In-Depth Review

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Collagenofibrotic glomerulopathy—a review

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Abstract
Collagenofibrotic glomerulopathy (CG) is a rare cause of idiopathic nephrotic syndrome characterized by massive accumulation of atypical Type III collagen fibrils within the mesangial matrix and subendothelial space of the glomeruli. A definite diagnosis can be established when typical histological findings are supported by electron microscopy. This disease exhibits indolent progression and as yet has no specific treatment. The present article reviews the clinicopathological features, epidemiology and proposed mechanisms of pathogenesis of CG. A search of the English language literature identified 38 cases of CG, of which 22 are reported from Asian countries. An additional three cases are being reported from this Institute in India and are illustrated herein. These reports contribute to a better understanding of this disease, which although not as prevalent, should be considered as a differential diagnosis in cases of mesangiocapillary form of glomerular injury.

Keywords: banded collagen; collagenofibrotic glomerulopathy; nephrotic syndrome; Type III collagen

Introduction

Collagenofibrotic glomerulopathy (CG) is a rare condition characterized by deposition of Type III collagen fibers in the subendothelial space and mesangium of the glomerulus [1–9]. Fewer than 40 cases have been described in the literature under several names, including primary glomerular fibrosis, Collagen III glomerulopathy and CG [4]. The first report of this entity, in the late 70s from a team of Japanese doctors, considered this disease to be a variation of the nail–patella syndrome in the absence of skeletal abnormalities [10, 11]. Later reports clarified that this entity is a new type of hereditary glomerulopathy [12]. The pathological features are characteristic, although the clinical picture can be varied. The patients range in age from 2–66 years, with no sex predilection. The most common clinical presentation is proteinuria with or without associated nephrotic syndrome, with minor alterations in renal function [4, 5].

Materials and methods

We have identified three cases of CG that occurred over a period of 5 years (2006–2010) from among 5370 native and allograft renal biopsies from the archival material of the Department of Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh (India). The clinicopathological features of the three cases are summarized in Table 1. A literature search for CG was conducted using PubMed, limited to the English language, using keywords 'CG' and 'Type III collagen glomerulopathy'. In this article, we have reviewed the pathogenesis, clinical

and pathological features and the histological differential diagnosis of this disease and added three cases of this rare entity to the existing literature.

Discussion and review

Epidemiology

CG appears to be relatively common in Asian countries. Sixteen of 38 reported cases have occurred in patients of Japanese descent. The other reports are by Gubler *et al.* [12] from France (10 cases), Dombros and Katz [11] from Canada (1 case), Imbasciati *et al.* [2] from Italy (1 case), Vogt *et al.* [13] from the USA (1 case) and Ferreira *et al.* [14] from Brazil (3 cases). It is also interesting to note that 10 of 12 cases in the pediatric age group are from France [12]. There are nine cases from India [15–17], including the three cases of the present study, further confirming that this disease is relatively common in Asia.

Etiopathogenesis

Although the etiopathogenesis of this glomerulopathy remains unclear, it appears that ethnic/genetic factors play an important role. Clustering of the cases from Japan points to either environmental or ethnic factors in the cause of the disease while occurrence of the disease in siblings points to a genetic etiology [6]. There are two major theories regarding the origin of the accumulated spiraled and frayed collagen. One concept is that the abnormal Type III collagen is produced endogenously by the mesangium; alternatively, there is some evidence of extra-renal involvement with CG leading to a hypothesis that CG may be a systemic disease with

Table 1. Morphological features in three cases of collagenofibrotic glomerulopathy

