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ORIGINAL ARTICLE

Collagenofibrotic glomerulopathy

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Abstract

Background: Collagenofibrotic glomerulopathy is a rare renal disease of unknown etiology that is secondary to deposition of type III collagen within the glomerulus. Only rare case series exist in the literature.

Methods: Renal biopsies diagnosed with collagenofibrotic glomerulopathy were prospectively collected at the Center for Renal and Urological Pathology (AAK) (Chennai, Tamil Nadu, India) from 2012 to 2015. Eight patients were entered into the study. The average age was 38 years with five males and three females.

Results: All patients presented with nephrotic syndrome, and five displayed hypertension. The average serum creatinine was 146.5 µmol/L (88.4–282.9 µmol/L range). All serologic testing was negative, and complement levels were normal. No clinical evidence of nail–patella syndrome was seen. All cases showed diffuse mesangial expansion and double contour formation by peroidic acid-Schiff (PAS)-negative material. All immunofluorescence studies were negative. By electron microscopy all cases showed electron dense, banded to curvilinear collagen bundles within the mesangium and subendothelial aspect of the peripheral capillary walls. All patients appear to have sporadic disease occurrence with no family history of renal disease. No hemolytic uremic syndrome, liver fibrosis, lymphoma or co-occurrence of other renal disease were seen.

Conclusion: Collagenofibrotic glomerulopathy is a rare disease that appears to occur more frequently in adult Indian populations in a sporadic, non-familial manner. To our knowledge, this is the largest cases series of collagenofibrotic glomerulopathy in an adult population.

Key words: collagenofibrotic glomerulopathy, primary glomerular fibrosis, type III collagen glomerulopathy

Introduction

Collagenofibrotic glomerulopathy is a rare renal disease, characterized by accumulation of type III collagen in the glomerular mesangial and subendothelial areas [1]. It was first described by Arakawa in 1979 [2], and the World Health Organization included this disease in the classification of glomerular diseases in 1995 [2, 3]. Collagenofibrotic glomerulopathy has been documented under various names in the literature such as collagen type III glomerulopathy and primary glomerular fibrosis [4, 5].

Collagenofibrotic glomerulopathy may present as an isolated, sporadic form usually seen in adults, or as a familial form, with autosomal recessive inheritance, seen in children [6]. Patients typically present with proteinuria, most often in the nephrotic range and hematuria which is usually microscopic. The disease produces a progressive decline in renal function often leading

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to end-stage kidney disease. Diagnosis is made on renal biopsy where characteristic electron microscopic findings in conjunction with supporting light microscopic findings and negative immunofluorescence studies are seen. Additionally, immunohistochemical assays specific for type III collagen can be used to support the diagnosis.

To date, fewer than 50 cases have been reported in the literature, mainly as isolated case reports, and mostly from Japan. The largest series reported to date includes 10 children [6]. To our knowledge, this case series is the largest to date in an adult population.

Materials and methods

Renal biopsies diagnosed with collagenofibrotic glomerulopathy were prospectively collected at the Center for Renal and Urological Pathology (AAK) (Chennai, Tamil Nadu, India) between April 2011 and May 2015. Eight patients were included in the study. All relevant clinical data were retrieved. All biopsies underwent renal biopsy processing as previously described [7, 8]. Congo red staining was performed on 6 µm sections in all cases. Immunoperoxidase staining for collagen type III (Cosmo Bio USA, Carlsbad, CA, USA) was performed on select cases. Tannic acid lead staining was not employed on electron microscopy. This study was performed in accordance with our institutional review board's approved policies and procedures regarding case series in renal biopsy and nephrectomy specimens. For comparison of rates of collagenofibrotic glomerulopathy diagnosis, the databases at the Center for Renal and Urological Pathology and Nephropath were utilized.

Results

Among the 10 128 native kidney biopsies performed (Center for Renal and Urological Pathology, Chennai, Tamil Nadu, India) during the study period, eight were diagnosed with collagenofibrotic glomerulopathy (0.0008%). The database at Nephropath (Little Rock, AR, USA), a large renal biopsy referral center in the USA, was queried for comparison of the rate of diagnosis of this disease in the USA. During the study period, 25 964 total native kidney biopsies were received with none diagnosed with collagenofibrotic glomerulopathy. Based on these findings between similar renal biopsy referral centers in India and the USA, collagenofibrotic glomerulopathy is significantly more commonly seen in India ($P \leq 0.001$).

