Collagenofibrotic Glomerulopathy

51

Guillermo A. Herrera

Contents

Abstract

Collagenofibrotic glomerulopathy is a very rare condition with a genetic component. In most cases, the inheritance pattern has been autosomal recessive which is consistent with the usual onset of symptoms in early childhood. Less than 50 cases have been described in the literature under several names including primary glomerular fibrosis, collagen III glomerulopathy, and collagenofibrotic glomerulopathy. It was initially considered a variant of nail-patella syndrome, but it is now recognized as a specific entity. Manifestations of renal dysfunction may occur in childhood or later in life. Renal biopsy is required to make a diagnosis. A high index of suspicion and recognition of the rather characteristic ultrastructural findings is needed for the pathologist to suspect the diagnosis and order the stain for collagen III to confirm the diagnosis. This condition in at least a subset of the patients is a progressive disease, and no specific treatment is available at the present time.

Keywords

Collagen III glomerulopathy · Collagenofibrotic glomerulopathy · Electron microscopy · Light microscopy · Immunohistochemistry

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Introduction/Historical Perspective

This entity was first reported by Arakawa in 1979 (Arakawa et al. 1979). Dombros and Kats published a case in 1982 which they thought was a variant of nail-patella glomerulopathy without skeletal abnormalities (Dombros and Katz 1982), and a second case was published 2 years later (Salcedo 1984). Ikeda recognized the peculiar fibers present in glomeruli in 1990 (Ikeda et al. 1990). In 1995, collagenofibrotic glomerulopathy was first included in the World Health Organization classification of glomerular diseases. Since then, more than 40 cases have been published, and understanding of this disorder has been significantly advanced (see Pathogenesis). Most cases have been identified in Asia, and the first patients in Latin America were reported in 2009 (Ferreira et al. 2009).

Clinical Presentation/Epidemiology Initial presentation of this disease is quite variable. The patients have ranged from 6 to 72 years with no sex predilection. Familial occurrence of this disorder has been documented, and an autosomal recessive pattern of inheritance has been proposed. Extrarenal symptoms and findings are almost always absent. The first symptoms of this disease may appear in early childhood or in late adulthood. The most common clinical presentation is persistent proteinuria with or without associated nephrotic syndrome with minor alterations in renal function. These patients can also exhibit varying degrees of hematuria (though hematuria is often absent) and hypertension (Duggal et al. 2012; Patro et al. 2011; Imbasciati et al. 1991; Gubler et al. 1993; Tamura et al. 1996; Yoshioka et al. 1989). No skeletal manifestations are present. Renal function deterioration appears to be a late event.

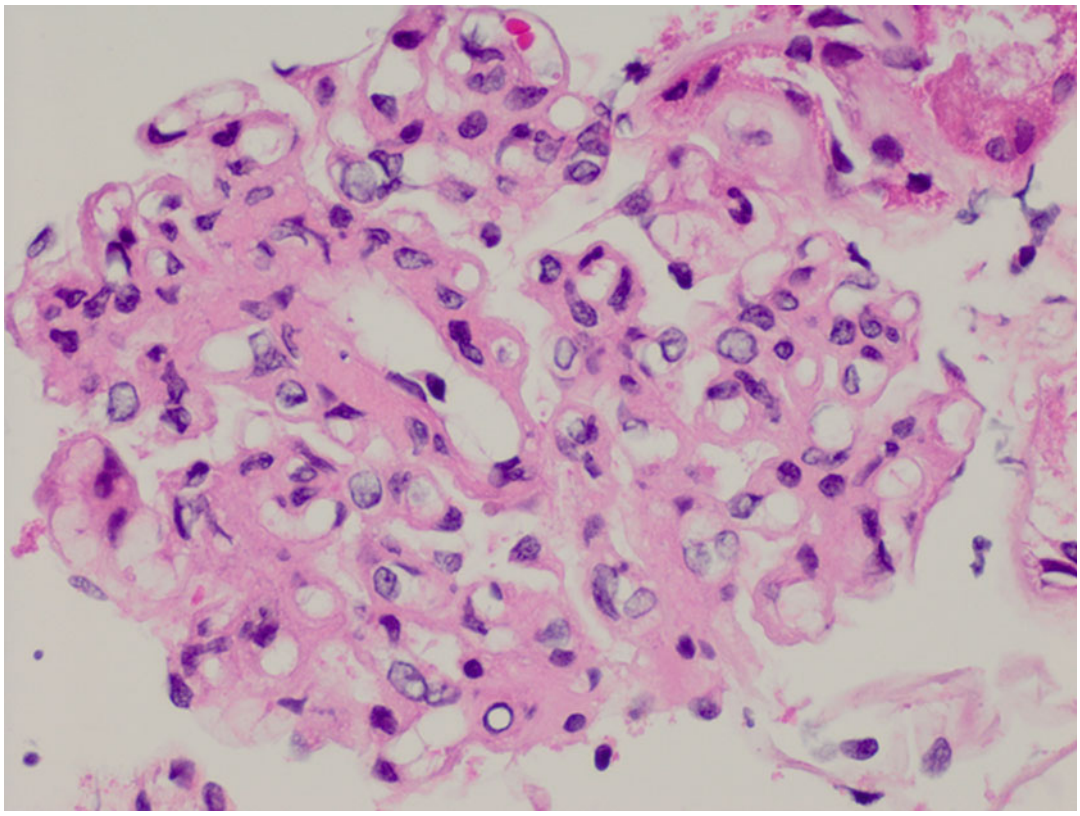

Fig. 1 Collagenofibrotic glomerulopathy, early stage. Hematoxylin and eosin stain. X750. Segmentally expanded mesangium with increased matrix

