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【 CASE REPORT 】

Collagenofibrotic Glomerulopathy

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Abstract:
Collagenofibrotic glomerulopathy or LMX1B-associated nephropathy is a rare disease in which type III collagen accumulates in the glomeruli. We herein report a 64-year-old Japanese woman with an elevated serum creatinine level and persistent proteinuria for 7 years. An electron microscopic study using tannic acid showed curved and frayed collagen fibers within mesangial and subendothelial regions compatible with type III collagen depositions. The distribution of type IV collagen α1-6 chains was normal. Since no pathogenic mutations were identified in the LMX1B gene, she was diagnosed with collagenofibrotic glomerulopathy and treated with angiotensin II receptor blocker and calcium antagonist to control her blood pressure.

Key words: collagenofibrotic glomerulopathy, LMX1B, type III collagen, type IV collagen

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Introduction

Collagenofibrotic glomerulopathy (CG) is a rare disease in which type III collagen accumulates in the glomeruli, and its major clinical presentation is proteinuria and/or hypertension, which leads to end-stage kidney failure (1). While type III collagen has been observed in blood vessels and renal interstitium in normal human kidneys, deposition of type III collagen in the glomeruli has never been observed (2).

The deposition of type III collagen in the glomeruli is observed in CG or nail-patella syndrome (NPS), which is a genetic disease caused by a mutation in LMX1B, which encodes LIM homeobox transcription factor 1-beta. The deposition of type III collagen in CG is observed in the subendothelial and mesangial areas, while that in NPS is observed in the lamina densa of the glomerular basement membrane (GBM). The major difference between CG and NPS is considered to be the presence of nail and/or patellar deformities in NPS.

However, there was a report of NPS without extrarenal manifestations (3). There have also been reports of LMX1B-associated nephropathy without an extrarenal phenotype (4, 5) and LMX1B-associated nephropathy with type III collagen deposition (6).

Therefore, we analyzed the genomic sequence of LMX1B in the present case.

Case Report

A 64-year-old Japanese woman was referred to our hospital because of elevated serum creatinine levels and persistent proteinuria for 7 years. The serum creatinine level had increased from 0.85 mg/dL to 1.16 mg/dL over the past 2 years. The degree of proteinuria had gradually increased from 1+ to 3+ over the past 4 years without hematuria. The patient had a more than 10-year history of hypertension, and her blood pressure had been found to be about 150/80 mmHg at a local clinic. She had no history of smoking and alcoholism. She had no family history of kidney disease.

A physical examination revealed no abnormalities. Laboratory investigations revealed the following: 24 hours urine protein was 4.03 g/day, Bence Jones Protein was not detected in the urine. Her hemoglobin level was 9.7 g/dL. Serum levels were as follows: total protein, 5.8 g/dL; albumin, 3.1 g/dL; blood urea nitrogen, 34 mg/dL; creatinine, 1.14 mg/dL; uric acid, 5.3 mg/dL. Blood glucose and HbA1c were within normal limits. The serum protein electrophoretic

