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CASE REPORT

Glomerulopathy with distinctive fibrillar deposits but lacking glomerular deposition of type III collagen

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Abstract A 62-year-old woman with nephrotic syndrome underwent a renal biopsy. Under light microscopy, the biopsy findings included lobulation and enlargement of glomeruli, occasional thickening of glomerular capillary walls, and narrowing of the capillary lumen by swollen endothelial cells. Congo red staining was negative for amyloid. No significant intraglomerular fibrin deposition was found by phosphotungstic acid hematoxylin staining. Immunofluorescence microscopy showed no deposition of immunoglobulin G, A, or M; no κ or λ light chains; and no C3 or C1q. Electron microscopy revealed distinctive subendothelial and mesangial fibrillar deposits, mesangial cell interposition, and swelling and vacuolization of endothelial cells resulting in capillary lumen narrowing. Although some curvilinear fibrillar deposits mimicked the bundles of type III collagen fibers seen in collagenofibrotic glomerulopathy, neither glomerular deposition of type III collagen nor elevation of serum procollagen III peptide was noted. This glomerulopathy does not fulfill any known disease entities with non-amyloid non-immunoglobulin-derived organized glomerular deposits.

Keywords Renal disease with organized deposits · Collagenofibrotic glomerulopathy · Type III collagen

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Introduction

In this report, we present the case of a 62-year-old woman with nephrotic syndrome, whose renal biopsy was significant for subendothelial and mesangial fibrillar electron-dense deposits. Although some curvilinear fibrillar deposits mimicked the bundles of type III collagen fibers seen in collagenofibrotic glomerulopathy and nail–patella syndrome, neither glomerular deposition of type III collagen nor elevation of serum procollagen III peptide was noted.

Case report

A 62-year-old Japanese woman was admitted to our hospital for treatment of edema. She had a 14-year history of hypertension and had been treated to maintain a blood pressure of approximately 150/80 mmHg at another clinic. Proteinuria had developed 12 years before admission to our hospital, but it had been followed without treatment. She had no history of alcoholism, exposure to chemicals, or drug abuse, but she had a smoking history of 10 cigarettes per day for 42 years (21 pack-years). There was no family history of renal disease. Physical examination showed periorbital and pretibial pitting edema, but there were no

