a day, compliant with the treatment.

There was no history of decreased urine output, nausea, vomiting, altered sensorium, seizures.

There was no history of preceding fever, sore throat, joint pain, rash, abdominal pain or hematuria. There was no past history of similar complaints, hypertension, diabetes, chronic analgesic or other drug abuse, blood transfusion, tuberculosis or any high-risk sexual behavior.

On admission, she was conscious, cooperative, and oriented to time, place, and person.

She was afebrile; had a pulse rate of 84 beats/min, regular, normal volume; and had blood pressure of 110/72 mmHg with a respiratory rate of 18 breaths/min.

There was the presence of facial puffiness and pitting pedal edema.

On per abdomen examination, there was generalized abdominal distention with fullness of flanks, and on percussion, along with presence of free fluid.

Her respiratory and cardiovascular examination was unremarkable. Ophthalmological examination revealed no abnormal findings.

Her laboratory investigations showed

- Hemoglobin 8.2 g/dl ,
- White blood cell (WBC) 10,500/mm³ and
- Platelets 3.61 lakhs,
- Creatinine 0.98 mg/dl,
- Urea 48 mg/dl, sodium 135.3 mEq/l, potassium, 4.81 mEq/l,
- Calcium (Ca) 7.4 mg/dl with corrected Ca of 9.7 mg/dl,
- Proteins 4.8 g/dl, albumin 1.1 g/dl, globulins 3.7 g/dl,
- Total cholesterol 247 mg/dl, random blood glucose 87 mg/dl.

- ELISA for HIV and hepatitis B and C was nonreactive.
- Urine routine and microscopic analysis revealed the presence of proteinuria 3+, red blood cell 10–12/HPF, WBC nil, and no cellular casts.
- Urine ACR was 350mg/g creatinine.
- T3, T4, TSH was 0.19 ng/ml, 3.29 mcg/dl and 2.95 mIU/ml.
- ANA was negative , APLA (anti phospholipid antibody) negative, C3 and C4 level were 90 and 40 respectively.
- Ascitic fluid routine microscopy showed proteins 1.5g/dl, sugar 125mg/dl, WBC count 30/cumm. Ascitic fluid ADA was 25.8 U/L.
- Ultrasound abdomen examination revealed the presence of ascites with kidney sizes as 8.1*4.3 cm in right kidney and 8.8*4.4 cm on left side, with preserved corticomedullary differentiation.
- A percutaneous kidney biopsy was performed under ultrasound guidance.

Kidney biopsy pathological findings revealed the presence of 20 glomeruli with 5 glomeruli are globally sclerosed and 1 glomerulus shows segmental sclerosis. Remaining glomeruli are unremarkable. No evidence of mesangial matrix expansion with mesangial hypercellularity. No definite lesion of segmental sclerosis seen. No collapsing pattern of glomerular injury seen. No endocapillary or extracapillary proliferation seen. No evidence of wire loop or necrotising lesion seen. Tubulointerstitial compartment show multifocal patches of tubular atrophy with associated interstitial fibrosis in 10-15% renal cortex. There is mild interstitial inflammation in chronic areas with mild patchy acute tubular injury seen non atrophic areas. Vascular compartment show mild medial thickening. No vasculitis or thrombotic microangiopathy seen. Immunofluorescence examination showed granular C1q (+2) in mesangium and C3 (+1) in mesangium. Kappa and lambda both show 2+ granular staining in mesangium. IgM is 1+ in mesangium. IgG, IgA are negative. Electron microscopy showing immunofluorescence findings as mesangial electron dense deposits. In addition, diffuse podocyte foot processes effacement is also identified, indicating podocyte injury.