Case no.	Age (years)/ sex	Clinical presentation	Histopathology	Direct immunoflorescence	Electron microscopy
1.	53/male	Known case of psoriasis with nephrotic syndrome (24-h urinary protein 5 g/day) hypertension (BP 180/90 mmHg), normal serum creatinine.	Mesangiocapillary pattern with capillary wall thickening and mesangial expansion by pale PAS-negative material.	Negative for all immunoglobulins except for segmental trapping for C3 in an occasional glomerulus.	Curvilinear collagen structures arranged in a disorganized manner in sub-endothelial and mesangial regions. The fibrils further demonstrated a specific banding pattern of 50–65 nm periodicity, thereby indicating banded Type III collagen. Lamina densa was unremarkable.
2.	32/male	Normotensive with generalized edema, nephrotic range proteinuria (24-h urinary protein 3.6 g/day), normal serum creatinine.	Glomeruli showed lobular accentuation with narrowing of the capillary lumina by pale PAS-negative material.	Negative for all immunoglobulins and complement.	Banded collagen fibrils in the subendothelial and mesangial location; however, no fibrils are noted in the lamina densa.
3.	40/male	Normotensive with pedal edema and nephrotic syndrome (24-h urinary protein 2.0 g/day with serum albumin 21 g/L; total cholesterol 9.2 mmol/L)	Glomeruli showed lobular accentuation due to deposition of homogeneous PAS and Congo red-negative deposits mainly in the expanded mesangium and sub-endothelial areas. An occasional glomerulus, in addition, revealed lesions of nodular glomerulosclerosis.	Negative for all immunoglobulins and complement	Disorganized collagen fibrils with typical periodicity in mesangial and subendothelial location. No fibrils noted in the lamina densa

abnormal metabolism of Type III collagen [8, 12, 18]. Although Type III collagen is not a normal constituent of the glomerular mesangium, *in vitro* studies have shown that mesangial cells contain messenger RNA for the interstitial collagen α1 (III), suggesting that a phenotypic alteration of mesangial cells can produce large amounts of Type III collagen [19]. Furthermore, mesangial cells in CG have been shown to undergo myofibroblastic transformation (as evidenced by production of α smooth muscle actin and formation of sub-plasmalemmal filaments), which are postulated to be the source of Type III collagen [20].

Type III collagen is synthesized as a large precursor molecule, Type III pro-collagen, which then is converted to Type III collagen after enzymatic cleavage of its N-terminal peptide. Thus, increased serum levels of this N-terminal pro-collagen Type III peptide (PIIINP), found in patients with diseases presenting with fibrosis, indicate excessive conversion of Type III pro-collagen into Type III collagen. Both urinary and serum PIIINP levels are useful indicators of the extent of renal fibrosis [21, 22]. Median serum PIIINP level in patients with chronic kidney disease was reported to be double of that in healthy subjects, whereas levels ranging from 10 to even 100 times greater than normal could often be detected in patients with CG. Hence, elevated serum pro-collagen III in patients of CG suggests up-regulation of collagen synthesis and this could be considered as a marker for this disease when interpreted in the proper clinicopathological context [23].

Clinical presentation

Analysis of the 41 reported cases [including the current series (Table 1)] shows that all age groups are affected and there is no sex predilection. The incidence of this entity is highest between the fourth and seventh decades; however, 13 cases in children up to the age of 15 years have been reported [12–14]. Notably, all 10 cases reported from France were in the pediatric age group [12] Hence, this disease may be divided into two different clinical sub-types, an adult-onset type and a pediatric type. The most common presenting feature of CG is edema and/or persistent proteinuria that may reach the nephrotic range in ~60% of patients (Table 2) [1–4, 7–9, 12, 14–17]. Hypertension is another early feature, which may be detected at the time of presentation (Table 2) [2, 6, 13–15, 17]. The natural history of CG is variable, but the disease is progressive, at least in a subset of patients. An occasional case has been associated with factor H deficiency [13]. Renal failure is described within 3 years of diagnosis in one patient [1]. In other patients, symptoms progress steadily with increasing renal insufficiency and eventual failure [4]. The disease appears to be primarily a renal process, barring an occasional case report of extra-renal involvement [4, 18]. The severity of the disease at presentation is highly variable, and its pace of progression is unpredictable.