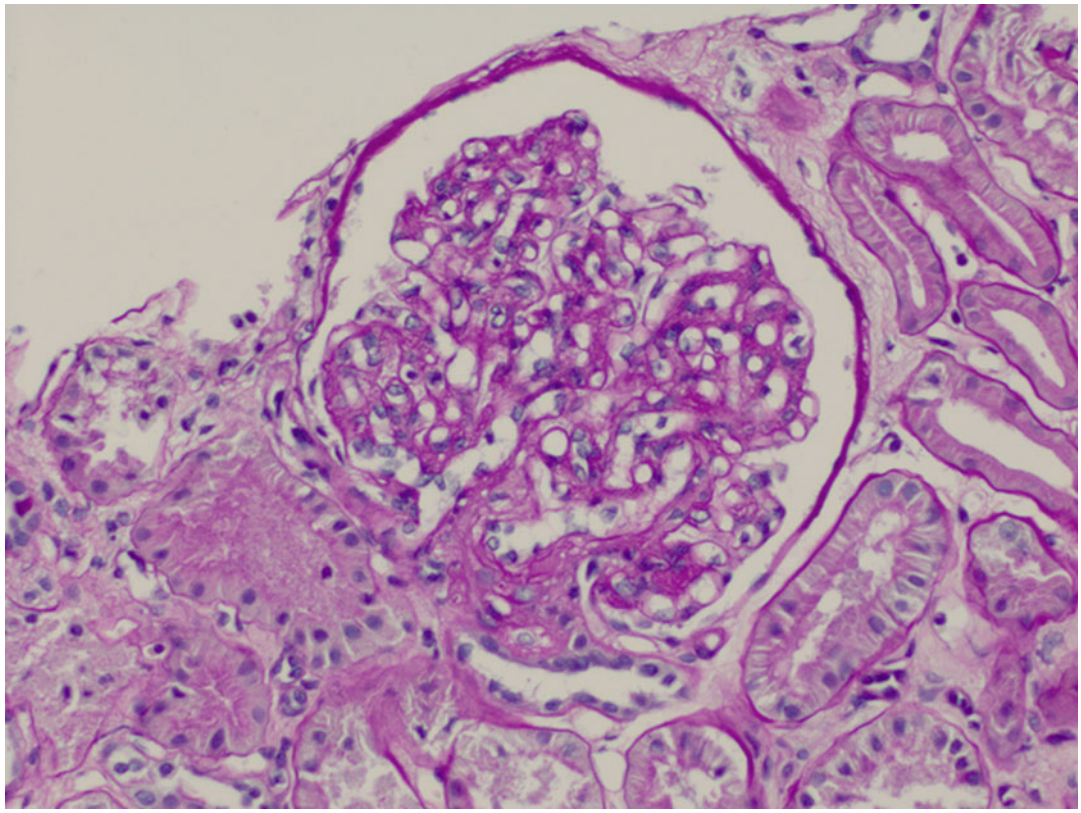

Fig. 2 Collagenofibrotic glomerulopathy. PAS stain. AX750. Note weak staining in expanded mesangial areas and segmentally expanded subendothelial zones

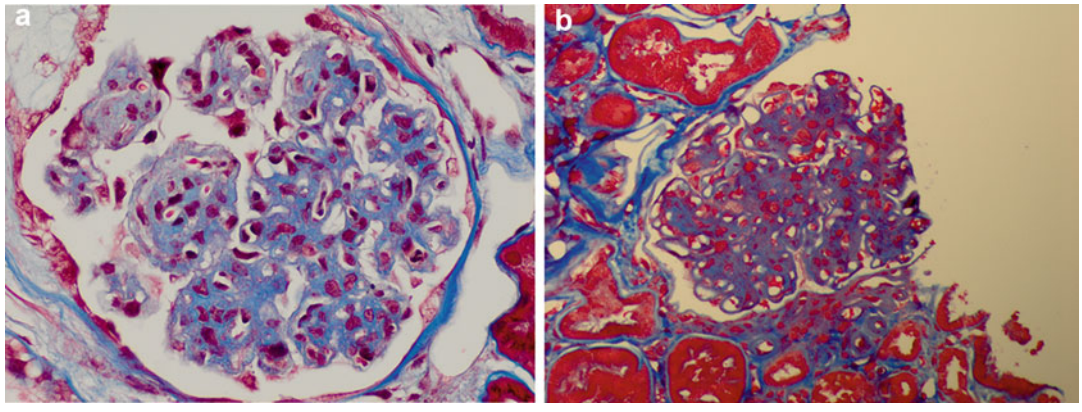

Fig. 3 Collagenofibrotic glomerulopathy. Trichrome stain. AX750, BX750. Note blue mesangial staining with increment from an early case (**a**) to a well-developed case with distinct mesangial expansion with increased matrix/nodular appearance (**b**)

