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Collagen Type III Glomerulopathy

AnnaLisa V. Wilson[1,4], Francesca Costigliolo[1,4], Alton B. Farris[2], Rohan Rengen[3] and Lois J. Arend[1]

[1]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [2]Department of Pathology, Emory University, Atlanta, Georgia, USA; and [3]Frederick Memorial Hospital, Frederick, Maryland, USA

Correspondence: Lois J. Arend, Department of Pathology, Johns Hopkins University School of Medicine, 600 N Wolfe St, Baltimore, MD, 21287 USA. E-mail: ljarend@jhu.edu

[4]AVW and FC contributed equally.

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INTRODUCTION

Collagen type III glomerulopathy (CG), also known as collagenofibrotic glomerulopathy, is caused by accumulation of collagen type III in glomeruli. Collagen type III is not a normal constituent of the extracellular matrix of glomeruli, but it is found in the interstitium and vessel walls. Clinical features of CG include proteinuria (often in the nephrotic range), edema, and hypertension.[1,2] The condition can progress to end-stage kidney disease, requiring dialysis or renal transplantation. While initial reports of CG were largely in patients of Asian descent, subsequent cases in patients of European descent were published.[1,3–7] Approximately 100 cases have been reported in the literature (Supplementary Table S1). We report the first case of CG in an African American patient, suggesting that the condition may be an unrecognized cause of proteinuria in patients of African American descent. Furthermore, our case, as well as 2 of the earliest reported cases,[3,8] documents CG in a female who presented with a history of proteinuria associated with pregnancy, highlighting the need to include CG in the differential of female patients who develop new-onset or worsening proteinuria and hypertension with pregnancy. This rare disease has overlapping clinical features with many conditions that can produce nephrotic-range proteinuria, leading to a clinical diagnostic dilemma (Table 1). Likewise, the histologic pattern can be confused with conditions that cause a nodular or membranoproliferative glomerular change, such as amyloidosis and/or fibrillary glomerulonephritis, diabetic nephropathy, fibronectin glomerulopathy, light chain deposition disease, and thrombotic microangiopathy, as well as other conditions with collagen deposition, such as hereditary multiple exostoses and nail–patella syndrome (NPS).

CASE PRESENTATION

Clinical History and Laboratory Data

A 42-year-old African American woman with a medical history significant for hypertension was recently diagnosed with type 2 diabetes and obesity. She was originally diagnosed with proteinuria 18 years earlier, during her first pregnancy, with 2 subsequent pregnancies each complicated by proteinuria. The proteinuria resolved after delivery in the first 2 instances; however, she remained proteinuric after her third pregnancy and had been maintained on an angiotensin-converting enzyme inhibitor. Two years before the current presentation, she had a possible transient ischemic attack (TIA) in the setting of suboptimal blood pressure control and had a second TIA almost 2 years later, after which additional antihypertensive treatment was added. On a regular follow-up visit, she was found to be persistently proteinuric with 10 g in a 24-hour urine collection. Remaining laboratory results included creatinine 1.2 mg/dl, serum albumin 3.1 g/dl, and Hgb 9.8 g/dl with a low mean corpuscular volume (69 fl). Hemoglobin A1c was 6.4%. Her blood pressure was adequately controlled.

She had no constitutional symptoms and her physical examination was unremarkable except for lower extremity edema. There was no family history of renal disease. Her medications included aspirin, statin, diltiazem, hydralazine, hydrochlorothiazide, Lisinopril, metoprolol, empaglifozin, liraglutide, iron and calcium supplements, loratadine, and fluticasone spray.

A kidney biopsy specimen was obtained.

Table 1. Teaching points

Collagen type III glomerulopathy (CG) is a rare condition and can present with signs and symptoms such as nephrotic-range proteinuria and mild hematuria that evoke a broad clinical differential diagnosis
The typical patient with CG is Asian, though the condition should be considered in patients of European and African descent as well
A pregnant patient with proteinuria and hypertension is most often assumed to have pre-eclampsia; however, other conditions should also be considered in the differential diagnosis, particularly if pre-existing proteinuria worsens during pregnancy
The diagnosis of CG depends on electron microscopy demonstrating atypical collagen fibrils in the subendothelial space and mesangium; contrarily, nail–patella syndrome is characterized by collagen fibrils within the glomerular basement membrane
Immunohistochemistry for collagen type III can be useful for confirmation of the diagnosis of CG

