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Case Report

Pathology Section

Collagenofibrotic Glomerulopathy with Thrombotic Microangiopathy: A Rare Case Report

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ABSTRACT

Collagenofibrotic Glomerulopathy (CG) is a very rare glomerular disease characterised by the massive accumulation of atypical type III collagen fibrils within the mesangial matrix and subendothelial space, as well as a marked increase in serum type III procollagen peptide levels. Owing to its rarity, the cause and pathogenesis of CG remain uncertain. While initial reports of CG were primarily in patients of Asian descent, subsequent cases in patients of European descent have also been published. Clinically, patients present with oedema and hypertension, often progressing to end-stage renal disease. Proteinuria is a cardinal manifestation of this disease. A definitive diagnosis is contingent upon recognising this entity, maintaining a high index of suspicion, and confirming it through immunohistochemistry and Electron Microscopy (EM), due to its rarity, non specific presenting signs and symptoms, and various differential diagnoses on histology. Here, a case of a 44-year-old non diabetic, hypertensive female who presented with pedal oedema and nephrotic range proteinuria. The biopsy showed nodular expansion of the mesangium by homogeneous, congo red-negative, eosinophilic material, along with vascular changes indicative of acute thrombotic microangiopathy. Many conditions, such as amyloidosis, fibrillary glomerulonephritis, diabetic nephropathy, fibronectin glomerulopathy, light chain deposition disease, and thrombotic microangiopathy, can cause nodular or membranoproliferative glomerular changes. The biopsy was initially reported as nodular glomerulosclerosis, which, upon EM, showed mesangial and subendothelial space expansion by banded fibrillary material. Further immunohistochemistry for type III collagen was performed, which yielded positive results. Thus, the diagnosis of CG was confirmed.

Keywords: Electron microscopy, Proteinuria, Type III collagen

CASE REPORT

A 44-year-old female presented with the chief complaints of generalised weakness, persistent pedal oedema, and facial oedema for three months. The patient was hypertensive and non diabetic, with no other co-morbidities reported. There were no bony deformities noted. On investigations, the serum creatinine level was 4.02 mg/dL (normal range: 0.4-1.4 mg/dL). A 24-hour protein test revealed 6.22 grams of protein in 24 hours. Routine urine microscopy showed no sediments. Complement levels were normal. Serum lactate dehydrogenase levels were elevated at 354 U/L (normal range: 100-190 U/L). Serum haptoglobin levels were <0.0078 g/L (normal range: 0.5-2.2 g/L). Serum Antinuclear Antibodies (ANA), dsDNA, p-ANCA, c-ANCA (Antineutrophil cytoplasmic autoantibodies), Antibodies to the Phospholipase A2 Receptor (PLA2R), and Anti-Glomerular Basement Membrane (Anti-GBM) antibodies were all within normal limits. The patient was sero-negative for Human Immunodeficiency Virus (HIV), Hepatitis B surface Antigen (HbsAg) and Hepatitis C Virus (HCV). A peripheral smear revealed evidence of haemolysis. Thrombocytopenia was noted, with a platelet count of 108,000/cumm (normal range: 150,000-450,000/cumm). Serum protein electrophoresis results were normal. On ultrasonography, the right kidney measured 9.2×3.6 cm, and the left kidney measured 9.8×4.7 cm.