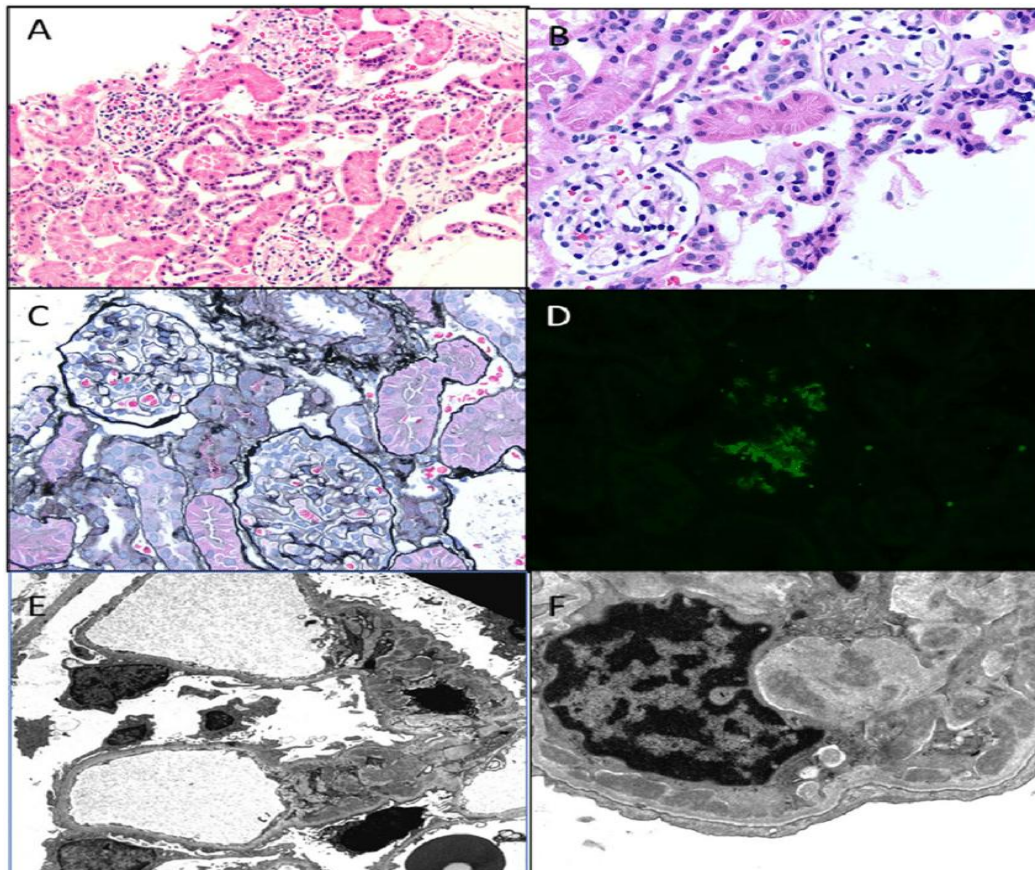
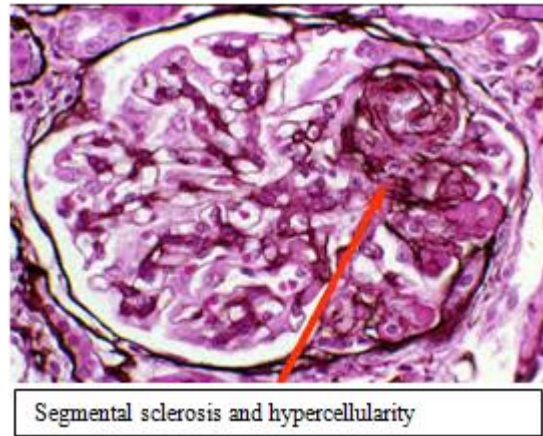
Therefore, a diagnosis of C1q nephropathy with FSGS like lesion was made. The patient was started on treatment with prednisolone 1 mg/kg/day (50 mg) and telmisartan 20 mg once a day. Patient achieved complete remission after 14 weeks of steroid therapy with complete resolution of facial and pedal edema with 24 h urinary protein reduced to 280 mg, clinically she improved with increase in Sr.albumin to 4

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and decrease in cholesterol with reduction in urinary protein, and hence steroid dose was subsequently tapered. After 5 months of treatment, the patient is still in complete remission and at present is on 20 mg of prednisolone (tapering dosage).