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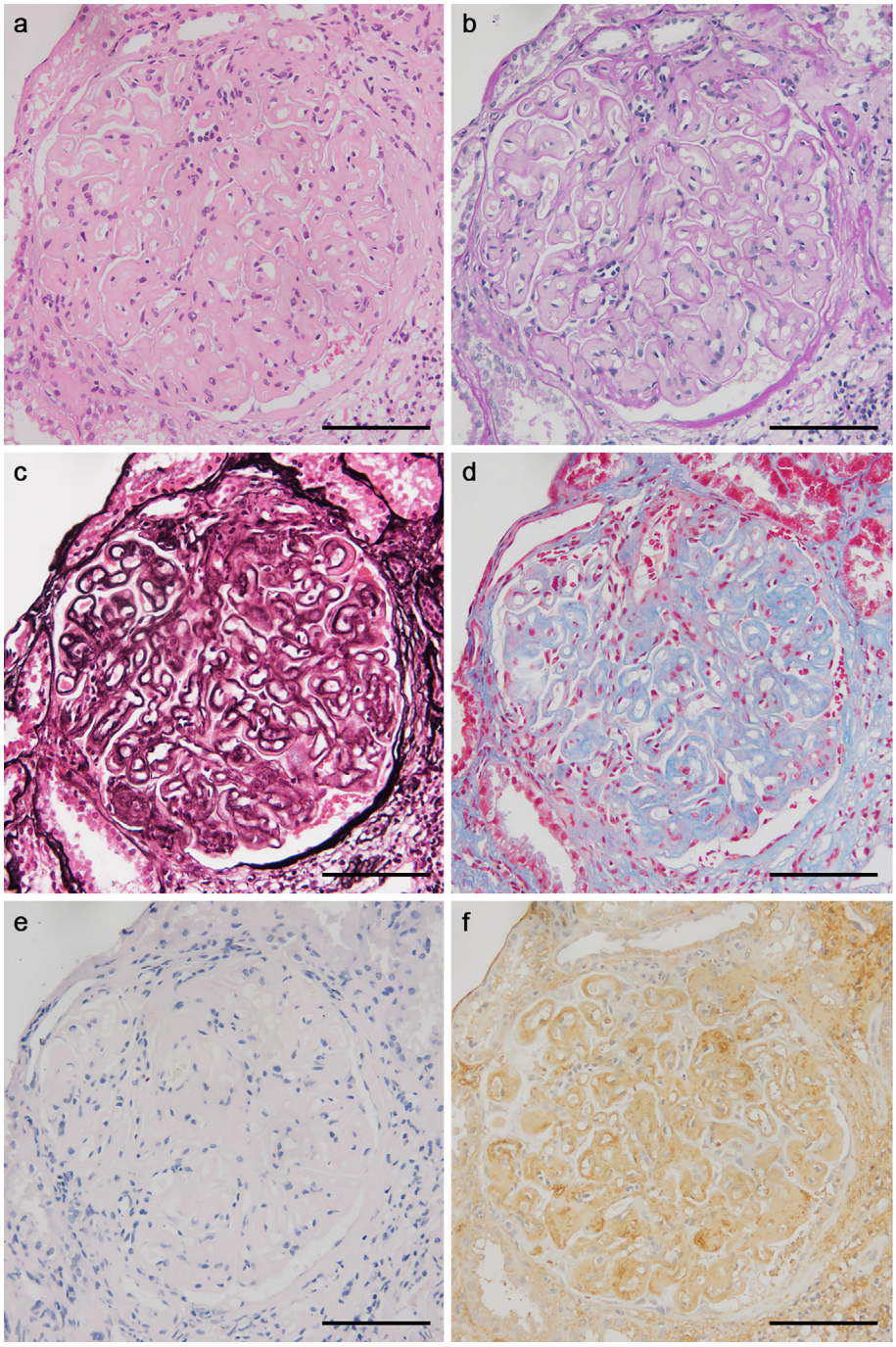

Figure 1. **Light microscopic study. (a) Hematoxylin and Eosin staining showed thickened glomerular capillary walls. (b) The thickened area was homogeneously weakly stained with Periodic acid-Schiff stain. (c) Double contour of the glomerular basement membrane was observed with Periodic acid methenamine silver stain. (d) Masson Trichrome stain showed a weak blue stain in the thickened area. (e) There was negative staining with Congo red stain. (f) Immunohistochemistry showed positive staining for type III collagen. Scale bars, 100 μm.**

showed no monoclonal peak. Serum immunoglobulin G (IgG), IgA, IgM, complement 3 (C3), C4 and hemolytic complement 50 (CH50) levels were all within normal limits. Antinuclear antibody, myeloperoxidase antineutrophil cytoplasmic antibody (ANCA), proteinase 3 ANCA and anti-glomerular basement membrane antibody were negative. Serum procollagen III N-terminal propeptide (PIIINP) and hyaluronic acid levels were elevated to 404 ng/mL (normal range 3.62-9.52 ng/mL) and 136,000 ng/mL (normal range <50 ng/mL), respectively.