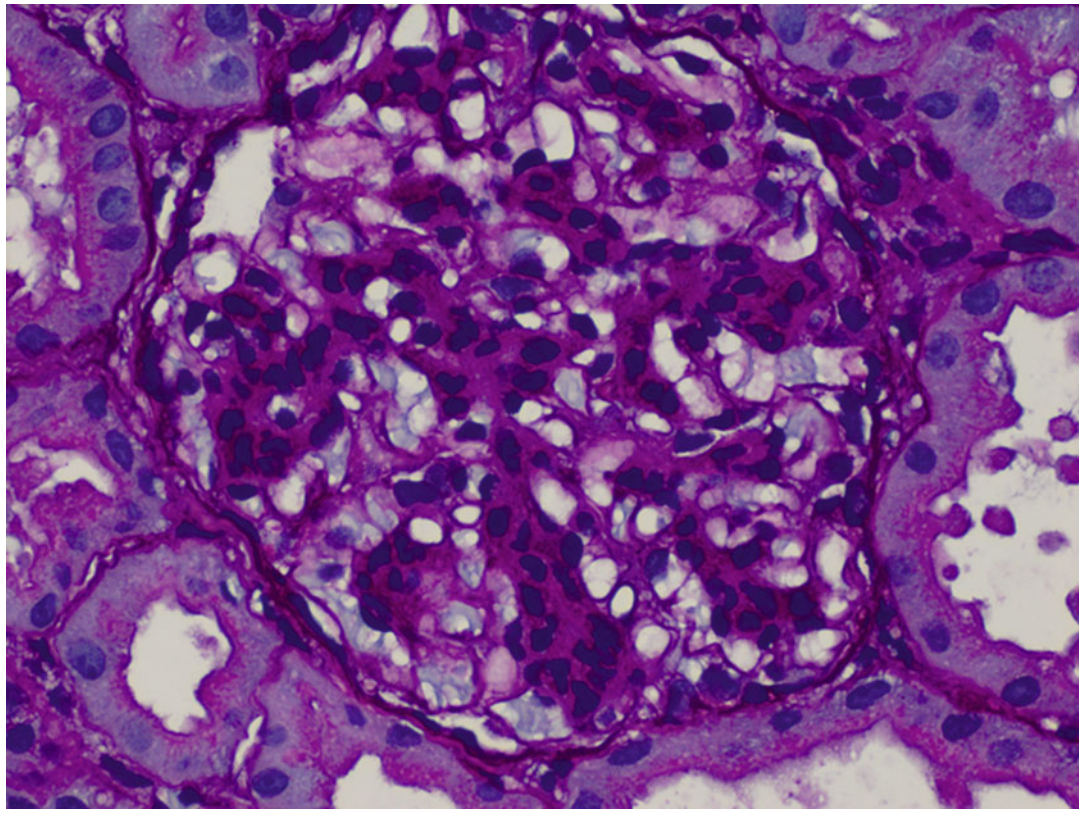

Fig. 4 Collagenofibrotic glomerulopathy. PAS stain. X750. Mesangial hypercellularity is present in selected cases

The disease appears to be primarily a renal process, but in one case, liver involvement with perisinusoidal fibrosis has been reported (Mizuiri et al. 1993). Collagen III deposition may be detected in other organs including the heart, liver, spleen, and thyroid gland, among other sites (Yasuda et al. 1999).

Hemolytic anemia, hemolytic uremic syndrome, and unexplained respiratory symptoms have been reported (Gubler 2008). A few cases have been associated with factor H deficiency (Gubler 2008; Vogt et al. 1995). A link between collagenofibrotic glomerulopathy and complement system defects has been proposed.

Many of the cases have been reported in Japan suggesting racial and geographic predilection; however, sporadic cases continue being reported (Tamura et al. 1996; Yoshioka et al. 1989).

Histology/Pathologic Findings/ Differential Diagnosis

Gross Pathology

There are no gross descriptions of the kidneys in this disorder.

Light Microscopy

The glomerular compartment is the one typically affected in this condition. Glomerular findings are generally diffuse and generalized. The glomeruli appear enlarged predominately as a result of mesangial expansion. Nevertheless, the light microscopic findings of this condition are rather non-specific with an increase in