Kidney Biopsy

Light microscopy showed approximately 30 glomeruli, of which 2 were globally sclerosed and 3 had segmental sclerosis. All patent glomeruli were characterized by a distinct global to near-global eosinophilic expansion of the mesangium and capillary walls, imparting a lobulated appearance with reduced overall cellularity (Figure 1a). Capillary walls had segmental duplication of the basement membranes and silver stain showed an unusual pattern of membrane staining with a normal outer layer, central clearing, and an inner complex layer (Figure 1b). There was indistinct staining of the mesangial regions. Much of the expanded subendothelial and mesangial areas were also negative on periodic acid–Schiff (PAS) stain (Figure 1c). The tubulointerstitium showed mild focal tubular atrophy and interstitial fibrosis in approximately 20% of the cortical sample with focal lymphocytic inflammation in the small areas of scarring. The small arteries sampled were unremarkable and the arterioles had moderate hyaline thickening. Immunofluorescence microscopy was negative for all immune reactants. Electron microscopy revealed marked subendothelial and mesangial accumulation of collagen fibers (Figure 2a and b), sometimes curved or frayed, some arranged in irregular bundles (Figure 2c), and many showing banding with periodicity that averaged 54.5 nm (Figure 2d). The fibrils were present in the expanded subendothelial space and not within the glomerular basement membrane. The fibers were less delicate than collagen fibers normally seen in the renal interstitium and sometimes found in the glomeruli in other sclerosing conditions. The fibers were much larger than those seen in amyloid or fibrillary glomerulonephritis. They also differed in appearance from the enhanced matrix proteins seen in nodular diabetic glomerulosclerosis, i.e., fibrillosis, in which the fibrils are smaller and less haphazardly arranged. There was also diffuse podocyte foot process effacement.

Additional Studies

Collagen type III immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue sections with antibody to collagen type III (BioGenex, San Ramon, CA; monoclonal clone HWD1.1; 1:80) using a Leica BOND-III automated stainer as previously described.[9] Immunohistochemistry demonstrated the expected internal control staining of the interstitium and showed prominent staining of expanded glomerular mesangium and capillary walls (Figure 1d).

We also searched the kidney biopsy archives of the Johns Hopkins Department of Pathology for cases of CG (institutional review board–approved study 00090103). From 1994 to 2018, there were 33,137 biopsies procedures performed. Searching for the term glomerulopathy (3999 cases) with subsequent searches of these cases using the terms collagen (106 cases) and type (62 cases) identified 1 case diagnosed as probable CG and 2 cases diagnosed as possible CG. Five other cases mentioned increased collagen fibers in the biopsy specimen report but were considered unlikely to be CG at the time of biopsy based on histologic features together with the clinical information. These 8 cases were reviewed and collagen type III immunohistochemistry was performed on the 3 cases considered possible or probable. None of these additional cases showed positive staining.

Clinical Follow-Up

The patient was diagnosed with alpha-thalassemia and as part of serologic work-up, was found to have positive antinuclear antibodies and SS-A. The patient's renal function is preserved, her proteinuria is stabilized, and her hypertension is under control.

DISCUSSION

Collagenofibrotic glomerulopathy is a rare condition caused by mesangial and subendothelial deposition of collagen type III in glomeruli. Collagen type III is a normal matrix protein found in the interstitium and vessels of most tissues, but it is not normally present in the glomerulus. Because of this atypical deposition of collagen type III, the disorder is also referred to as CG. Initially, CG was thought to be a subset of the genetic disorder NPS, also known as hereditary osteo-onychodysplasia. NPS is an autosomal dominant condition caused by a mutation in *LMX1B* transcription factor and usually presents during childhood[S1]; CG may have a genetic basis in some affected individuals, particularly when presenting in childhood, as suggested by several sibling pairs with CG,[6,8,S2,S3] but in many cases there is no evidence of familial or genetic correlation and it is considered a sporadic disorder when manifesting in adulthood. NPS is a pleiotropic disorder with symptoms ranging from maldeveloped nails and kneecaps to glaucoma, and can involve the skin and kidneys, with renal effects that mimic the symptoms present in CG.[S1] However, in NPS, nephrotic symptoms are not noted in the absence of skeletal abnormalities, and the disease course