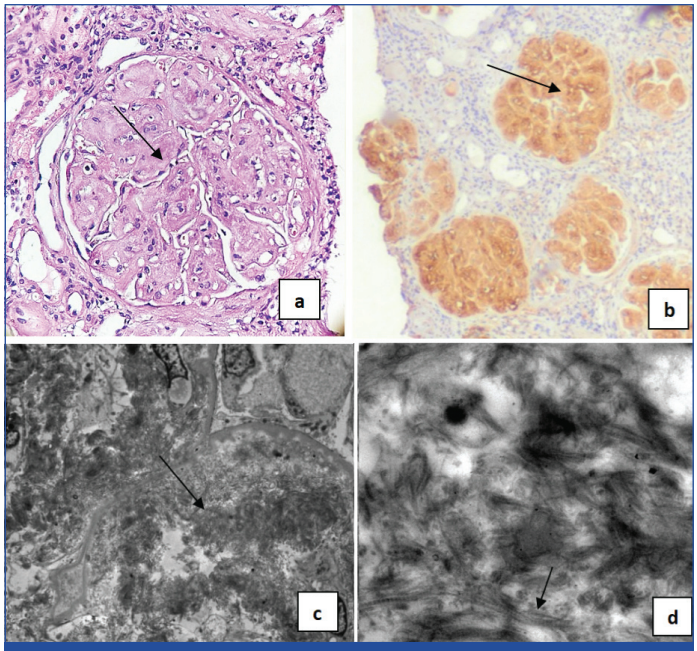
A renal biopsy was performed and showed 110 glomeruli, none of which were sclerosed. All glomeruli exhibited nodular mesangial expansion by an acellular eosinophilic material [Table/Fig-1a], which was negative for Periodic Acid Schiff (PAS) and Jones Methenamine Silver (JMS) staining. There was no duplication of capillary membranes. Some of the tubules showed hyaline and cellular casts. The sampled cortex demonstrated approximately 35-40% interstitial fibrosis and tubular atrophy. A few small-calibre arteries were thrombosed, with segmental fibrinoid necrosis of the vessel wall; however, the glomeruli did not show any features of thrombotic microangiopathy. A few small-calibre arteries also revealed nodular/circumferential hyalinosis, while medium-calibre arteries revealed mild fibrointimal thickening.

In light of the nephrotic range proteinuria and nodular mesangial expansion by an acellular eosinophilic material, a histologic differential diagnosis of amyloidosis was considered first. However, the congo red stain was negative. Other differential diagnoses considered included diabetic glomerulopathy and light chain deposition disease. The absence of any history of diabetes and the lack of PAS positivity in the mesangial nodules ruled out diabetic nephropathy. Direct immunofluorescence was performed to exclude light chain deposition disease. Direct immunofluorescence tests showed negativity for all immunoglobulins, complements, and light chains; therefore, light chain deposition disease or any other immune complex deposition disease was excluded.

In view of nodular mesangial expansion and the negativity for congo red, PAS, and JMS, a diagnosis of CG was suggested after ruling out all other differential diagnoses. Additionally, findings of acute thrombotic microangiopathy involving only the vessels were also present. Immunohistochemistry was positive for Type III collagen within the glomerulus [Table/Fig-1b]. EM revealed marked expansion of the lamina rara interna and mesangium due to the massive accumulation of curvilinear bundles of collagen fibrils with frayed edges, exhibiting periodicity [Table/Fig-1c,d]. Thus, CG was confirmed as the final diagnosis.

DISCUSSION

Arakawa M et al., initially reported a novel glomerular condition involving collagen fibrils in the subendothelial region and mesangial matrix in 1979 [1]. Later, in 1990, Ikeda K et al., used IHC staining to demonstrate that the collagen fibrils in the renal glomerulus were



[Table/Fig-1]: a) Nodular expansion of the mesangium (black arrow) by a homogenous eosinophilic material (H&E, 200x); b) Positive staining (black arrow) for Collagen Type III on immunohistochemistry (IHC, 100x); c) Expansion of the subendothelial and mesangial space (black arrow) by a banded fibrillary material on electron microscopy (250x; uranyl acetate and lead citrate); d) Fibrillary material with banded appearance and periodicity (black arrow) on electron microscopy (2500x; uranyl acetate and lead citrate).

type III collagen fibrils [2]. The formal designation of collagen type III glomerulopathy was given to this novel glomerular illness by Imbasciati E et al., in 1991 [3].