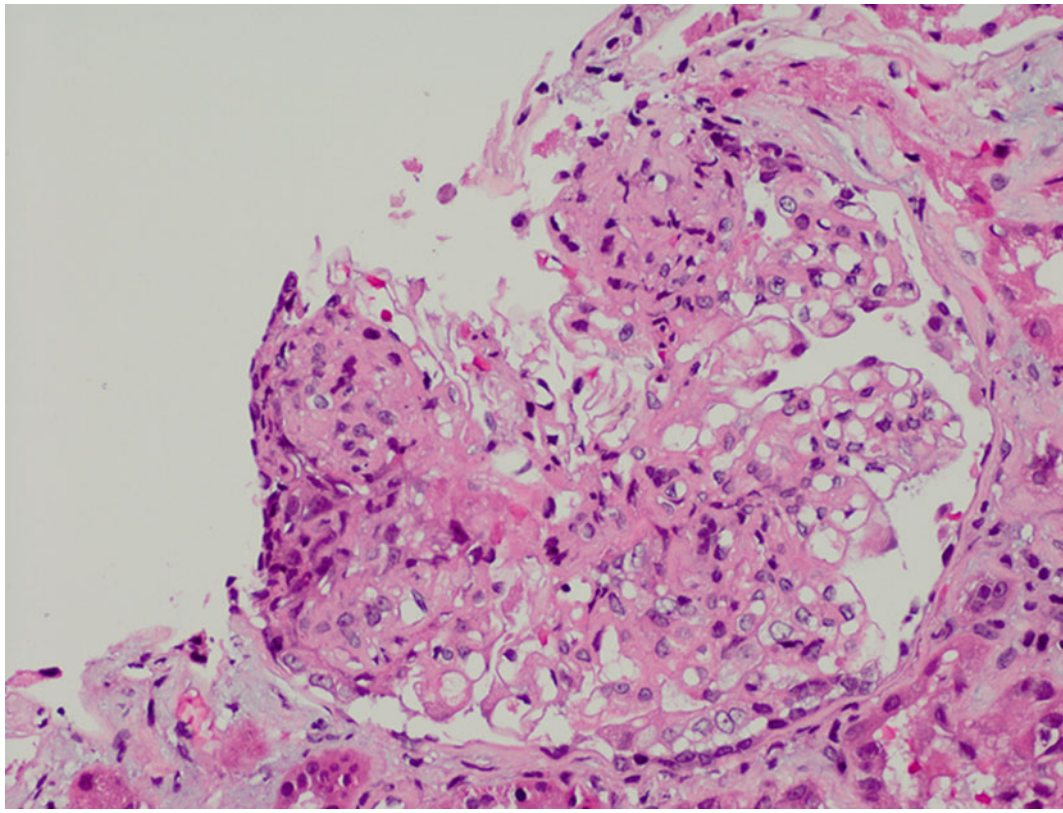

Fig. 5 Collagenofibrotic glomerulopathy, advanced stage. Hematoxylin and eosin stain. X750. Expanded mesangial areas with increased matrix acquiring a lobulated appearance segmentally

mesangial matrix (Fig. 1) which shows enhanced argyrophilia and occasional thickening of peripheral capillary walls, especially in early manifestations of the glomerular process. Weak PAS positivity is seen in the expanded mesangial areas and in the expanded subendothelial zones (Fig. 2). Trichrome stain highlights collagen deposition (Fig. 3a) and eventual mesangial nodularity (Fig. 3b). Mesangial hypercellularity may be identified in some cases (Mizuiri et al. 1993; Vogt et al. 1995) (Fig. 4). No glomerular necrosis and no crescents are observed. The expanded mesangial areas may compress the adjacent capillary spaces, and the glomeruli may acquire a somewhat lobulated appearance as the disease process advances and mesangial expansion becomes more pronounced (Fig. 5).

Immunofluorescence/ Immunohistochemistry

The typical immunofluorescence battery of stains is negative in the majority of the cases. Non-specific IgM and C3 deposition in mesangial areas has been reported.

Collagen III Immunohistochemical Stain

Collagen III immunohistochemical stain shows either focal, segmental, or diffuse, generalized mesangial staining (Fig. 6) primarily depending on the stage of the disease process, representing the hallmark of the diagnosis. The deposition of collagen III is impressive and far more than

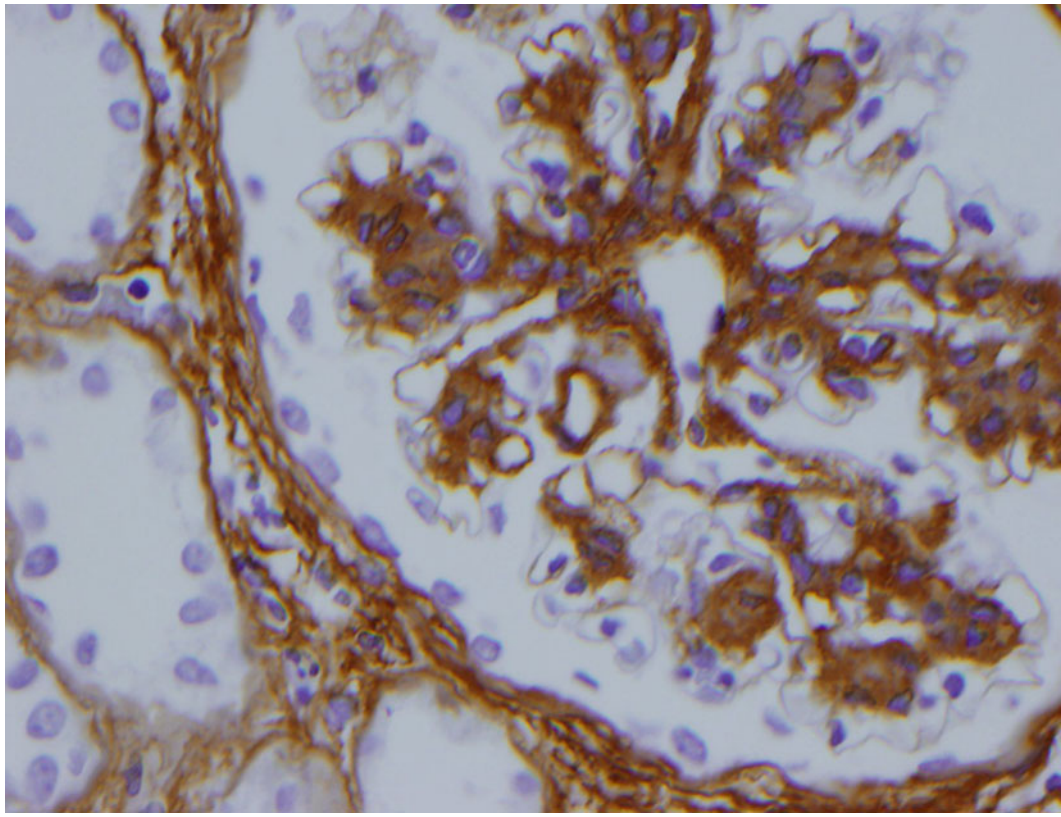

Fig. 6 Collagenofibrotic glomerulopathy. Immunohistochemical stain for collagen III. Peroxidase anti-peroxidase stain, diaminobenzidine. X750. Intense mesangial staining in expanded mesangial areas and also staining in the interstitium

can be seen in other glomerulopathies focally in mesangial areas (Salcedo 1984; Ikeda et al. 1990; Ferreira et al. 2009; Imbasciati et al. 1991; Gubler et al. 1993; Tamura et al. 1996; Yoshioka et al. 1989; Mizuiri et al. 1993; Yasuda et al. 1999; Gubler 2008; Vogt et al. 1995; Striker et al. 1984).