Clinical findings

Patients consisted of five males and three females (see Table 1). All patients showed negative serologies for ANA, hepatitis C, hepatitis B and HIV and had normal serum C3 and C4 levels. ANCA serologies were performed for three patients and were negative. None of the patients had a previous family history of renal disease or signs/symptoms of nail–patella syndrome.

Renal biopsy findings

All renal biopsies showed adequate tissue by light microscopy, immunofluorescence and electron microscopy. An average of 24 (14–32 range) glomeruli were present for evaluation by light microscopy with an average of 30% global glomerulosclerosis (13–73% range) (see Table 2). Double contour formation was seen in all biopsies. Diffuse mesangial expansion by PAS-negative, flocculent material was seen in all biopsies (Figure 1A–C). This material was also frequently seen on the luminal side of the peripheral capillary loops and between double contours. No extension into the extraglomerular arterioles/arteries, Bowman space, podocytes or the tubulointerstitium was present. Staining for Congo red was negative in all biopsies. Staining for collagen type III was performed on three biopsies where tissue was available and showed positive staining within the mesangium and capillary walls in all (Figure 1D). By immunofluorescence, staining for IgA, IgG, IgM, C3, C1q,

Table 1. Clinical data

Patient	Age/gender	Urine protein (g/24 h)	Serum creatinine (µmol/L)	Hematuria	Hypertension	Systemic disease	Family history of renal disease
1	31/M	3	88.4	No	Yes	No	No
2	29/M	7.1	159.1	Microscopic	Yes	No	No
3	39/M	3.5	282.9	No	Yes	No	No
4	36/F	4.5	150.3	Microscopic	No	No	No
5	32/M	8.3	88.4	Microscopic	No	No	No
6	38/M	3.9	203.3	Microscopic	Yes	No	No
7	27/F	6.1	Unknown	No	Yes	No	No
8	34/F	5.9	53.0	Microscopic	No	No	No

Table 2. Morphologic data

Patient	Mesangial expansion	Distribution of collagen fibrils	Basement membrane duplication	Interstitial fibrosis	Arteriosclerosis
1	Yes	Mesangial, subendothelial	Segmental	None	None
2	Yes	Mesangial, subendothelial	Segmental	75%	Moderate
3	Yes	Mesangial, subendothelial	Global	50%	Moderate
4	Yes	Mesangial, subendothelial	Segmental	30%	None
5	Yes	Mesangial, subendothelial	Global	10%	Moderate
6	Yes	Mesangial, subendothelial	Segmental	30%	None
7	Yes	Mesangial, subendothelial	Global	10%	No vessels present
8	Yes	Mesangial, subendothelial	Global	None	None