A kidney biopsy contained six glomeruli, and one of them showed global sclerosis. All glomeruli were enlarged, and the glomerular capillary walls were thickened on Hematoxylin and eosin stain (Fig. 1a). The thickened area was homogeneously weakly stained with Periodic acid-Schiff (PAS) stain (Fig. 1b). Double contour of the glomerular basement

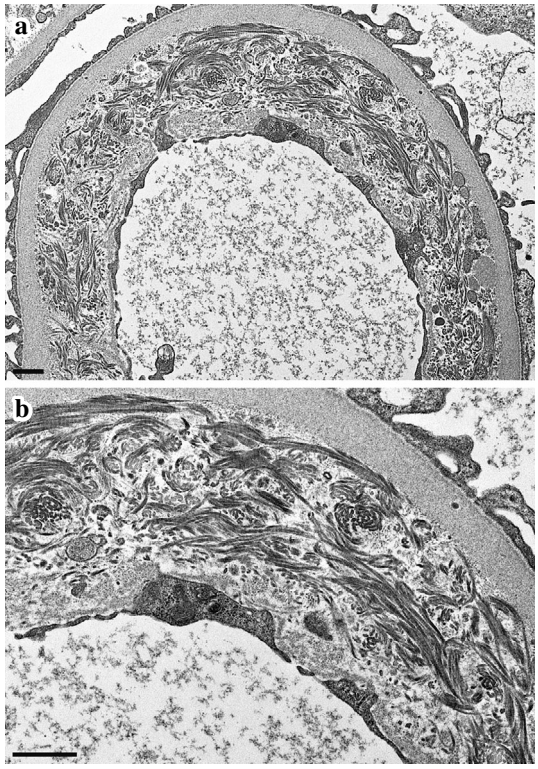

Figure 2. Electron microscopic study. (a) There were fibrous materials in the endothelial region along with narrowing of the capillary lumen under low magnification. (b) The collagen fibers were curved and frayed on the long axis, and transverse sections of the fibers showed a flower-like appearance under high magnification. Scale bars, 1 μm.

membrane was observed, and there was no spike formation with Periodic acid methenamine silver (PAM) stain (Fig. 1c). The thickened area was blue with Masson Trichrome stain (Fig. 1d). There was no specific stain with Congo red stain (Fig. 1e). Immunohistochemistry showed positive staining for anti-human type III collagen antibody on the GBM (Fig. 1f) but negative staining for anti-human IgG, IgA, IgM, C3, C1q and fibrinogen antibodies.

An electron microscopic study using tannic acid showed fibrous materials under endothelial region together with narrowing of the capillary lumen (Fig. 2a). The collagen fibers were curved and frayed on the long axis, and individual fibrils showed a characteristic banding pattern with 63 nanometers in periodicity. Transverse sections of the fibers showed a flower-like appearance under high magnification (Fig. 2b).

Since the deposition of type III collagen was diffuse, the distribution of type IV collagen was of interest. An immunofluorescence study for type IV collagen showed positive linear stain with alpha 3, 4 and 5 chains, which was compatible with a normal distribution of type IV collagen chains (Fig. 3). In addition, a genetic analysis of LMX1B showed no mutation in exons, and there was a heterozygous mutation of c.326+7G>C in intron 2 of LMX1B, which was suggested to be benign in the ClinVar database.

The present case was diagnosed with CG and treated with angiotensin II receptor blocker and calcium antagonist to control her blood pressure (Fig. 4). Although her blood pressure improved after drug administration, her proteinuria increased gradually, and her estimated glomerular filtration rate declined progressively (Fig. 4).