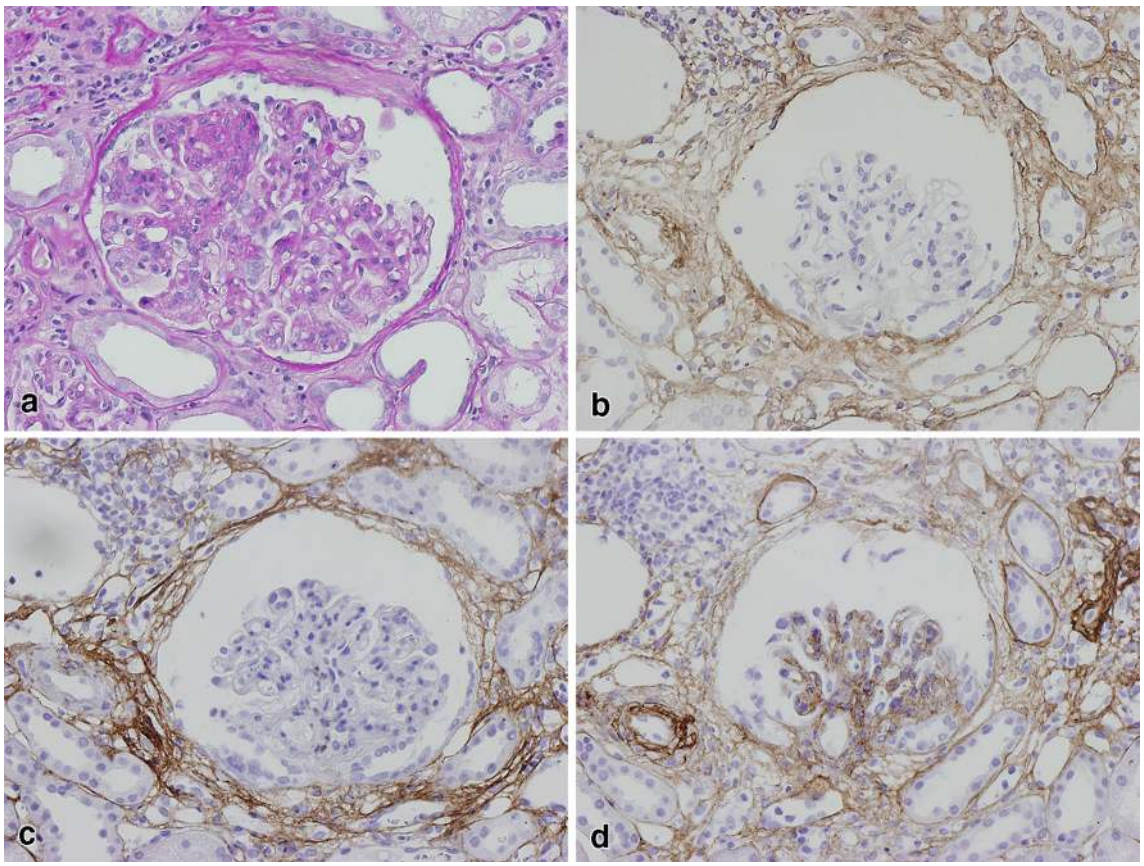

Fig. 1 Light microscopic findings and immunohistochemical demonstration of type I, III, and IV collagen. **a** Lobulation and enlargement of the glomerulus, occasional thickening of the glomerular capillary walls, and narrowing of the capillary lumen by swollen endothelial cells were observed. There was no glomerular deposition of type I (**b**) and III (**c**) collagen, whereas glomerular deposition of type IV (**d**) collagen was observed. The increased deposition of type I, III, and IV collagen was observed in the periglomerular and interstitial fibrotic lesions. **a** PAS staining, original magnification, ×200. **b**–**d** Serial sections, original magnification, ×200

abnormalities in the patellas or nails. Laboratory investigation revealed proteinuria of 6,170 mg/day and microhematuria. The concentration of hemoglobin was 13.0 g/dL; serum total protein, 5.6 g/dL; albumin, 2.9 g/dL; creatinine, 0.67 mg/dL; urea nitrogen, 13 mg/dL; uric acid, 6.7 mg/dL; and cholesterol, 315 mg/dL. Serum electrolytes, blood glucose, hemoglobin A1c (HbA1c), immunoglobulin A (IgA), IgM, C3, C4, and CH50 were within normal limits, but IgG was slightly decreased to 789 mg/dL. No evidence of auto-antibodies, HBV or HCV infection, cryoglobulinemia, Bence Jones proteinuria, or serum monoclonal peak was detected. Findings of chest and abdominal radiography were normal. Increases in plasma aldosterone concentration (PAC) to 17.6 ng/dL and PAC/plasma renin activity (PRA) ratio to 25.1, the lack of suppression of the PAC/PRA ratio of 25.5 at 2 h after administration of 50 mg of captopril, and the presence of a right adrenocortical adenoma 15 mm in diameter, as demonstrated by computed tomography, suggested the presence of primary aldosteronism, but the patient refused to undergo adrenal venous sampling. Nephrotic syndrome was diagnosed, and a percutaneous renal biopsy was performed.

Under light microscopy, the specimen showed 13 glomeruli. Of the 13, three glomeruli showed global obsolescence. The other glomeruli showed lobulation and enlargement, with occasional thickening and double contours of the glomerular capillary walls, and narrowing of the capillary lumen by swollen endothelial cells (Fig. 1a). Congo red staining was negative for amyloid. No significant intraglomerular fibrin deposition was noted by phosphotungstic acid hematoxylin (PTAH) staining. Immunofluorescence microscopy showed no depositions of IgG, IgA, IgM, C3, C1q, or κ and λ light chains. Electron microscopy showed fibrillar subendothelial and mesangial electron-dense deposits, mesangial cell interposition, and swelling and vacuolization of endothelial cells resulting in capillary lumen narrowing (Figs. 2, 3). Some deposits were also

