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
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 antihuman 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 LMX1B. 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 LMX1B 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.

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

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

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

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