Discussion

We experienced a case of CG that was diagnosed with an electron microscopic study. Our patient had progressive chronic kidney disease with proteinuria and hypertension. Sequential sections in a light microscopic study showed enlarged glomeruli with expansion of the subendothelial and mesangial areas, which were weakly stained with PAS or blue with Masson Trichrome stain and stained with anti-human type III collagen antibody. An electron microscopic study using tannic acid showed the typical structure of type III collagen in the subendothelial and mesangial areas. The present case was therefore diagnosed as CG.

Initially, most cases of CG reported from Japan showed a sporadic or autosomal recessive pattern (7). There have also been reports of CG accompanied by a systemic disease, such as diabetes mellitus or Hodgkin's lymphoma (8, 9). However, its etiology remains elusive. The specific characteristic of CG is the accumulation of type III collagen in the subendothelial space of the glomeruli, whereas NPS shows the accumulation of type III collagen in the lamina densa of the GBM. The serum level of PIIINP was very high in the present case, suggesting increased conversion from type III procollagen to type III collagen. Although an autopsied case of CG showed systemic deposition of type III collagen (10), whether or not CG is a systemic disease is unclear, as mesangial cells *in vitro* can produce type III collagen (11). There is a report that interleukin-4 facilitated the synthesis of type III collagen (12); however, the precise mechanism was not mentioned.

NPS has characteristics that are similar to those of CG with regard to the deposition of type III collagen in the glomeruli. It was previously considered easy to differentiate CG from NPS because NPS usually involves some deformity in the nail or patella. The causative gene of NPS is LMX 1B. However, there have been reports of LMX1B-associated nephropathy without an extrarenal phenotype (4, 5), which prompted us to examine the sequence of the LMX1B gene in the present case. We obtained a negative result, as the heterozygous mutation of c.326+7G>C in intron 2 of LMX1 B was suggested to be benign in the ClinVar database. Furthermore, since CG is a collagen deposition disease, it might be interesting to examine the distribution of type IV collagen, which is a major component of the GBM. The distribution of type IV collagen alpha 1-6 chains was not influenced by the deposition of type III collagen in the present study.

The serum hyaluronan concentration was markedly increased in the present case, an observation that was consistent with a previous report (13). This finding suggests that serum hyaluronan might be a useful marker for CG, like PI-