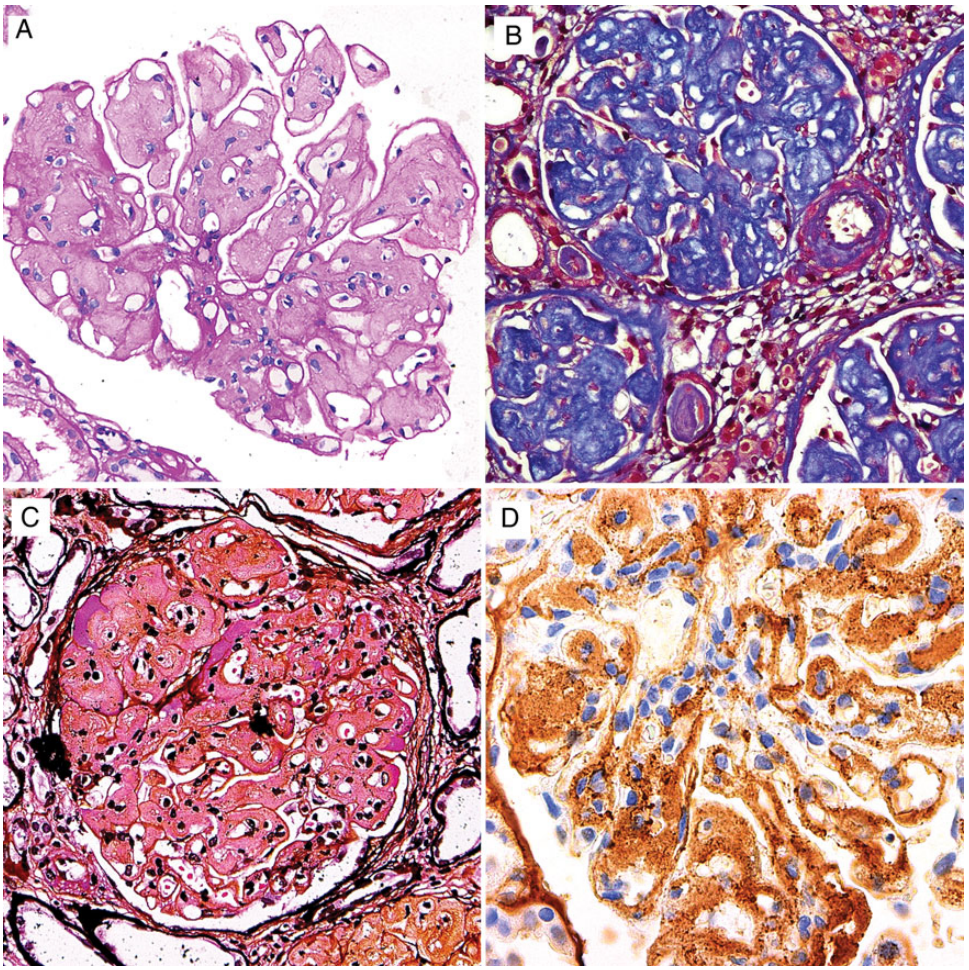

Fig. 1. Morphology of collagenofibrotic glomerulopathy. (**A**) Global mesangial expansion and focal double contour formation (H&E stain, ×400 original magnification). (**B**) Mesangial expansion and peripheral capillary loop double contour formation staining a variegated blue on Masson trichrome stain (×200 original magnification). (**C**) Jones silver stain showing loss of silver staining within the expanded mesangium and peripheral capillary loop double contours (×400 original magnification). (**D**) Type III collagen immunohistochemical stain showing staining of the peripheral capillary loops and mesangium (×600 original magnification).

kappa and lambda light chains was negative in intact glomeruli in all biopsies. By electron microscopy all cases showed flocculent expansion of the mesangium and subendothelial aspect of the peripheral capillary wall with deposition of electron-dense, frayed, banded to curvilinear fibrillar material consistent with collagen bundles (Figure 2A–D). No collagen deposition was present within the intramembranous or subepithelial compartments of the peripheral capillary walls.

Discussion

Type III collagen is absent in the normal glomerulus. However, it has been reported in glomeruli with underlying glomerular disease and rarely within the vascular pole in a focal and segmental manner [9]. Nail–patella syndrome is the only other known glomerular disease to show significant accumulation of type III collagen within intact glomeruli [1]. Initially, some groups suggested that collagenofibrotic glomerulopathy was a glomerular limited form of nail–patella syndrome, however it is now considered a novel form of glomerulopathy due to the unique clinicopathologic characteristics of this disease [6, 10, 11]. No clinical signs or symptoms of nail–patella syndrome were present in our patients, and no secondary glomerular diseases were seen.

Collagenofibrotic glomerulopathy has unique clinicopathologic features in children when compared with adults. The largest case series of collagenofibrotic glomerulopathy to date describes ten pediatric patients and provides evidence to support an autosomal recessive mode of transmission in these children with disease [6]. However, most reported cases of adult-onset collagenofibrotic glomerulopathy appear to be sporadic with no family history of renal disease as is true for all of our patients. Gubler *et al.* also report frequent association of hemolytic uremic syndrome with collagenofibrotic glomerulopathy in children [6]. However, in our adult population no previous or co-occurrence of hemolytic uremic syndrome was seen. Likewise, other rarely reported associations such as perisinusoidal fibrosis, Hodgkin's lymphoma and glomerular immune complex deposition were not present in our patients [12–15].

Some authors have suggested that collagenofibrotic glomerulopathy is a systemic disease citing the increase in serum and urine procollagen type III peptide and reports of non-renal deposition as evidence [16]. However, increases in serum and urine procollagen type III peptide can be seen in advanced renal fibrosis and are not specific to collagenofibrotic glomerulopathy. Other authors have reported mesangial cell activation and suggest a mesangial source of collagen type III production [17]. In our patients, no clinical evidence of a multi-system disease was