Collagen type III is not found in normal glomeruli; it is a component of the extracellular of many diverse glomerular lesions as they undergo fibrosis [4], which includes organising crescents, fibrosis surrounding the afferent arteriole as it enters the tufts (especially in older individuals), and the urinary spaces of ischaemic glomeruli. Additionally, it may occasionally be found in the mesangial matrix in segmental glomerulosclerosis and diabetic glomerulosclerosis [5].

Many conditions, such as amyloidosis and/or fibrillary glomerulonephritis, diabetic nephropathy, fibronectin glomerulopathy, light chain deposition disease, and thrombotic microangiopathy, can cause nodular or membranoproliferative glomerular changes. Additional conditions that cause collagen deposition include Nail Patella Syndrome (NPS) and hereditary multiple exostoses. For the diagnosis to be confirmed, EM is required.

There is no gender predilection for this illness; symptoms can appear at any age, but adults make up the majority of recorded cases. Nephrotic-range proteinuria is present in more than half of the patients. Upon presentation, hypertension and microscopic haematuria are often observed. Renal function gradually deteriorates, and approximately 60% of cases can advance to end-stage renal disease [3,4,6].

A significant number of cases have been reported from Japan and other Asian countries, with about 21 cases reported from India [7]. The largest series has been reported by Kurien AA et al., from India and Gubler MC et al., from France, comprising eight adult cases and ten paediatric cases, respectively [7,8]. The latest case reports published in India were in 2020—one by Modi SS et al., and another by Manocha A et al., [9,10]. The classic histopathological features of CG include double contour formation by PAS-negative flocculent material extending along the luminal side of the peripheral capillary loops and mesangial enlargement. Immunofluorescence shows no staining. Furthermore, the diagnosis of CG is confirmed by EM, which reveals electron-dense, banded, curvilinear structures characteristic of collagen, exhibiting periodicity in the range of 58-61 nm within the enlarged mesangium and subendothelial region. This was similar to present case, and collagen III IHC further confirmed the diagnosis.

Present case also exhibited vascular changes indicative of acute thrombotic microangiopathy. The peripheral smear showed features of haemolysis, serum haptoglobin was low, and serum LDH was elevated. Gubler MC et al., described that three of the ten paediatric patients also had thrombotic microangiopathy [4]. Vogt BA et al., described one patient with persistent hypocomplementemia and inherited factor H deficiency associated with collagen type III glomerulopathy, suggesting that factor H deficiency may be linked to collagen III glomerulopathy [5,8]. Nevertheless, the relationship between these abnormalities and CG remains uncertain.

In present case, testing for factor H was not performed, and the cause of thrombotic microangiopathy was unknown. The patient did not present with any bony deformities; therefore, no genetic workup was conducted for NPS. The patient is currently on steroids, and the last recorded serum creatinine was 8.51 mg/dL. The patient was lost to follow-up thereafter.

Diabetic glomerulosclerosis, light chain deposition disease, and amyloidosis were our primary differential diagnoses based on light microscopy. There was no history of diabetes or PAS positivity indicative of diabetic glomerulopathy. The Congo red stain was negative for amyloidosis in this instance, and there was no kappa or lambda positivity on immunofluorescence.

A clinical history of longstanding diabetes, the distribution of nodular lesions (whether uniform or variable), staining characteristics, immunofluorescence findings for immunoglobulins/complements/kappa-lambda light chains, and ultrastructural studies aid in differentiating among almost all differential diagnoses [11].

There is no established course of treatment for this illness. It may be helpful to treat symptoms like oedema and hypertension. Dialysis or kidney transplantation may be advised in cases of end-stage renal disease. As of now, no known recurrences have been reported in the literature [12].

CONCLUSION(S)

The pathologist must maintain a high degree of suspicion and awareness of CG due to its extreme rarity. Before this diagnosis is established, several distinct histopathological differentials must be ruled out. Type III collagen deposits must be identified using IHC and EM. Furthermore, in order to precisely classify and validate the diagnosis, any deposition disease needs to be investigated using EM.

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