Pathological features

Histopathologically, light microscopy shows lobular bland-appearing glomeruli due to global expansion of the mesangium with thickening of the peripheral capillary walls but no substantial mesangial hypercellularity (Figure 1a and b). The mesangial expansion is due to the accumulation of amorphous, weakly periodic acid Schiff (PAS)-positive material mimicking amyloid deposits. However, Congo red and thioflavine stains are completely negative. On Masson's trichrome stain, the deposited material reveals blue staining (Figure 2d). The capillary lumina are narrowed but not occluded. The thickened capillary walls show focal reduplication; however, PAS and methenamine silver stains clearly highlight that the capillary basement membranes are normal and thickening of the wall is due to sub-endothelial deposition of pale amorphous material (Figure 1c). Usually, no endocapillary or extracapillary proliferation is seen in CG. In the advanced stage, capillary lumens are narrowed by the expanded mesangium and thickened capillary walls and glomeruli show a nodular appearance suggestive of diabetic nephropathy or monoclonal immunoglobulin deposition disease. However, unlike these two entities, the nodular lesions are weakly PAS positive or PAS negative in CG. Patchy tubular atrophy and interstitial fibrosis may be present, and these changes are proportional to the degree of global glomerulosclerosis. Arteriolar hyalinosis and thickening of the walls of arteries can be seen, probably secondary to hypertension.

Table 2. Clinical profile of published cases of collagenofibrotic glomerulopathy in literature

Reference year	Country of study	Age in years (no. of cases)	Sex (no. of cases)	Clinical presentation (no. of cases)	Blood pressure (mmHg)	Proteinuria (g/day)	Microscopic hematuria (no. of cases)	Creatinine (μmol/L)
Arakawa et al. [4]; 1979	Japan	32	F	Edema, proteinuria	130/70	0.1–0.8	+	114.9
Dombros and katz [11]; 1982	Canada	34	F	Hematuria	NR	0	+	53.0
Kurosawa et al. [4]; 1984	Japan	64	M	Edema, proteinuria	190/104	1.5–5.0	+	229.8
Yasuda et al. [4]; 1984	Japan	42	F	Proteinuria	108/80	3.6	−	61.9
Isoda et al. [4]; 1985	Japan	36	M	Proteinuria	170/100	4.9	NR	371.3
Fukuta and monden [4]; 1985	Japan	65	M	Proteinuria	184/84	2.7	NR	141.4
Sanaka et al. [4]; 1986	Japan	49	M	Proteinuria	180/106	8.6	+	88.4
Ono et al. [4]; 1989	Japan	30	F	Proteinuria	NR	0.5–1.3	+	229.8
Ikeda et al. [1]; 1990	Japan	38	M	Gout, proteinuria	146/80	3–5	NR	203.3
Imbasciati et al. [2]; 1991	Italy	49	F	Hypertension, proteinuria	180/110	0.8–1.2	−	79.6
Gubler et al. [12]; 10 cases; 1993	France	1–15 (10)	M(7) F(3)	Proteinuria (4) Hematoproteinuria (6)	Hypertension (5)	Nephrotic range (1)	+ (6) − (4)	Renal insufficiency (3)
Yoshida et al. [3]; 1993	Japan	54	F	Proteinuria	180/92	3–5	NR	79.6
Mizuiri et al. [4]; 1993	Japan	49	F	Proteinuria	160/94	0.6	−	70.7
Ozu et al. [4]; 1994	Japan	49	F	Proteinuria	182/90	8.0	−	88.4
Vogt et al. [13]; 1995	USA	2	M	Hypertension, heart failure	166/28	0.6	+	NR
Tamura et al. [6]; 1996	Japan	33	F	Facial edema, hypertension	180/120	6.5	−	167.9
Hisakawa et al. [7]; 1998	Japan	66	M	Edema, proteinuria	160/90	2.5	NR	97.2
Yasuda et al. [8]; 1999	Japan	38	M	Edema, proteinuria	170/100	4.9	+	371.3
Morita et al. [9]; 2003	Japan	65	F	Anemia, hypertension, proteinuria	140/70	3.6–6.3	−	88.4
Suzuki et al. [4]; 2004	Japan	6	F	Hematoproteinuria	160/80	3.2	+	26.52
Ferreira et al. [14]; 2009	Brazil	55	F(3)	Hypertension, hematoproteinuria	NR	1.18	+	NR
		21		Hemoproteinuria	NR	1.6	+	NR
		15		Hypertension, hemoproteinuria	NR	2.49	+	108.7
Khubchandani et al. [15]; 2010	India	43	F(1)	Hypertension, proteinuria	170/110	5.8	−	NR
		20	M(2)	Hypertension, proteinuria	150/100	Nephrotic range	−	114.9
		20		Hypertension, proteinuria	190/100	Albumin+	−	176.8
Soni SS et al. [16]; 2011	India	26	M	Hodgkin lymphoma with proteinuria	NR	1.6	−	114.9
Patro KC et al. [17]	India	43	F	Hypertension, hematoproteinuria	190/110	5.8	+	74.3
		20	M	Proteinuria, hypertension	160/90	3.4	−	176.8
Present series	India	53	M	Proteinuria, hypertension, Psoriasis	180/100	5.0	−	97.2
		32	M	Proteinuria	140/70	3.6	−	88.4
		40	M	Proteinuria	130/70	2.0	−	90.2