Reliable antibodies to collagen III are commercially available. Normal human glomeruli do not have or reveal minimal amounts of collagen III (D'Ardenne et al. 1983; Razzaque et al. 1994), but collagen III may be found in the interstitium, especially when fibrosis is present; however, this finding is of no specific diagnostic importance, as has nothing to do with making a diagnosis of collagenofibrotic glomerulopathy.

One case in the literature documented widespread staining for collagen V in glomeruli as well in a case of collagenofibrotic glomerulopathy (Morita et al. 2003). This may be an isolated incident or a feature of collagenofibrotic glomerulopathy. The significance of this finding is unclear at the present time.

Electron Microscopy

However, the ultrastructural findings are quite characteristic and characteristic enough to make a presumptive diagnosis in most instances. The mesangial areas and affected peripheral capillary walls show a clear to mottled appearance, and phosphotungstic or tannic acid treatment of the electron microscopy sections enhances the collagen fibers making them much easier to identify in areas where they are not abundant (Alchi et al. 2007). The electron microscopic findings will

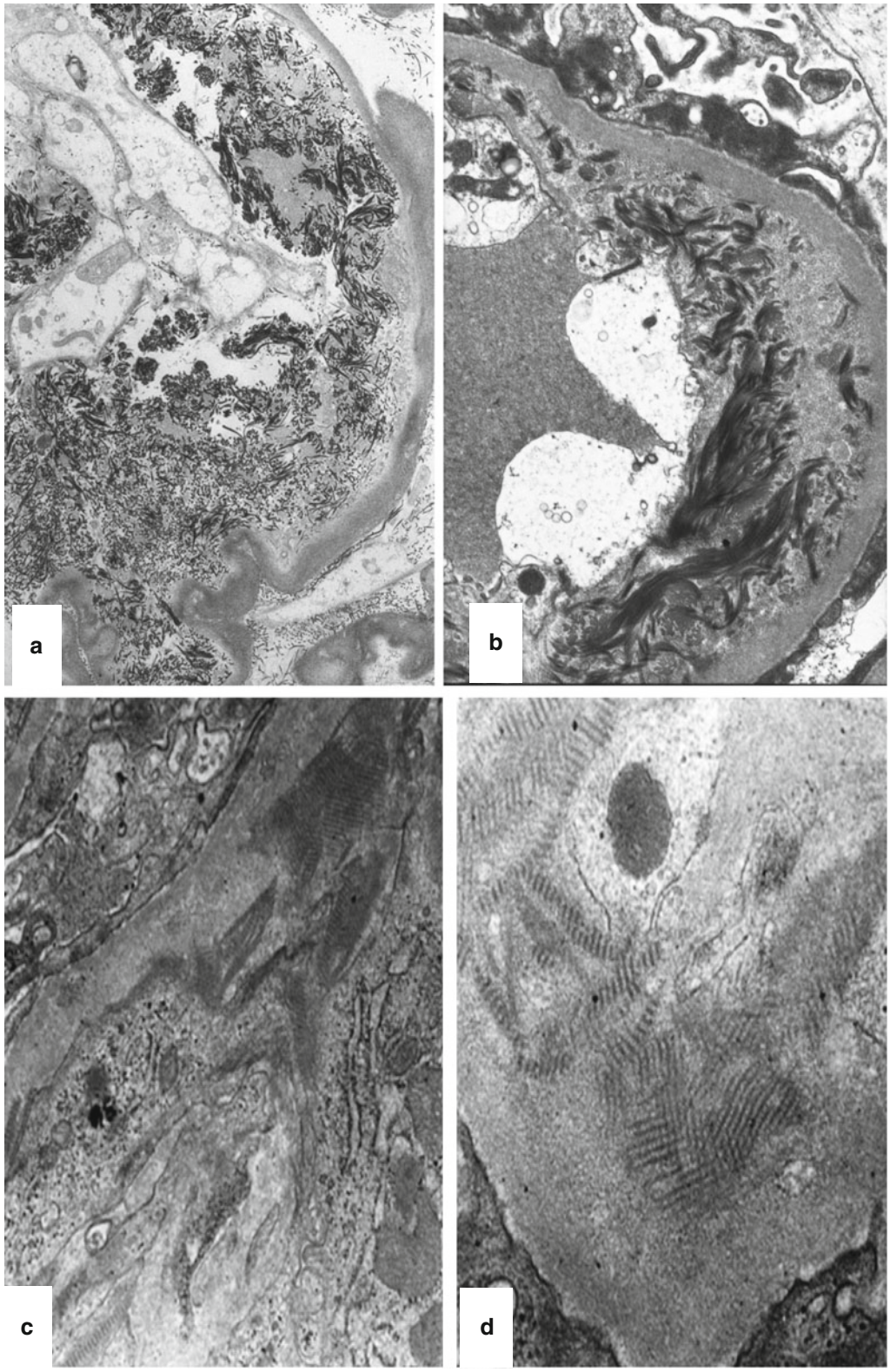

Fig. 7 (continued)