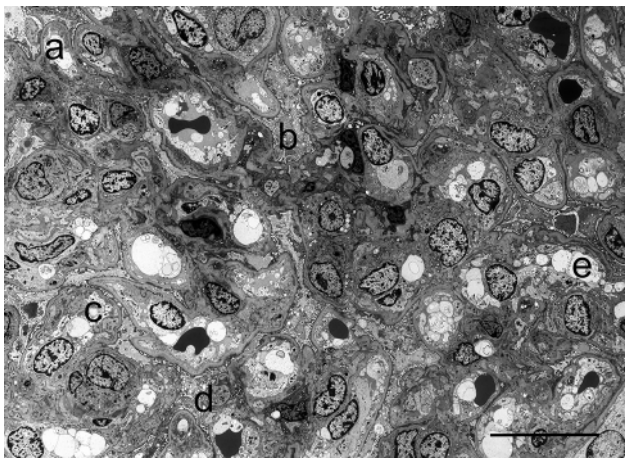

Fig. 2 Electron micrograph showing the distribution of subendothelial and mesangial electron-dense deposits at low magnification. Mesangial cell interposition, and swelling and vacuolization of endothelial cells resulting in capillary lumen narrowing were also noted. Some deposits were observed in the midportion of the glomerular basement membranes. The deposits found in the glomerular capillary area marked with *d* demonstrated the curvilinear fibrillar appearance. The fibrillar structures of the deposits in the five glomerular capillary areas, which were marked with *a–e*, are shown at high magnification in Fig. 3a–e, respectively. The length of the *bar* in the *lower right* represents 20 μm

observed in the midportion of the glomerular basement membranes. The banded structure was observed in some curvilinear fibrillar deposits at high magnification (Fig. 3f).

Immunohistochemical testing for type I, III, and IV collagen was conducted using the EnVision/HRP kit (Dako, Glostrup, Denmark) in consecutive kidney sections. Microwave irradiation was performed to enhance antigen retrieval. To stain type I and IV collagen, the samples were pretreated with proteinase K (Dako) at 37 °C for 45 min. The primary antibodies were mouse monoclonal anti-human type I collagen (Daiichi Fine Chemical Co., Takaoka, Japan), anti-human type III collagen (Daiichi Fine Chemical Co.), and anti-human type IV collagen (Dako) antibodies. There was no deposition of type I and III collagen in the glomeruli, although glomerular deposition of type IV collagen was observed in the sclerosing glomeruli (Fig. 1b–d). Increased deposition of type I, III, and IV collagen was also observed in the periglomerular and interstitial fibrotic lesions and in the glomerular tuft lesions adhesive to the Bowman's capsules.

The patient was treated with 500 mg/day of methylprednisolone pulse therapy for three consecutive days followed by 40 mg/day of prednisolone for 4 weeks. The patient's blood pressure was maintained at approximately 130/80 mmHg by combination therapy consisting of imidapril hydrochloride, nifedipine, furosemide, and spironolactone. However, the nephrotic syndrome persisted, and the serum level of creatinine increased progressively. The dose of prednisolone was decreased gradually and hemodialysis was initiated 23 months after the renal biopsy. The serum levels of procollagen III peptide were <0.5, 0.9, and 1.0 U/mL (normal range: <1.0 U/mL) at 12, 18, and 22 months after renal biopsy, respectively; we did not measure serum procollagen III peptide at the time of the renal biopsy.

Discussion

Renal diseases with organized deposits are divided into those with amyloid origins and those with non-amyloid origins. Among those with non-amyloid origins, the deposits which are composed of immunoglobulin components are seen in fibrillary glomerulonephritis, immunotactoid glomerulopathy, cryoglobulinemic glomerulonephritis, and light and/or heavy chain-deposition disease; those without immunoglobulin components are seen in fibronectin glomerulopathy, nail–patella syndrome, collagenofibrotic glomerulopathy, fibrin tactoids in inflammatory glomerular diseases, and diabetic nephropathy [1, 2]. The electron-dense deposits in fibronectin glomerulopathy, an autosomal dominant hereditary disorder characterized by large mesangial and subendothelial electron-dense deposits composed of fibronectin, are predominantly amorphous and granular, but they may contain electron-lucent areas and scattered, focal fine filaments 10–14 nm in diameter [3, 4].

