Collagenofibrotic glomerulopathy – A rare disease diagnosed with the aid of transmission electron microscopy

Smita Mary Matthai, Anjali Mohapatra¹, Neelaveni Duhli², Vinoi G. David¹, Santosh Varughese¹

Department of GI Sciences, Central Electron Microscopy Facility, Wellcome Trust Research Laboratory, Departments of ¹Nephrology and ²General Pathology, Christian Medical College, Vellore, Tamil Nadu, India

Address for correspondence:
Dr. Anjali Mohapatra, Department of Nephrology, Christian Medical College, Vellore - 632 004, Tamil Nadu, India.
E-mail: auroanjali@gmail.com

ABSTRACT

Collagenofibrotic glomerulopathy (CFG) is a rare idiopathic kidney disease characterized by abnormal deposition of atypical Type III collagen fibers in the glomerulus causing subendothelial and mesangial expansion, manifesting as progressive renal dysfunction accompanied by proteinuria. The majority of CFG cases reported in literature are from Japan where this disease entity was initially recognized. There is an increased awareness and diagnosis of this rare renal disease in India with the recent increase in utilization of electron microscopy (EM) in clinical diagnostic settings. We describe a 28-year-old Bangladeshi woman who presented with hypertension and nephrotic range proteinuria not amenable to treatment with steroids and cyclophosphamide, whose renal biopsy demonstrated diagnostic ultrastructural features of CFG. This illustrative case is presented to highlight the role of EM analysis for diagnostic accuracy in renal biopsy evaluation in addition to demonstrating the unusual renal biopsy findings of this rare entity.

KEY WORDS: Collagenofibrotic glomerulopathy, nephrotic syndrome, renal ultrastructural pathology, Type III collagenopathy

INTRODUCTION

Collagenofibrotic glomerulopathy (CFG) is a rare renal disease of unknown etiology, characterized by massive intraglomerular accumulation of banded Type III collagen fibers resulting in prominent mesangial expansion extending to subendothelial spaces of glomeruli. It is classified under the umbrella term “Type III collagenopathy” which includes Nail–Patella syndrome (NPS) as the other constituent. Although there is a preponderance of reported cases from Japan where it was identified first in the 70s,[1‑3] an increasing number of cases have been reported from India of late,[4‑11] possibly due to increased awareness of this entity coupled with increasing use of electron microscopy (EM) in clinical diagnostic settings. We report a case of CFG, elaborating the classical clinicopathological features and diagnostic ultrastructural findings.

CASE REPORT

A 28-year-old Bangladeshi woman presented with pedal edema, persistent proteinuria and hypertension, nonresponsive to steroids and cyclophosphamide for 6 months. Her past and family histories were unremarkable. Her blood pressure was 180/110 mm Hg and fundus was normal. Physical examination revealed pedal edema and facial puffiness; there was no evidence of bone or nail dysplasia. Laboratory investigations showed proteinuria of 3.8g/24 h with urine protein-to-urine creatinine ratio of 5.54 and active urine sediments. The serum creatinine (0.81mg/dL) and complement levels (serum C3 167mg/dL and serum C4 36.3mg/dL) were normal. Myeloma screening and serology for HIV, hepatitis B and C viral infections were negative. Autoimmune work-up (antinuclear antibody, anti-double stranded DNA) was noncontributory. Ultrasound of the abdomen showed normal sized kidneys with increased echo texture.

An ultrasound-guided renal biopsy was performed which showed 18 glomeruli, exhibiting lobular accentuation and prominent mesangial expansion due to pale eosinophilic acellular deposits along with C3 167mg/dL and serum C4 36.3mg/dL were normal. Myeloma screening and serology for HIV, hepatitis B and C viral infections were negative. Autoimmune work-up (antinuclear antibody, anti-double stranded DNA) was noncontributory. Ultrasound of the abdomen showed normal sized kidneys with increased echo texture.
capillary wall thickening resulting in partially obliterated capillary lumina [Figure 1a]. There were no sclerotic segments, evidence of necrosis, proliferative features or crescents. The deposits stained weakly positive with periodic acid–Schiff stain (PAS), showed positive blue staining with Masson Trichrome, and yielded negative results with Congo Red stains [Figure 1b-d]. Immunoﬂuorescence (IF) studies were negative for IgG, IgA, IgM, C3, C1q and C4 stains. There was no light chain restriction on staining for kappa and lambda.

EM revealed marked expansion of lamina rara interna and mesangium by massive accumulation of curvilinear bundles of collagen fibrils with frayed edges, exhibiting periodicity in the range of 58–61 nm [Figure 2a-d]. There was sparing of lamina densa of glomerular basement membranes (GBMs), extensive foot process effacement and segmental loss of endothelial fenestrations [Figure 2a and b]. The characteristic appearance and distribution of collagen fibers demonstrated on EM, consolidated the diagnosis of CFG.

The patient was treated conservatively with anti-hypertensive agents including angiotensin II receptor antagonists. On follow-up after 8 months, her proteinuria has increased to 6.3 g/24 h and serum creatinine increased to 1.69 mg/dL.