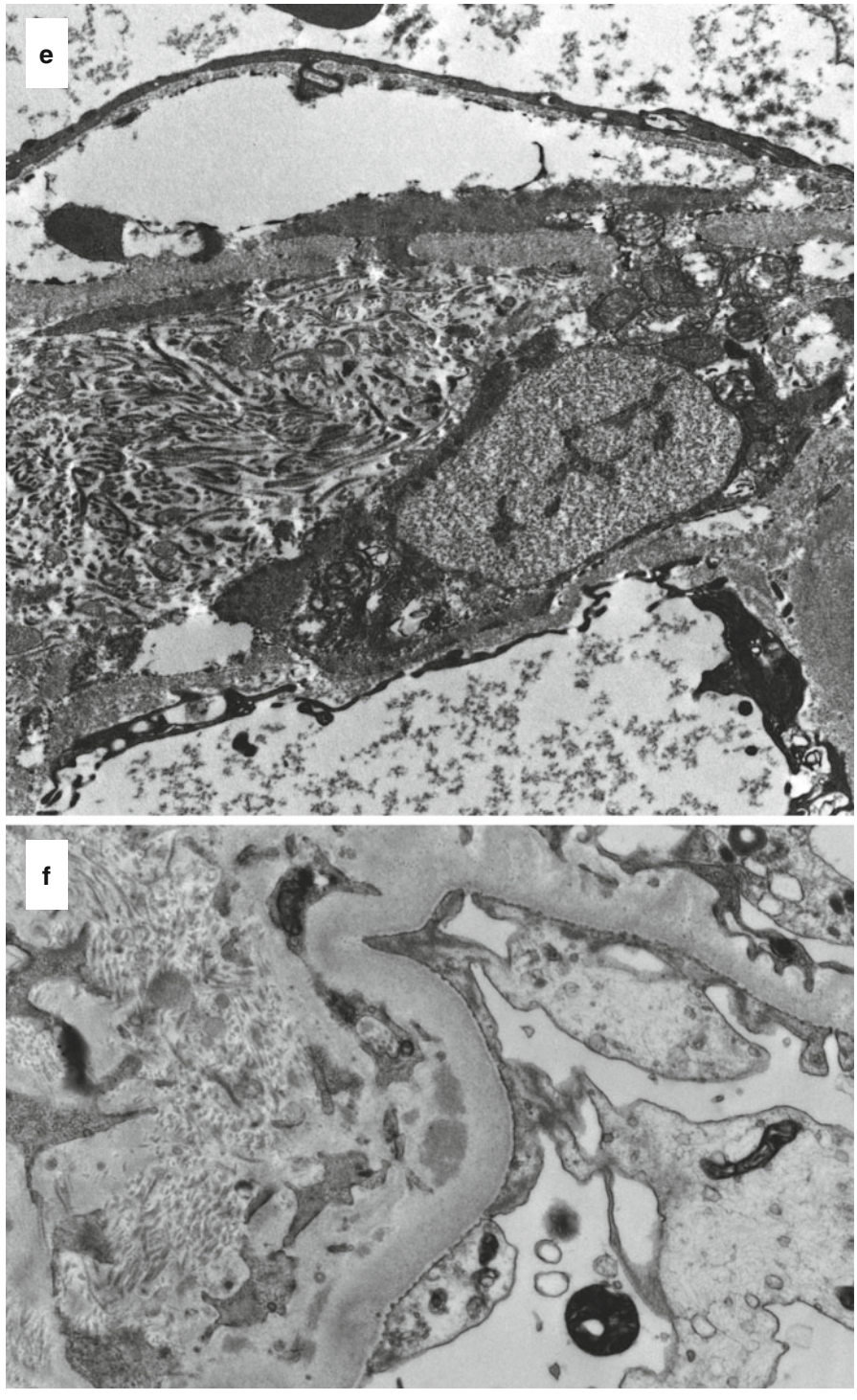

Fig. 7 (**a**–**f**) Collagenofibrotic glomerulopathy. (**a**, **b**, **c**, **d**) Collagen III in mesangium and along peripheral capillary walls. Collagen IV with different ultrastructural appearances. (**e**) Nonimmune complex-mediated glomerulopathy and (**f**) IgA nephropathy. AX12 500, BX 155000, CX9500, DX 27700. Transmission

prompt the request for a collagen III stain to confirm the suspected diagnosis (Gubler 2008; Vogt et al. 1995; Striker et al. 1984; Herrera 2016; Iskandar and Herrera 2014). The fibers deposited predominantly in the mesangium and to a lesser extent in the subendothelium reveal unusual features ultrastructurally (Fig. 7a, b). The fibers appear curved, frayed, spiraled, or worm or comma shaped when sectioned transversely and show a distinct periodicity from 43 to 65 nm. The fibers typically arrange in irregular bundles when cut longitudinally. In some cases, the collagen III fibers form peculiar lattices as they arrange in bundles that intersect (Fig. 7c, d). In contrast to nail-patella syndrome, the lamina densa of the glomerular basement membranes almost always remains intact with no collagen fibers deposited in this location (Herrera 2016; Iskandar and Herrera 2014). However, there have been two children with collagenofibrotic glomerulopathy that have exhibited abnormal collagen fibers in the lamina rara interna and externa of glomerular basement membranes, creating some confusion with nail-patella syndrome glomerular lesions (Tamura et al. 1996; Gubler 2008).