The deposition of banded fibrils of type III collagen is noted in nail–patella syndrome and collagenofibrotic glomerulopathy [1]. Nail–patella syndrome is a hereditary disorder caused by a genetic mutation of LMX1B, an LIM-homeodomain transcription factor that plays a key role in limb development [5]; it is clinically characterized by the association of nail hypoplasia or dysplasia, absence or delayed development of the patella, dysplasia of the knees and elbows, and iliac horns. Bundles of fibrillar type III collagen are usually deposited in the midportion of the glomerular basement membrane, but in some patients, deposits are found in the subepithelial or subendothelial space. However, the possibility of nail–patella syndrome was excluded in the present case because there were no deformities of the nails and bones.

Collagenofibrotic glomerulopathy, also called collagen type III glomerulopathy, is a rare disease characterized by accumulation of curled subendothelial and mesangial deposits containing type III collagen fibrils. It is associated with a marked elevation of serum procollagen III peptide [6], an indicator of increased type III collagen synthesis [7, 8]. Most adult cases are sporadic, and many have been reported in Japan, suggesting a geographical or racial predilection [1, 6, 9]. Other cases have been reported, mainly from Europe, of children with an autosomal

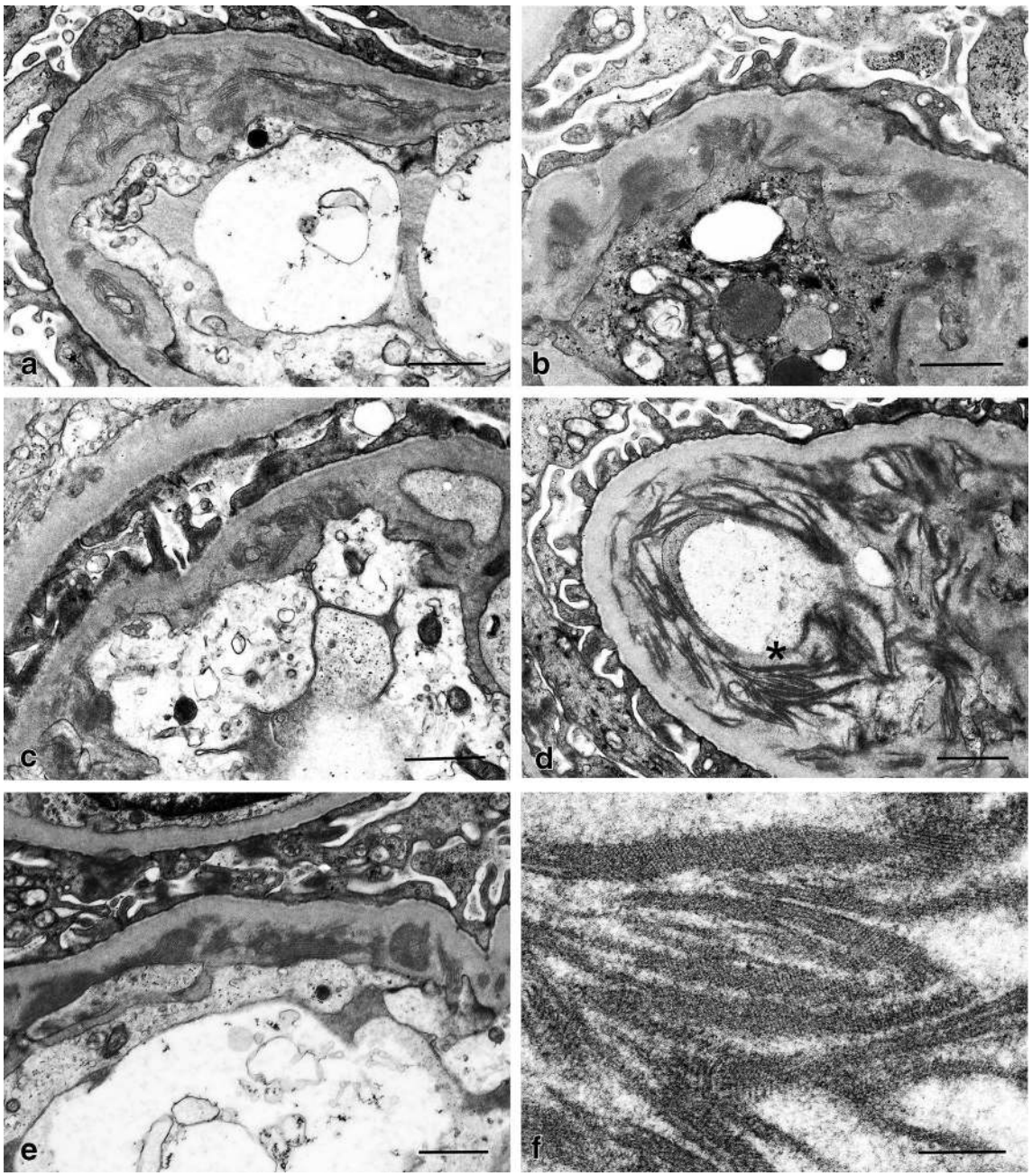

Fig. 3 Electron micrographs showing fibrillar structures of the deposits in the glomerular capillary areas marked with **a**–**e** in Fig. 2 are shown at high magnification in **a**–**e**, respectively. **f** Higher magnification of the curvilinear fibrillar deposits marked with an *asterisk* in **d** revealed the banded structure in the fibrils. The length of the *bars* in the *lower right* in **a**–**e** represents 1 μm and that in **f** represents 200 nm

recessive mode of transmission and early disease progression, which suggests a difference in gene penetrance in different populations [10–12]. One case with collagenofibrotic glomerulopathy has been associated with factor H deficiency [13]. There is no evidence of a sex predilection.

Although some banded fibrils in the present case mimicked the type III collagen fibers seen in collagenofibrotic glomerulopathy, no significant glomerular deposition of type I or III collagen was observed despite the increased deposition of type IV collagen in the sclerosing glomeruli and that of type I, III, and IV collagen in the periglomerular and interstitial fibrotic lesions and the glomerular tuft lesions adhesive to Bowman's capsule. Glomerular accumulation of type I collagen has also been demonstrated in collagenofibrotic glomerulopathy [14, 15]. One case of collagenofibrotic glomerulopathy with massive glomerular deposition of both