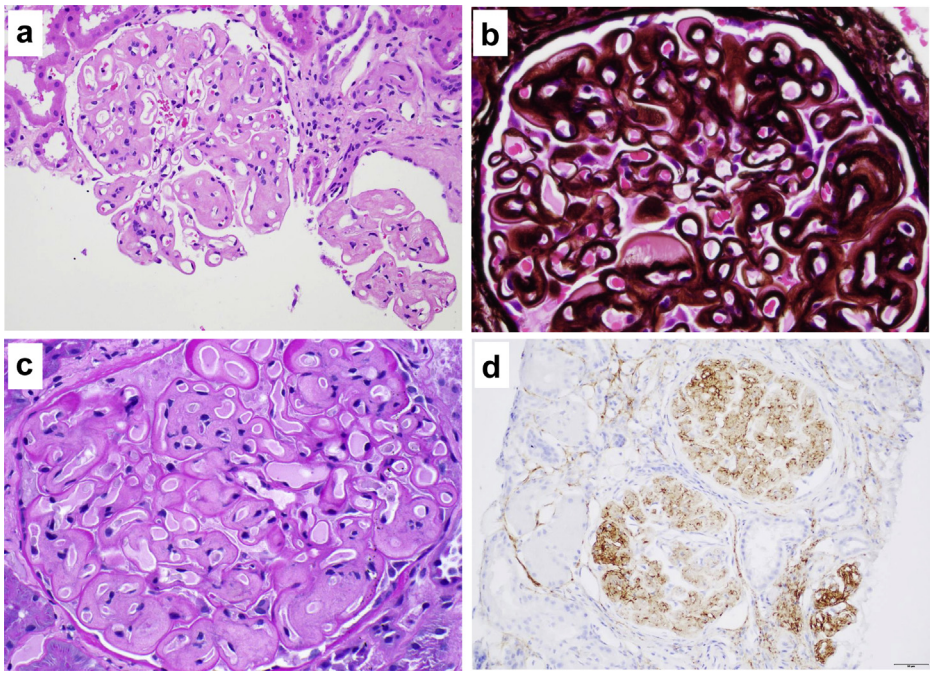

Figure 1. (a) Glomeruli show eosinophilic expansion of mesangium and capillary walls without increased cellularity. Hematoxylin and eosin stain; original magnification ×200. (b) Nonargyrophilic expansion of mesangium and capillary walls with segmental double contour formation. Periodic acid–Schiff (PAS) methenamine silver stain; original magnification ×400. (c) PAS-negative mesangial and capillary wall expansion. PAS stain; original magnification ×400. (d) Collagen type III in glomeruli and interstitium. Immunohistochemical stain for collagen type III; original magnification ×200.

does not always lead to kidney failure. In CG, skeletal and cutaneous abnormalities are not present, though rare cases of extrarenal organ involvement have been reported.[S4,S5] Patients with CG typically present with proteinuria (often in the nephrotic range), edema, hypertension, variable hematuria, and usually mild impairment of renal function. These features overlap with a wide variety of disorders affecting the kidney, leading to a broad clinical differential diagnosis. The disease course of CG ultimately leads to renal failure, often within 10 years,[S6,S7] with some patients, particularly younger patients, experiencing a more rapid decline.[6,S8]

The initial cases of CG were described in Japanese patients in the late 1970s; Arakawa *et al.*[3] presented the