Differential Diagnosis

Making a definitive diagnosis of collagenofibrotic glomerulopathy on the basis of light microscopic findings is impossible. Mesangial expansion, either focal, segmental (early), or diffuse and generalized (far more common), is the most characteristic finding. The expanded mesangium displays increased argyrophilia. Due to the expansion of subendothelial spaces and even double-contoured basement membranes, some cases may be confused with thrombotic microangiopathy.

Demonstration of abundant collagen III in the expanded mesangial areas is imperative to confirm the diagnosis (Herrera 2016; Cohen 2013). It is also common to find collagen III in the interstitium, but this is of no diagnostic significance. Immunohistochemistry or immunofluorescence stains are available for testing.

In some cases, membranoproliferative glomerulonephritis is also in the differential diagnosis, as well as diabetic nephropathy and even amyloidosis. Differential diagnosis in selected cases includes distinction of collagen III deposition in mesangium from other fibrillary collagens at the ultrastructural level that can also be identified in the same location. Non-collagen III fibrillary collagen generally appears composed of straight fibrils with periodicity at 65 nm when sectioned longitudinally and circular when cut transversely. These collagen fibers typically dispose themselves in an organized parallel arrangement and, in rare cases, represent the main extracellular material in the mesangium. This type of fibrillary collagen is most commonly observed in focal, segmental glomerulosclerosis in segmentally sclerosed glomerular areas and in diabetic glomerulosclerosis in mesangial nodules (Fig. 7e). It is unusual to see fibrillary collagen in subendothelial zones, unless glomerular remodeling has occurred, but it is not uncommon to identify it in collagenofibrotic glomerulopathy. Rarely, in immune complex-mediated glomerular processes, there can be focal mesangial deposition of fibrillary collagen (Fig. 7f) in expanded mesangial areas.

Differentiation from nail-patella syndrome is also important in some instances (Salcedo 1984). The clinical manifestations of the latter disorder are rather specific in the great majority of the cases, but skeletal manifestations may be absent in selected cases. Ultrastructurally, the collagen fibrils are of

Fig. 7 (continued) electron microscopy. Uranyl acetate and lead citrate. In (**a** and **b**), the collagen fibers are located subendothelially and display curved, frayed appearance. In (**c** and **d**), they are in an expanded mesangium and display a peculiar lattice arrangement. Compare with well-aligned collagen fibers (not collagen III) in nonimmune complex (**e**) and immune complex-mediated glomerulopathies (**f**) (**a** and **b**, courtesy of Kensuke Joh, MD)

the classical type with the usual periodicity and are found along the glomerular basement membranes rather than in the mesangium.

Pathogenesis

The pathogenesis of this disorder remains unclear. Mesangial cells appear to be the most reasonable candidates for the overproduction of collagen III, but systemic overproduction of collagen III has also been suggested as an etiologic factor. Serum procollagen III is usually significantly elevated in these patients and could be considered a marker for this disease when interpreted in the proper clinicopathologic context (Vogt et al. 1995).

Collagen III glomerulopathy has been documented to occur in monkeys, dogs, pigs, and cats (Adachi et al. 2005; Fujisama-Imura et al. 2004; Kamiie et al. 2009; Kobayashi et al. 2009; Shirota et al. 1995; Nakamura et al. 1996). A naturally occurring autosomal recessive model of collagen III glomerulopathy has been published. This model displays morphologic features similar to those seen in humans with this condition. This animal model has shown that the canine Col3A gene is not involved in the pathogenesis of this disorder. It also demonstrated with the use of in situ hybridization analysis that mesangial cells are engaged in the production of de novo collagen III in this disease (Rorveit et al. 2012).

Therapeutics: Treatment and Prognosis

There is no specific treatment for this disorder. Renal failure was reported within 3 years of diagnosis in one patient (Ikeda et al. 1990). In other patients, symptomatology has progressed steadily to an increase in clinical manifestations, renal insufficiency, and, eventually, failure (Imbasciati et al. 1991; Yasuda et al. 1999; Kurasawa et al. 1984). The severity of the disease at presentation is highly variable and its pace of progression unpredictable. However, progression appears to be more severe when the first symptoms occur in early childhood (Salcedo 1984; Gubler 2008; Vogt et al. 1995). In some cases, abrupt deterioration of renal function may be a result of hemolytic uremic syndrome (Gubler 2008). Successful renal transplantation has been reported with no recurrence 3 years later (Suzuki et al. 2004).

References

Adachi K, Mori T, Ito T et al (2005) Collagenofibrotic glomerulonephropathy in a cynomolgus macaque (*Macaca fascicularis*). Vet Pathol 42:669–674

Alchi B, Nishi S, Morita I et al (2007) Collagenofibrotic glomerulopathy: clinicopathologic overview of a rare glomerular disease. Am J Kidney Dis 49:499–506

Arakawa M, Fueki H, Hirano H (1979) Idiopathic mesangio-degenerative glomerulopathy (Jpn). Jpn J Nephrol 21:914–915

Cohen AH (2013) Collagen III glomerulopathies. Adv Chronic Kidney Dis 19:101–106

D'Ardenne AJ, Burns J, Sykes BC, Kirkpatrick P (1983) Comparative distribution of fibronectin and type III collagen in normal human tissues. J Pathol 141:55–69

Dombros N, Katz A (1982) Nail patella-like renal lesions in the absence of skeletal abnormalities. Am J Kidney Dis 1:237–240