**DISCUSSION**

Type III collagenopathies are rare conditions in which there is diffuse deposition of banded collagen fibrils in the glomerulus and comprise two distinct entities, NPS and CFG.\(^{12}\) NPS is a pleiotropic autosomal dominant disorder with renal involvement characterized by mesangial and mottled GBM deposits (“moth-eaten” lamina densa) of Type III collagen fibers. CFG, on the other hand, is mostly sporadic in occurrence except few instances of pediatric cases which have shown an autosomal recessive pattern of inheritance.\(^{13}\) Moreover, the abnormal collagen fibrillary deposition pattern in CFG is characterized by flocculent expansion of mesangial and subendothelial spaces, lamina densa remaining intact.\(^{12}\)

CFG is extremely rare worldwide with a total of approximately 40 cases reported in literature, but is currently being increasingly reported from Asia. India alone accounts for 20 of the reported cases so far,\(^{10,11}\) and interestingly, this clustering of cases is limited to the present decade, suggesting a contributory role for improved diagnostic capabilities such as availability of routine EM services, in addition to ethnic and racial predilectors.

The pathogenesis of CFG remains elusive with an ongoing debate on whether it is a primary renal disease or secondary manifestation of a systemic disease. Type III collagen is normally found only in renal interstitium and blood vessels and not in the glomerulus. Glomerular deposition has been attributed to local activation of mesangial cells possibly by chemokines such as interleukin-4. In contrast, a systemic origin of the collagen is also suspected based on elevated serum and urinary procollagen Type III peptide (PIIINP) levels.\(^{12}\) PIIINP is a post-translational cleavage product of Type III collagen, levels of which are mildly elevated in many conditions causing renal fibrosis, but marked elevation of 10–100 times normal is characteristically observed in CFG and serves as a diagnostic serum marker of this entity. While pathogenetic mutations in the LMX1B gene have been identified in the inherited disorder NPS, no underlying genetic basis has been identified yet in CFG, not withstanding an autosomal recessive inheritance pattern documented in pediatric CFG.\(^{13}\)
The natural history of CFG is variable with proteinuria and hypertension as the commonest presenting clinical features. Hypertension is documented at the time of presentation in more than one-third of the patients. In addition to the sporadic nature (in adults) of its occurrence, absence of a demonstrable genetic mutation and extra renal manifestations help distinguish CFG from NPS clinically. The diagnosis rests on ultrastructural demonstration of curvilinear bundles of Type III collagen fibrils with characteristic cross striations and frayed edges. Immunohistochemistry and IF are also available for confirming the presence of Type III collagen in the glomeruli, but were not done in this case. But distinction between NPS and CFG on renal biopsy is possible only at the ultrastructural level, based on respective involvement or sparing of lamina densa of GBMs as visualized on EM. The intraglomerular localization of the deposits is better if the ultrathin sections are treated with phosphotungstic acid for EM analysis. The diagnostic ultrastructural features of the atypical Type III collagen fibers in CFG include abnormal periodicity with varying proportions of fibers in the range of 40–64 nm (normal Type III collagen has periodicity of 64nm), arrangement in curvilinear bundles (Type III collagen is arranged in parallel bundles in interstitium), bent, curled or spiral shaped on longitudinal sections with worm-like appearance on transverse sections and frayed edges (interstitial Type III collagen is straight on longitudinal section and circular on transverse section).

On histopathological examination, the main differential diagnoses are amyloidosis, membranoproliferative glomerulonephritis (MPGN) Type I, monoclonal immunoglobulin deposition disease (MIDD), fibrillary and immunotactoid glomerulonephritis (FGN and ITGN), diabetic glomerulosclerosis, idiopathic nodular glomerulosclerosis and rarely chronic thrombotic microangiopathy (TMA), based on mesangial expansion detected at the light microscopy level which may be nodular in some cases, along with evidence of capillary wall deposits. Paucity of double contours and absence of hypercellularity and immune complexes or complement deposits on IF and EM examination rule out MPGN Type I. Similarly, FGN and ITGN can be excluded by lack of demonstrable IgG or C3 deposits on IF, further confirmed by EM analysis. Negative/weak staining with PAS helps differentiate from diabetic glomerulosclerosis and MIDD, the latter being categorically excluded on recorded absence of light chain or heavy chain restriction by IF and/or IHC. Congo Red and thioflavin T staining yielding negative results rule out amyloidosis. Idiopathic nodular glomerulosclerosis is a diagnosis of exclusion in patients with history of smoking. Absence of extra glomerular vascular findings helps eliminate TMA from the differentials in this case prior to EM evaluation.

Treatment is supportive and only a subset of patients show disease progression as seen in our patient. Renal replacement therapy has been offered to patients who developed end-stage renal disease and to date there has been no report of recurrence following renal transplantation.

In conclusion, CFG is emerging as a relatively common idiopathic glomerulopathy in Asian populations which invites further research in its direction. A comprehensive renal biopsy evaluation inclusive of EM is imperative to diagnosis and future studies of this entity.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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