F, female; M, male; +, Positive; −, Negative; NR, not reported

Staining for immunoglobulins and complement components is usually negative. Focal and segmental trapping for immunoglobulin M and complement C3 may be found in glomeruli, corresponding to the sub-endothelial hyaline deposits seen on light microscopy, which probably represent insudated plasma proteins and are not indicative of immune complex-mediated process. However, a single case of CG associated with immune complex deposits has been reported in the literature [7].

Electron microscopy is essential to establish a definitive diagnosis of CG and the pathological findings should be recognized with certainty. It is characterized by massive accumulations of banded collagen in glomerular mesangial and sub-endothelial zones. Abnormal accumulation of banded
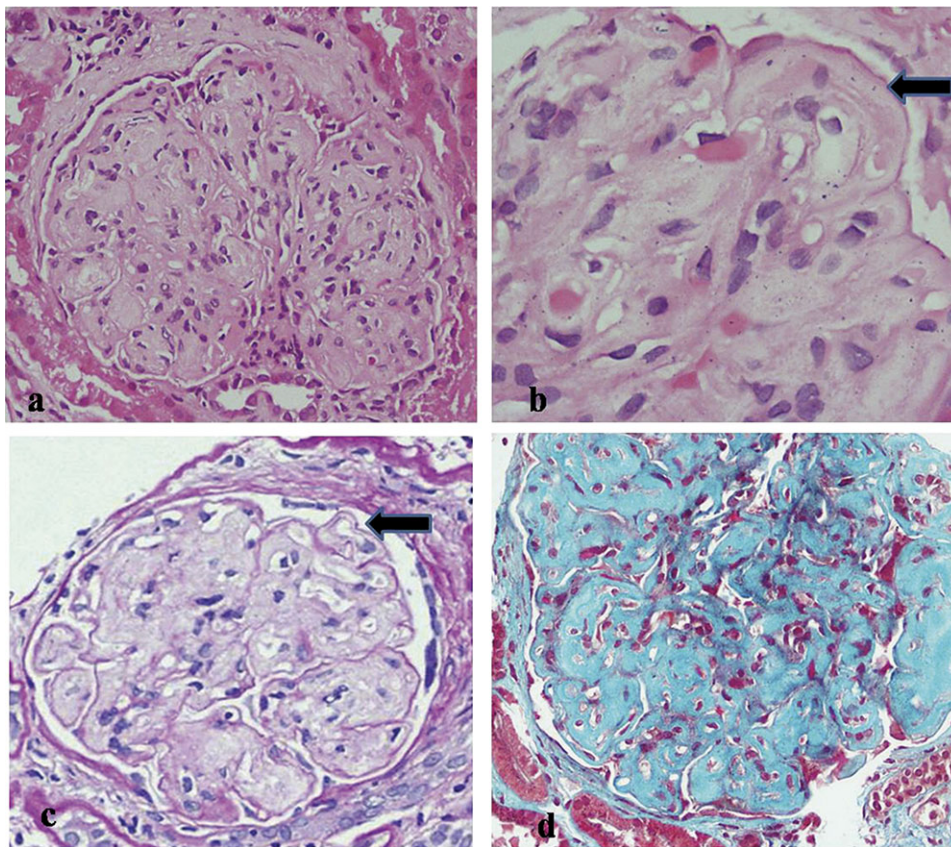
Fig. 1. Light microscopic features of collagenofibrotic glomerulopathy. (**a**)Glomerulus with mesangiocapillary pattern of injury in form of mesangial expansion and capillary wall thickening without increase in mesangial cellularity (hematoxylin–eosin, original magnification ×400); (**b**) glomerulus with subendothelial (indicated by arrow) and mesangial expansion by pale amorphous vaguely fibrillar material (hematoxylin–eosin, original magnification ×1000); (**c**) glomerulus showing thin delicate PAS-positive basement membrane (indicated by arrow), while the capillary wall thickening is contributed by pale PAS-negative material (PAS, original magnification ×400); (**d**) Masson's trichrome shows blue staining of the deposited material thereby indicating it to be collagen (trichrome stain, original magnification ×400).