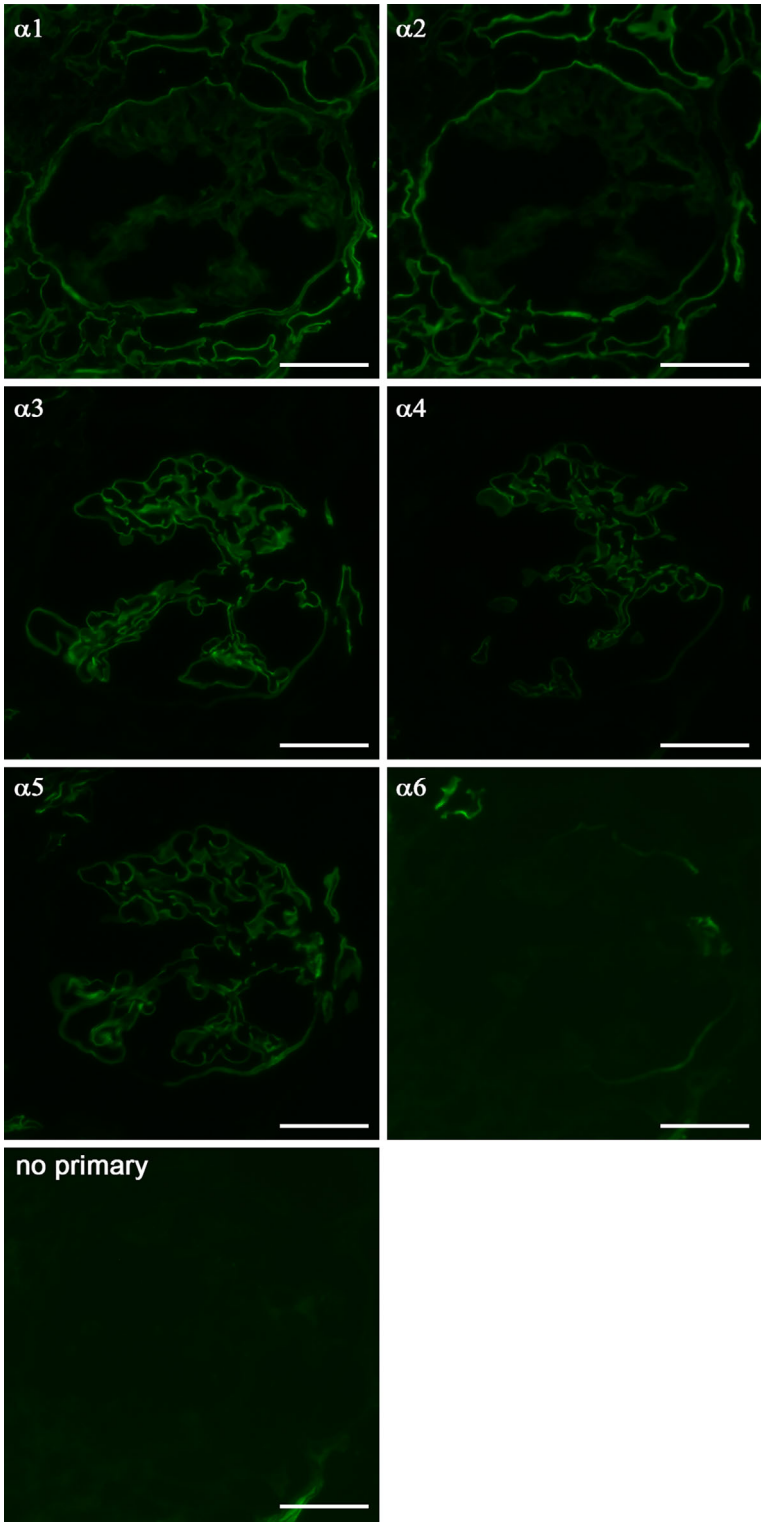

Figure 3. Immunofluorescence study for type IV collagen. There was strong linear staining for the alpha 3, 4 and 5 chains, while the alpha 1 and 2 chains were weakly positive in the glomerular basement membrane. The alpha 6 chain was positive in the basement membrane of Bowman's capsule. No primary antibody served as a negative control. Scale bars, 100 μm.

IINP. No other characteristic markers are available for CG aside from PIIINP and hyaluronan.

In conclusion, we experienced a case of CG with a normal distribution of type IV collagen alpha 1-6 chains.

Consent to perform genetic screening was obtained from the patient.

Written informed consent was obtained from the patient for the publication of this case report.

The authors state that they have no Conflict of Interest (COI).

