A Case of Fibronectin Glomerulopathy Caused by Missense Mutations in the Fibronectin 1 Gene

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INTRODUCTION

Fibronectin glomerulopathy (FNG) is an autosomal dominant inherited kidney disease of unknown etiology that was reported for the first time in 1995, and it is characterized by a large amount of fibronectin (FN) deposits in the renal glomeruli.1 This disease develops mostly in people who are approximately 10.5 to 30 years old.1 Patients with FNG have a similar clinical course to those with chronic nephritis, which causes hematuria and albuminuria, and almost half of patients with FNG have high blood pressure simultaneously; in addition, approximately 25% of patients with FNG receive renal replacement therapy because of end-stage renal failure.1,2 Immunohistologically, marked deposition of serum-derived FN in the glomeruli and its redeposition in transplanted kidneys are observed;3 thus, FN is considered to be blood derived (soluble plasma FN) and not produced in the glomerulus.1,2 The fibronectin 1 gene was identified as a responsible gene for this disease in 2008.4 However, the mechanism underlying the development of this disease is unknown, and there is no established treatment approach. Furthermore, symptoms vary among family members of the same pedigree even if they have the same genetic mutations, and the mixed existence of kidney failure cases and asymptomatic cases of the same pedigree is known.1 Only a small number of pedigrees have been reported,3 and physicians rarely encounter this disease in daily medical practice.

CASE PRESENTATION

Clinical History and Initial Laboratory Data

A 45-year-old woman with no chief complaints visited our hospital because proteinuria was found during a previous medical checkup. Urinary protein level was assessed at her medical checkup every 2 to 3 years. Urinary blood level was sometimes assessed. She had no remarkable history, but her father’s sister had a history of severe renal dysfunction since she was 74 years old. There were no consanguineous marriages among her parents and grandparents. The physical examination did not show notable abnormalities; her blood pressure was normal (134/84 mm Hg), and no edema was observed. There were no specific findings suggestive of connective tissue disease.

The initial laboratory evaluation (Table 1) showed a normal complete blood count: serum creatinine, 0.61 mg/dl (estimated glomerular filtration rate by creatinine: 82.6 ml/min per 1.73 m²). Urinalysis with a dipstick showed occult blood (1+) and confirmed proteinuria (3+). The creatinine ratio was 3.6 g/g on a spot measurement. Serologic workup results were negative. She underwent renal biopsy through the lower pole of the left kidney under ultrasonography guidance.

Kidney Biopsy Results

Eighteen glomeruli were collected, and deposits were observed in all of them (Figure 1a). The glomeruli were positively stained with periodic acid-Schiff, negatively stained with periodic acid-methenamine silver, and stained red with Masson trichrome (Figure 1b–d). Deposits were seen mostly in the mesangial area, spreading to the glomerular capillary wall, and images suggested wire-loop lesions in some areas. Mesangiolysis was observed in some areas, and the ballooning of glomerular capillaries was seen. Proliferative changes...
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Diagnosed with FNG. This was immunohistochemistry performed for FN, and microscopy showed no Ig, light chain, or complement marked increase in the mesangial matrix (Figure 1f).

Clinical Follow-up

Heterozygous missense mutations (c.5821T < C, p.1974L > P) in exon 37 were identified by gene analysis, leading to a definitive diagnosis of FNG with a genetic defect. The patient’s renal dysfunction did not progress, but she continued conservative treatment (dietary therapy and angiotensin II receptor blockers). Because the urine protein/creatinine ratio was 1.5–2.5 g/g on a spot measurement, concurrent administration of mizoribine (150 mg/day), an immunosuppressive agent, was started, but there has been little benefit.

DISCUSSION

FNG is characterized by massive glomerular deposits of FN, and it is an autosomal dominant disease that results in end-stage kidney disease.1 Clinically, this disease is considered to cause proteinuria and hematuria, leading to end-stage renal failure. Regarding clinical symptoms of FNG, the disease reportedly develops as nephrotic syndrome in relatively young patients.6 According to one report, FN levels in the blood did not differ between patients with FNG and healthy people, and FN deposits were not detected in other organs (e.g., the lungs, heart, brain, liver, and spleen).1

When renal biopsy is performed after clinical findings are obtained, the following pathological characteristic findings are obtained:7 almost all glomeruli observed are markedly enlarged, periodic acid-Schiff-positive substances deposit across the mesangial area, and as a result, the mesangial area is expanded. These findings often indicate a lobular pattern. The disease is characterized by globulin-negative results in immunostaining.7 Electron microscopy reveals homogeneous granular fine fibers that are much thinner and smaller than those in fibrillary nephritis, which exhibit similar pathological findings. The results of immunostaining with anti-FN monoclonal antibodies (IST-4 and IST-9) were IST-4 positive (cellular FN + serum FN) and slightly IST-9 positive (cellular FN), which proves serum FN deposition.