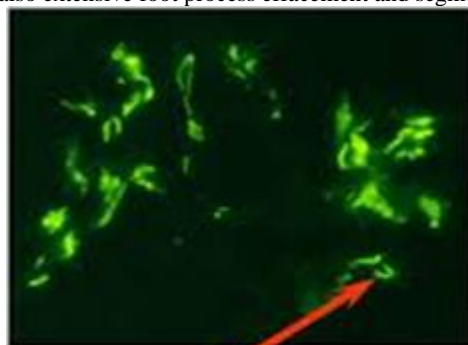
A, B- A glomerulus shows mesangial and endocapillary proliferation accompanied by extensive fibrocellular crescent (periodic acid Schiff)

C- A glomerulus shows mesangial and endocapillary proliferation accompanied by extensive fibrocellular crescent (periodic acid Schiff)

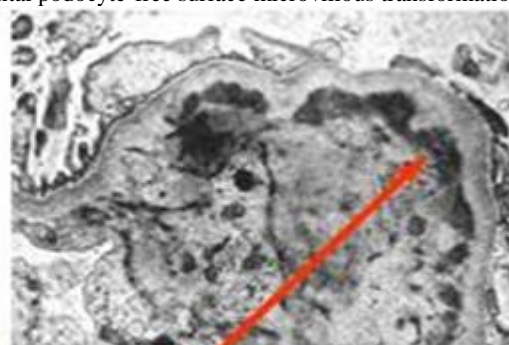
D- Immunofluorescence shows conspicuous mesangial and segmental capillary

E- V wall C1q staining

F- On electron microscopy, dense deposits are seen in the widened mesangial matrix beneath the glomerular basement membrane. Note also extensive foot process effacement and segmental podocyte-free surface microvillous transformation



Stain for C1q



View on Electron microscopy

2. Discussion

Our patient had presented with nephrotic syndrome and renal biopsy on light microscopy was suggestive of FSGS. Immunofluorescence examination showed granular C1q (+2) in mesangium and C3 (+1) in mesangium. Kappa and lambda both show 2+ granular staining in mesangium. IgM is 1+ in mesangium (IgM was present on sclerosed part which was non specific trapping).

C1q nephropathy is a rare glomerular disease characterized by the presence of mesangial C1q staining either dominant or codominant with the absence of clinical or serological findings of SLE.

The pathogenesis of C1q nephropathy is unclear. C1 is the first component of classical pathway of complement system. Classical pathway activation involves binding of C1q to Fc region of IgG and IgM containing immune complexes. C1q receptors are present in mesangial cells.

It has been proposed that C1q binds to immunoglobulins trapped nonspecifically in mesangium in course of glomerular proteinuria.

C1q nephropathy has heterogeneous light microscopic features. Vizjak et al. studied - (1) MCD/FSGS group and (2) immune complex mediated proliferative **glomerulonephritis** (GN) group

All patients with FSGS presented with nephrotic syndrome. Our patient had also presented with nephrotic syndrome and had FSGS on LM.³

The treatment of C1q nephropathy depends on underlying light microscopic lesion.

The mainstay of treatment is glucocorticoids. Cyclophosphamide, cyclosporine, tacrolimus, or mycophenolate mofetil have been used in patients unresponsive to steroids. C1q Nephropathy is generally treated in the same manner as Nephrotic Syndrome.²

Minimal change disease has a more favorable response to therapy as compared to FSGS. Vizjak et al. followed up 53 patients with C1q nephropathy; 76.9% of the minimal change-like group but only one-third (33.3%) of the FSGS group were in complete remission after 4 months to 21 years, and four patients had partial remission after 4 months to 3 years.³

There were no clinical features of SLE, and serological markers for lupus were absent in our patient (ANA and anti-dsDNA). Hence, the diagnosis of C1q nephropathy was made, and in view of nephrotic syndrome, patient was started on prednisolone 1 mg/kg, to which patient responded well and achieved complete remission in 14 weeks.

3. Conclusion

In conclusion, C1q nephropathy often manifests as asymptomatic proteinuria or nephrotic syndrome. Light microscopic features are heterogeneous and comprise no

glomerular lesions, focal segmental glomerulosclerosis (FSGS), and proliferative glomerulonephritis, and diagnosis is based on immunofluorescence. Complete remission of the nephrotic syndrome is observed in approximately 77% of those with a minimal change-like lesion, progression to end-stage renal disease occurred in 33% of those with FSGS, and renal disease remained stable in 57% of those with proliferative glomerulonephritis. There are identified two predominant clinicopathologic subsets of C1q nephropathy: (1) Podocytopathy with a minimal change-like lesion or FSGS, which typically presents with nephrotic syndrome, and (2) a typical immune complex-mediated glomerular disease that varies from no glomerular lesions to diverse forms of glomerular proliferation, which typically presents as chronic kidney disease. Clinical presentation, histology, outcomes, and presumably pathogenesis of C1q nephropathy are heterogeneous.

Treatment of choice being steroids.

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