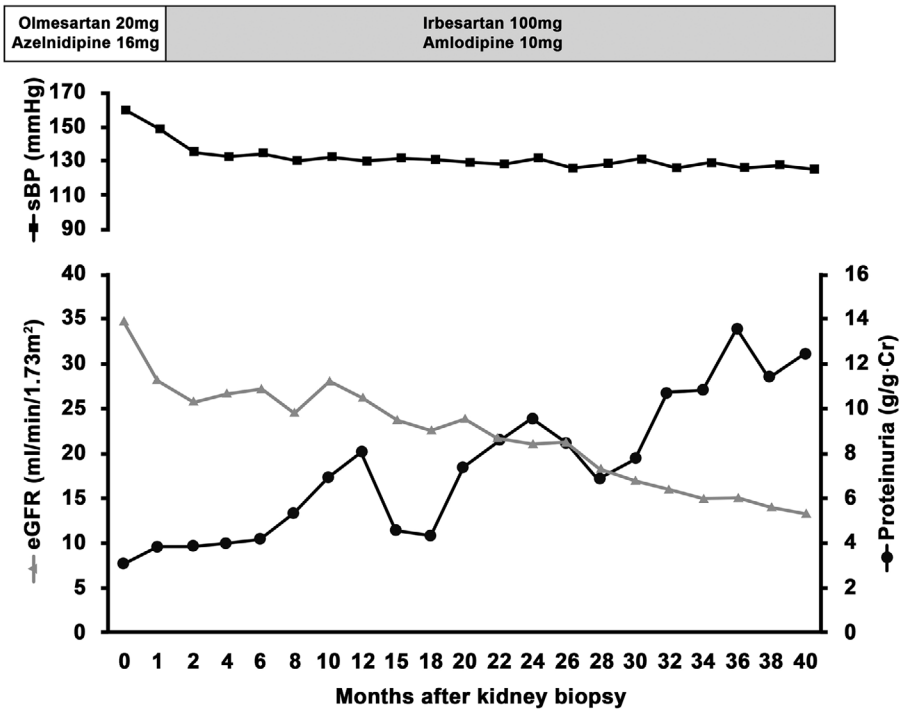

Figure 4. **The clinical course. Cr: creatinine, eGFR: estimated glomerular filtration rate, sBP: systolic blood pressure**

References

1. Alchi B, Nishi S, Narita I, Gejyo F. Collagenofibrotic glomerulopathy: clinicopathologic overview of a rare glomerular disease. Am J Kidney Dis **49**: 499-506, 2007.
2. Yoshioka K, Takemura T, Tohda M, et al. Glomerular localization of type III collagen in human kidney disease. Kidney Int **35**: 1203-1211, 1989.
3. Dombros N, Katz A. Nail patella-like renal lesions in the absence of skeletal abnormalities. Am J Kidney Dis **1**: 237-240, 1982.
4. Isojima T, Harita Y, Furuyama M, et al. LMX1B mutation with residual transcriptional activity as a cause of isolated glomerulopathy. Nephrol Dial Transplant **29**: 81-88, 2014.
5. Harita Y, Kitanaka S, Isojima T, Ashida A, Hattori M. Spectrum of LMX1B mutations: from nail-patella syndrome to isolated nephropathy. Pediatr Nephrol **32**: 1845-1850, 2017.
6. Andeen NK, Schleit J, Blosser CD, Dorschner MO, Hisama FM, Smith KD. LMX1B-associated nephropathy with type III collagen deposition in the glomerular and tubular basement membranes. Am J Kidney Dis **72**: 296-301, 2018.
7. Aoki T, Hayashi K, Morinaga T, et al. Two brothers with collagenofibrotic glomerulopathy. CEN Case Rep **4**: 85-89, 2015.
8. Alsaad KO, Edrees B, Rahim KA, Alanazi A, Ahmad M, Aloudah N. Collagenofibrotic (Collagen Type III) glomerulopathy in association with diabetic nephropathy. Saudi J Kidney Dis Transpl **28**: 898-905, 2017.
9. Soni SS, Gowrishankar S, Nagarik AP, et al. Collagenofibrotic glomerulopathy in association with Hodgkin's lymphoma. Saudi J Kidney Dis Transpl **22**: 126-129, 2011.
10. Yasuda T, Imai H, Nakamoto Y, et al. Collagenofibrotic glomerulopathy: a systemic disease. Am J Kidney Dis **33**: 123-127, 1999.
11. Foidart JM, Foidart JB, Mahieu PR. Synthesis of collagen and fibronectin by glomerular cells in culture. Ren Physiol **3**: 183-192, 1980.
12. Nakazato Y, Okada H, Tajima S, et al. Interleukin-4 modulates collagen synthesis by human mesangial cells in a type-specific manner. Am J Physiol **270**: F447-F453, 1996.
13. Goto S, Nakai K, Ito J, et al. Marked elevation of serum hyaluronan levels in collagenofibrotic glomerulopathy. Intern Med **53**: 1801-1804, 2014.