collagen is also an ultra-structural hallmark of nail–patella syndrome glomerulopathy, in which the profiles of banded collagen occur predominantly within the lamina densa of the glomerular basement membranes. The two diseases can thus be distinguished by the location of Type III collagen (Figure 2a and b). At high magnification, the fibrils are arranged in irregular bundles, show a distinct periodicity of 43–65 nm and appear curved, frayed, and worm and comma shaped when sectioned transversely (Figure 2c and d). Because of the abnormal shape, size and organization of the bundles of Type III collagen fibrils, these appear 'atypical' or abnormal and can be clearly differentiated from the fibrils of regular Type III collagen (which are arranged in straight lines) and from other types of organized glomerular deposits, e.g. the deposits of amyloid, fibrillary glomerulonephritis and immunotactoid glomerulopathy [23]. Although the banded morphology of collagen fibrils can be identified with routine staining for electron microscopy, it is better visualized by special staining with tannic acid lead or phosphotungstic acid. Discrete electron-dense immune complex-type deposits usually are not present, although subendothelial dense deposits can be seen infrequently. A variable degree of epithelial foot process effacement is usually seen [23].

Collagen III immunohistochemistry shows focal, segmental or diffuse and generalized mesangial staining, primarily depending on the stage of the disease process. Immunostaining for other fibrillar collagen types typically is negative and

Type IV collagen is normal. However, in an occasional case, both Types III and I or III and V collagens could be detected [3, 4, 9].

Histological differential diagnosis

CG at the light microscopy level has enlarged lobular glomeruli, with the membranoproliferative/mesangiocapillary pattern. Thus, it has to be differentiated from (i) membranoproliferative glomerulonephritis, (ii) diabetes, (iii) amyloidosis and other fibrillary glomerulopathies and (iv) monoclonal immunoglobulin deposition disease [4, 19]. Although the confirmation of a diagnosis of CG has to be obtained by electron microscopy or specific immunohistochemistry, clues to its diagnosis can be obtained at light microscopy level. The tram track appearance, mesangial cellularity and typical immunofluorescence pattern of MPGN are not seen in these cases. The sub-endothelial and mesangial collagen deposits lack the strong PAS positivity, which is consistently seen in diabetes and light-chain deposition disease. Congo red stain and Thioflavin T (for amyloid) are negative. Masson's trichrome stain is useful as it identifies the blue-colored collagen within the capillary loops and mesangium.