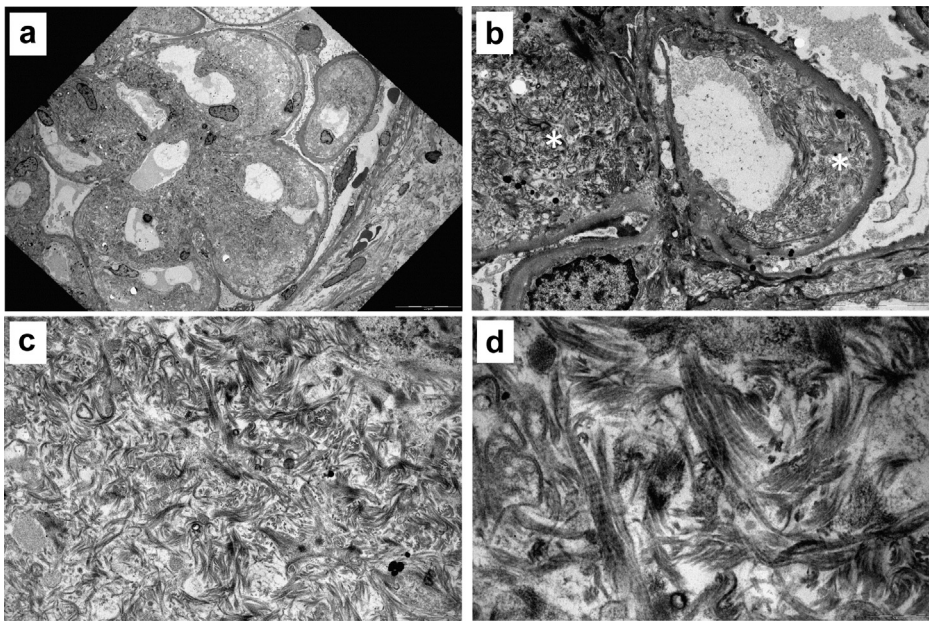

Figure 2. (a) Markedly expanded mesangium and capillary walls. Scale bar = 20 μm. (b) Expanded mesangium and subendothelial aspect of capillary wall (asterisks). Scale bar = 5 μm. (c) Expanded areas contain bundles of thick fibrils. Scale bar = 2 μm. (d) Fibrils contain banding with periodicity of 54.5 nm, focal fraying, and a haphazard arrangement. Scale bar = 500 nm.

first known cases in 1979 as an abstract on 2 biopsy specimens with a peculiar glomerulopathy described as mesangio-degenerative. One case was a 34-year-old woman who had proteinuria since 23 years of age and developed increased proteinuria and hypertension during 2 pregnancies, and a 65-year-old man with nonnephrotic proteinuria and hypertension. Biopsy specimens from both cases demonstrated collagen fiber collections in the mesangium and subendothelial space. In 1982, Dombros and Katz[4] described a case with morphologic features similar to NPS but without skeletal abnormalities in a 34-year-old white woman. Ikeda *et al*.[5] identified the fibers as type III collagen and referred to the condition as primary glomerular fibrosis. Those cases were followed over the next several decades by cases documented in France,[6] China,[S2,S9] Japan,[S4,S10–S12] India,[2,S13–S16] Italy,[1] Argentina,[S17] Brazil,[S18] Saudi Arabia,[S8] and the United States.[7,S19] A case of CG was reported in a Croatian man in Australia in 2018.[S20] To our knowledge, there are no reported cases of CG in an African American patient.

A diagnosis of CG requires a renal biopsy and relies heavily on the ultrastructural finding of characteristic extracellular collagen accumulation in the mesangium and along the capillary walls of the glomeruli. The presence of collagen III is not abnormal in the kidney; the human kidney normally has collagen III present in the interstitium and blood vessel walls, but collagen III is not normally present in the glomeruli. On electron microscopy, the collagen fibers can be localized and segmental or extensively deposited throughout the glomerulus, in the mesangium and in the subendothelial aspect of the capillary wall. The collagen often has an unusual appearance, being thicker than typical collagen fibers, forming curved bundles, and showing frayed ends. In CG, collagen III deposition is distinct from NPS by its presence within the glomerular basement membrane in NPS, while in CG the collagen is found in the subendothelial aspect of the capillary wall. In NPS, the collagen deposition is usually difficult to discern using standard techniques for EM and often requires treatment with phosphotungstic acid.

On light microscopy the changes are variable; at least 2 patterns have been reported, with features on hematoxylin and eosin that could be mistaken for amyloid, thrombotic microangiopathy (TMA), or the nodular Kimmelstiel–Wilson lesions of diabetes. As in our case, most have striking pale eosinophilic capillary walls and mesangial expansion. Others have less severe capillary wall thickening with double contour formation evident on special stains and mild mesangial expansion. Some cases show a more distinct but usually mild mesangial expansion with minimal capillary wall thickening. The areas of expansion are characteristically PAS- and silver-negative. There is no apparent correlation of clinical features with any of the patterns; however, the pattern noted in our case, with massive deposition of collagen, may indicate more chronic or advanced forms of the disease in adults. Regardless of the pattern on light microscopy, immunofluorescence studies show minimal if any immune deposition, usually immunoglobulin M and/or C3, believed to be nonspecific. Immunohistochemistry with antibody for collagen III can be used to confirm the diagnosis if electron microscopy is not available or as an adjunct to electron microscopy; Congo red and special stains such as PAS and silver can assist in excluding amyloid, diabetes, or TMA.