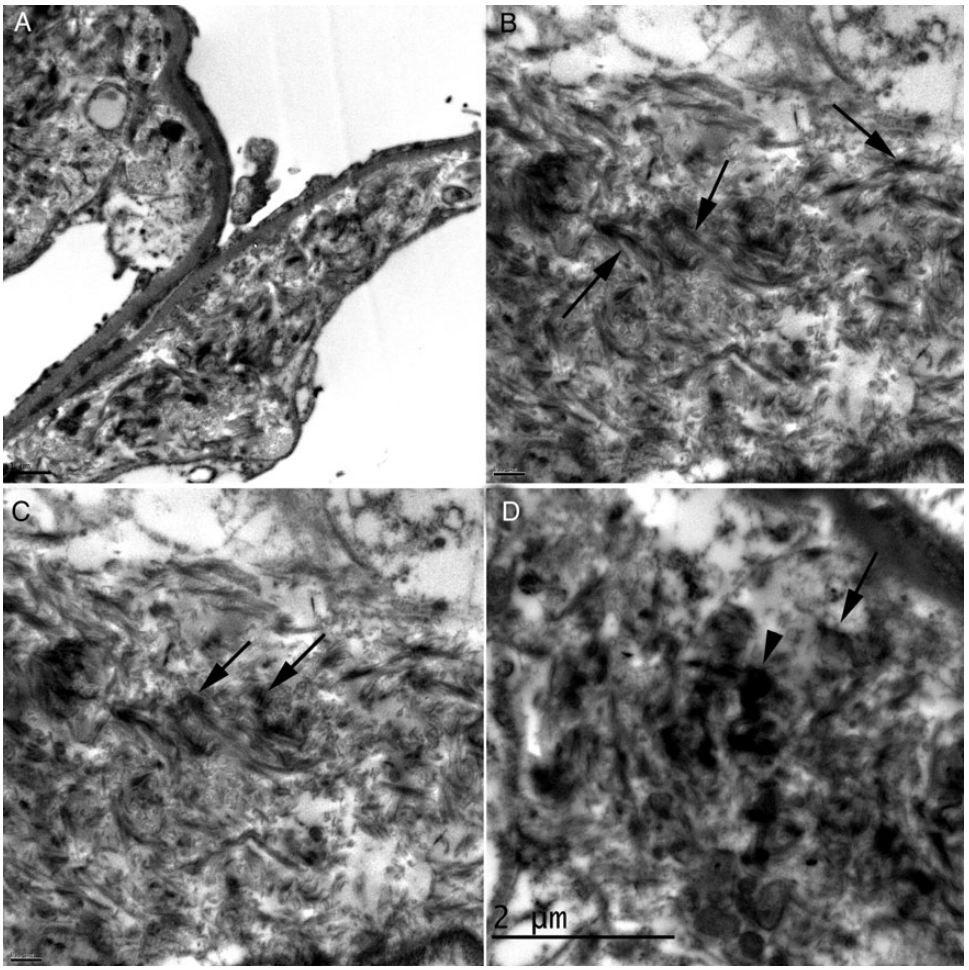

Fig. 2. Electron microscopic findings in collagenofibrotic glomerulopathy. (**A**) Peripheral capillary loop with expanded subendothelial space containing stacked collagen bundles (×10 000 original magnification). (**B**) Curvilinear collagen fibrils (arrows) with frayed ends consistent with type III collagen (×20 000 original magnification). (**C**) Curvilinear collagen fibrils forming stacks (arrows) consistent with type III collagen (×20 000 original magnification). (**D**) Curvilinear collagen with frayed ends (arrow) show frequent arrangement into dense stacks (arrowhead) (×30 0000 original magnification).

noted, however most patients were at initial presentation [16]. To date, consensus has yet to be reached on the location and extent of type III collagen production in collagenofibrotic glomerulopathy.

The histopathology of collagenofibrotic glomerulopathy in our cases included classic findings such as mesangial expansion and double contour formation by PAS negative, flocculent material that extended along the luminal side of the peripheral capillary loops. No staining was seen by immunofluorescence. And, by electron microscopy, all cases showed electron-dense, banded, curvilinear structures diagnostic of collagen occurring within the expanded mesangium and subendothelial space confirming the diagnosis of collagenofibrotic glomerulopathy.

Although only representing a small minority of diagnoses, collagenofibrotic glomerulopathy is much more commonly diagnosed in an Indian population when compared with a similar American population. The reason for this increase is unknown. However, it is possible that decreased access to treatment of chronic infections and disease may play a role or that differing genetic factors may be involved. Also, a significant difference in environmental factors exists between Indian and American populations. However, until the underlying etiology of collagenofibrotic glomerulopathy is identified the reason for this increase will likely remain opaque.

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Conflict of interest statement

None declared.

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