Treatment and prognosis

No specific treatment is available for this entity. Supportive measures for control of hypertension and edema may help
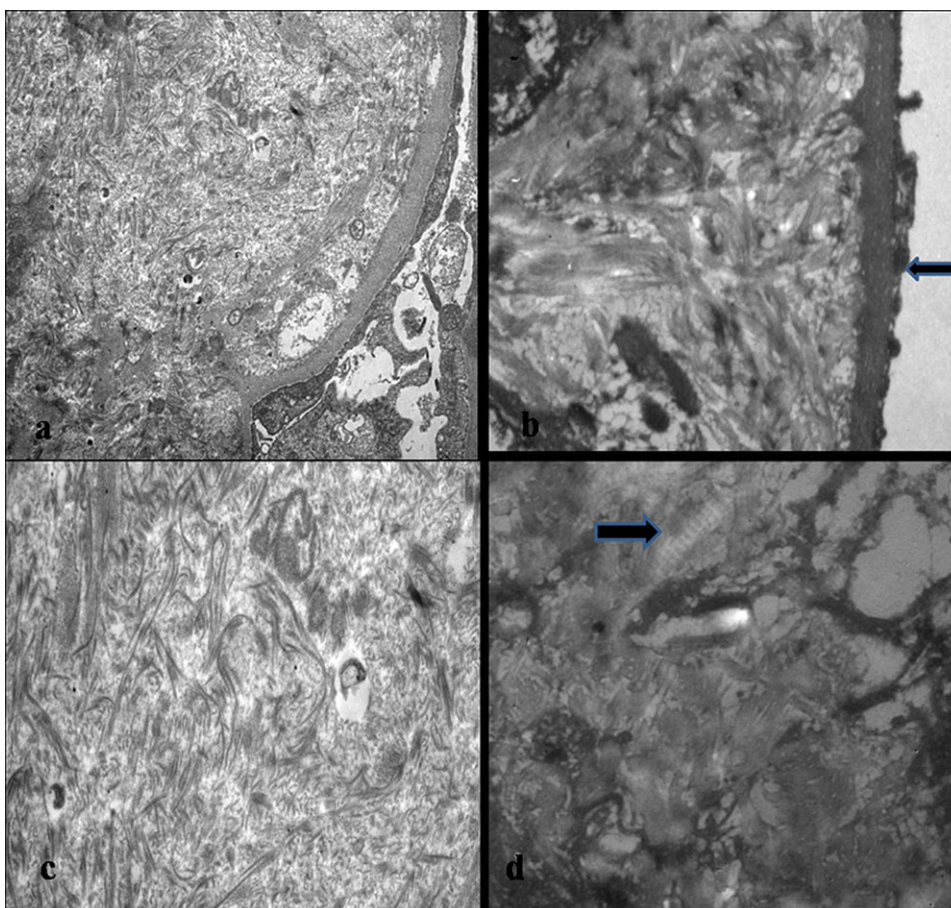
Fig. 2. Electron microscopic features of collagenofibrotic glomerulopathy. (**a**) Expanded subendothelial and mesangial space by deposition of fibrillary material. The overlying podocytes show foot process effacement (uranyl acetate and lead citrate; original magnification ×10 000); (**b**) the collagen deposits are noted in the sub-endothelial location and have a disorganized appearance. The glomerular basement membrane (indicated by arrow) itself shows no collagen fibrils (uranyl acetate and lead citrate; original magnification ×17 000); (**c**) collagen fibrils have typical curvilinear and disorganized morphology when transversely cut indicative of atypical Type III collagen (uranyl acetate and lead citrate; original magnification ×21 500); (**d**) On high magnification, the organized deposits have banded appearance (indicated by arrow) with typical periodicity of 60 nm, indicative of fibrillary Type III collagen (uranyl acetate and lead citrate; original magnification ×28 000).

to relieve the symptoms. Dialysis/renal transplantation may be required for patients with end-stage renal disease. Although very few patients have received a transplant, to date none have shown recurrence of the disease [4]. It is well documented in dermatological conditions that the use of systemic glucocorticoids can diminish the deposition of interstitial collagens [24]. However, their role in CG is doubtful and a future clinical trial on the regular use of steroids is unlikely because of the rarity of the disease.

Conflict of interest statement. None declared.

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