The pathogenesis of the abnormal type III collagen deposition in the kidney is unclear, though it is associated with greatly increased levels of serum procollagen type III peptide (PIIINP).[5] Elevated PIIINP can also be associated with other conditions that result in fibrosis and is not a specific indicator of CG,[S21] although the levels found in patients with CG are typically much higher than in patients with other fibrosing conditions.[5,S5]

Whether CG is a primary renal disease process or a manifestation of a systemic disease is also not known. Collagen fibers, even collagen type III, can be seen in glomeruli in some chronic glomerular diseases, though usually in small amounts; what causes the massive accumulation seen in CG is not known. Naruse *et al*.[S22] found that mesangial cells in patients with CG expressed alpha-smooth muscle actin and proposed that myofibroblastic transformation of the cells occurred, allowing them to synthesize type III collagen. Kreisberg and Karnovsky [S23] showed that mesangial cells in culture can produce types I, III, and IV collagen, and Scheinman *et al*.[S24] found that mesangial cells have messenger RNA signal for procollagen alpha 1 (III), though isolated cells could have undergone transformation in culture leading to expression of interstitial-type collagen. Alchi *et al*.[S7] noted that interleukin-4 stimulates type III collagen synthesis by mesangial cells. Thus, mesangial cells could be responsible for the accumulation of collagen III caused by glomerular injury and/or cytokine stimulation. The increase in synthesis of type III collagen could explain the increased serum levels of PIIINP. Serum levels of procollagen type III peptide as well as hyaluronan are elevated in patients with CG, with a reduction in both serum hyaluronan levels and symptoms of CG after a kidney transplant, which supports an intrarenal origin for the collagen III.[S12]

Vogt *et al*.[7] documented an association between inherited factor H deficiency and CG. It has been noted in isolated cases of hemolytic uremic syndrome and may contribute to glomerular endothelial injury from complement-mediated damage and thus could allow abnormal access by collagen III to the subendothelial compartment. A frequent finding of anemia in patients with CG may suggest a similar pathogenesis to thrombotic

microangiopathy, which the condition can mimic on light microscopy. Abnormally high serum levels of PIIINP along with the fact some CG patients show substantial deposition of abnormal collagen fibers in organs other than the kidney suggests a systemic cause is possible or at least may contribute to the development of CG.[S7]

In terms of clinical outcomes, NPS does not always lead to renal failure, whereas CG often progresses to end-stage renal disease.[1,5,6,S5] Treatment is generally supportive and is focused on addressing proteinuria, edema, and hypertension with the use of angiotensin-converting enzyme therapy.[S9] Steroids have been used in some cases with at least temporary improvement.[S6] Although kidney transplant is not the first line of treatment for CG, in the few cases where patients received kidney transplants there has been no recurrence of CG symptoms or pathology.[S7,S25]

Patients with CG all have some variation of presenting signs and symptoms that include proteinuria, hypertension, and edema. These features overlap with those of pre-eclampsia. Our patient as well as one of Arakawa *et al.*'s initial cases of CG[3] were both noted to have proteinuria before pregnancy that increased during pregnancy, with a renal biopsy specimen obtained because of the persistence of proteinuria after delivery. Tamura *et al.*[8] also described a patient who developed proteinuria during pregnancy, with temporary resolution of proteinuria after delivery, who was later diagnosed with CG. The pathophysiology of a CG-related increase in proteinuria with pregnancy may stem from the increased perfusion pressure that occurs during pregnancy in the setting of an already compromised filtration barrier because of the presence of abnormal collagen along the capillary wall. Alternatively, changes in the endothelial layer during pregnancy and in conditions with microangiopathic injury could allow accumulation of collagen in the subendothelium that would not otherwise be possible. This theory seems less likely given the presence in males, children, and other adults without hemolytic uremic syndrome or TMA, and the persistence of the collagen many years after pregnancy. In addition, the relatively common occurrence of microangiopathies compared with the rare incidence of CG suggests that other mechanisms are at least in part responsible for the accumulation of collagen type III in the glomerulus.

CONCLUSION

In summary, CG is a diagnosis that should be considered in a patient of African ancestry with proteinuria, though most cases reported are in individuals of Asian or Western European descent. Further, this study highlights the necessity of broadening the differential diagnosis of the pregnant female patient who develops proteinuria during pregnancy or has an increase of pre-existing proteinuria while pregnant.

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

The authors obtained consent from the patient discussed in the report.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Table S1Compilation of previously published Collagen Type III cases

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