type III and V collagen has been reported [16]. However, the present case differs from collagenofibrotic glomerulopathy because of the lack of glomerular type III collagen deposition; we did not investigate type V collagen deposition. In addition, the serum procollagen III peptide level is increased to 10–100 times the normal level in patients with collagenofibrotic glomerulopathy, and it is nearly doubled in patients with chronic renal failure [6, 11]; however, no significant increases in procollagen III peptide levels were noted in the present case. Taken together, this glomerulopathy did not fulfill the diagnostic criteria for collagenofibrotic glomerulopathy.

There may be deposits of fibrin in inflammatory glomerular diseases, and the polymerized fibrin usually forms amorphous electron-dense masses. Rarely, there are fibrin tactoids with characteristic periodicity [2]. Fibrin tactoids were excluded in our case because no significant intraglomerular fibrin deposition was demonstrated by PTAH staining. Our patient had no clinical manifestation of diabetes mellitus. Recently, Ohtani et al. reported a case with progressive glomerulopathy with unusual organized deposits of non-amyloid non-immunoglobulin origins with striated structures [17]. However, most striated deposits were lumpy and only a few deposits showed fibrillar structure in their case.

This patient had a longstanding history of smoking and hypertension. In the smoking-related nodular or diffuse mesangial glomerulosclerosis, the endothelial cell injuries which resemble chronic thrombotic microangiopathy characterized by endothelial swelling, subendothelial widening, new basement membrane formation and cellular interposition have been demonstrated [18, 19]. Although no organized deposits are generally seen in smoking-related glomerulopathy, Salvatore et al. recently found a case with focal fibrillary degeneration of the collagen matrix along the subendothelial zone out of 10 cases with smoking-related glomerulopathy [19]. However, the possibility that the fibrillar deposits in the present case were relevant to the fibrillary degeneration of the collagen matrix in smoking-related diffuse mesangial glomerulosclerosis is unlikely because of the lack of intraglomerular deposition of types I and III interstitial collagen.

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Compliance with ethical standards

Conflict of interest All the authors have declared no competing interest.

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