Duggal R, Nada R, Rayat CS, Rane VS, Joshi K (2012) Collagenofibrotic glomerulopathy- a review. Clin Kidney J 5:7–12

Ferreira D, Custodio FB, Guimaraes CS, Correa RRM, Reis MA (2009) Collagenofibrotic glomerulopathy: three case reports in Brazil. Diagn Pathol 4:33–37

Fujisama-Imura K, Takasu N, Tsuchiya N et al (2004) Spontaneous collagenofibrotic glomerulonephropathy in a young cynomolgus monkey. J Toxicol Pathol 17:279–282

Gubler MC (2008) Inherited diseases of the glomerular basement membranes. Nat Clin Pract Nephrol 4:24–37

Gubler MC, Dommergues JP, Foulard M et al (1993) Collagen type III glomerulopathy: a new type of hereditary nephropathy. Pediatr Nephrol 7:354–360

Herrera GA (2016) Renal diseases associated with hematopoietic disorders or organized deposits. In: Zhou XJ, Laszik Z, Nadasdy T, D'Agati VD, Silva F (eds) Silva's diagnostic renal pathology. Cambridge University Press, New York, pp 385–448

Ikeda K, Yokoyama H, Tomosugi N, Kida H, Ooshima A, Kobayashi K (1990) Primary glomerular fibrosis: a new nephropathy caused by diffuse intra-glomerular increase in atypical type III collagen fibers. Clin Nephrol 33:155–159

Imbasciati E, Gherardi G, Morozumi K, Gudat F, Epper R, Basler V, Mihatsch MJ (1991) Collagen type III glomerulopathy: a new idiopathic glomerular disease. Am J Nephrol 11:422–429

Iskandar S, Herrera GA (2014) Chapter 23, Organized deposits. In: Jennette JC, Olson JL, Schwartz MM,

Silva FG (eds) Heptinstall's pathology of the kidney, 7th edn. Wolters Kluwer, Philadelphia, PA. pp 1051–1038. pp 1015–1037

Kamiie J, Yasuno K, Ogihara K et al (2009) Collagenofibrotic glomerulonephropathy with fibronectin deposition in a dog. Vet Pathol 46:688–692

Kobayashi R, Yasuno K, Ogihara K et al (2009) Pathological characterization of collagenofibrotic glomerulonephropathy in a young dog. J Vet Med Sci 71:1137–1141

Kurasawa K, Kyougoku Y, Saito T, Yamakage T, Sato H, Koyama T, Yoshinaga K (1984) A case of nephrotic syndrome with peculiar changes in the basement membrane characterized by abundant collagen formation: a new clinical entity. Jin to Toseki (Tokyo) (Jpn) 16:241–249

Mizuiri S, Hasegawa A, Kikuchi A et al (1993) A case of collagenofibrotic glomerulopathy associated with hepatic perisinusoidal fibrosis. Nephron 63:183–187

Morita H, Hasegawa T, Minamoto T, Oda Y, Inui K, Tayama H, Nakao N, Nakamoto Y, Ideura T, Yoshimura A (2003) Collagenofibrotic glomerulopathy with widespread expression of type V-collagen. Virchows Arch 442:163–168

Nakamura S, Shibata S, Shirota K et al (1996) Renal glomerular fibrosis in a cat. Vet Pathol 33:696–699

Patro KC, Jha R, Sahay M, Swarnalatha G (2011) Collagenofibrotic glomerulopathy. Case report with review of the literature. Indian J Nephrol 21:52–55

Razzaque MS, Koji T, Taguchi T et al (1994) In situ localization of type III and type V collagen expressing cells in human diabetic nephropathy. J Pathol 174:131–138

Rorveit R, Lingaas F, Bonsdorff T, Eggertsdottir AV, Grondahl AM, Thomassen R, Fogo AB, Jansen JH (2012) A canine autosomal recessive model of collagen II glomerulopathy. Lab Invest 92:1483–1491

Salcedo JR (1984) An autosomal recessive disorder with glomerular basement membrane abnormalities similar to those seen in the nail patella syndrome: report of a kindred. Am J Med Genet 19: 579–584

Shirota K, Masaki T, Kitada H et al (1995) Renal glomerular fibrosis in two pigs. Vet Pathol 32:236–241

Striker LM-M, Killen PD, Chi E, Striker GE (1984) The composition of glomerulosclerosis. I. Studies in focal segmental sclerosis, crescentic glomerulonephritis, and membranoproliferative glomerulonephritis. Lab Invest 51:181–192

Suzuki T, Okubo Y, Ikezumi Y (2004) A favorable course of collagenofibrotic glomerulopathy after kidney transplantation and questionnaire survey about the prognosis of collagenofibrotic glomerulopathy (Jpn). Jpn J Nephrol 46:360–364

Tamura H, Matsuda A, Kidoguchi N, Matsumura O, Mitarai T, Isoda K (1996) A family with two sisters with collagenofibrotic glomerulonephropathy. Am J Kidney Dis 27:558–595

Vogt BA, Wyatt RJ, Burke BA, Simonton SC, Kashtan CE (1995) Inherited factor H deficiency and collagen type III glomerulopathy. Pediatr Nephrol 9:11–15

Yasuda T, Imai H, Nakamoto Y et al (1999) Collagenofibrotic glomerulopathy: a systemic disease. Am J Kidney Dis 33:123–127

Yoshioka K, Takemura T, Tohda M, Akano N, Miyamoto H, Ooshima A, Maki S (1989) Glomerular localization of type III collagen in human kidney disease. Kidney Int 35:1203–1211