A genetic test is performed when FNG is suspected pathologically. In recent years, mutations in the fibronectin 1 locus at 2q32 have been identified, but these mutations account for approximately 40% of all cases with FNG.5 Our patient had missense mutations in the fibronectin 1 gene, which enabled us to make the definitive diagnosis genetically as well. The patient’s mutation sites were consistent with those reported by Castelletti et al. in 2008.4 Ohtsubo et al.5 reported that various phenotypic patterns exist; some patients develop proteinuria at a relatively early stage in their life (by 10 years), whereas others are asymptomatic.

were seldom seen in the glomeruli, and neither mesangial cell proliferation nor intratubular cell proliferation was observed. Immunofluorescence microscopy showed no Ig, light chain, or complement deposition (Figure 1e). Electron microscopy revealed a marked increase in the mesangial matrix (Figure 1f).

Immunohistochemistry was performed for FN, and glomerular deposits stained with anti-FN antibodies (IST-4, positive; IST-9, weakly positive). This was diagnosed with FNG.

| Parameter | Value | Reference range |
|-----------|-------|-----------------|
| Urine     |       |                 |
| pH        | 6.5   | 5.0–6.5         |
| Red blood cell (HPF) | 10–19 | <5              |
| Hyaline casts (WF) | 5–9  | Negative        |
| Urine protein/creatinine ratio (g/g) | 3.6   | <0.15           |
| Ig2 microglobulin (µg/l) | 318   | 0–308           |
| N-Acetyl-β-1-glucosaminidase (UI) | 25.9  | 0.3–20.3        |
| Urine M protein | Negative | Negative |
| Blood     |       |                 |
| Leukocyte count (µl) | 4000  | 4500–9000       |
| Hemoglobin (g/dl) | 13.1  | 13.6–17.0       |
| Platelet count (×10³ µl) | 24.4  | 14–38           |
| Urea nitrogen (mg/dl) | 12.4  | 8.0–22.0        |
| Creatinine (mg/dl) | 0.67  | 0.60–1.10       |
| Uric acid (mg/dl) | 4.6   | 3.6–7.0         |
| eGFR-Cr (m/min per 1.73 m²) | 74.5  | ≥90.0           |
| Cystatin C (mg/l) | 0.66  | 0.52–0.88       |
| Total protein (g/dl) | 6.4   | 7.4–8.1         |
| Albumin (g/dl) | 3.7   | 4.0–5.0         |
| C-reactive protein (mg/dl) | 0.06  | <0.30           |
| Sodium (mEq/l) | 141   | 138–146         |
| Potassium (mEq/l) | 4.0   | 3.6–4.9         |
| Chloride (mEq/l) | 106   | 99–109          |
| Corrected serum calcium (mg/dl) | 8.8   | 8.6–10.4        |
| Phosphate (mg/dl) | 3.6   | 2.5–4.7         |
| Hemoglobin A1c, NGSP (%) | 5.4   | 4.6–6.2         |
| Cr, creatinine | 0.102 | 0.70–1.10       |
| C3 (mg/dl) | 120   | 65–135          |
| C4 (mg/dl) | 25    | 13–35           |
| IgG (mg/dl) | 1012  | 870–1700        |
| IgA (mg/dl) | 148   | 110–410         |
| IgM (mg/dl) | 310   | 33–190          |
| IgE (IU/ml) | 68.8  | <269            |
| Serum M protein | Negative | Negative |
| Anti-nuclear antibody | <40   | <40             |
| Anti-double stranded DNA antibody (IU/ml) | <25   | <5.9            |
| Anti-Smith antibody (IU/ml) | <7.0  | <9.9            |
| PR3-ANCA (U/ml) | <1.0  | <3.5            |
| MPO-ANCA(U/ml) | <1.0  | <3.5            |
| Anti-SS-A/Ro antibody (U/ml) | <7.0  | <9.9            |
| Anti-SS-B/La antibody(U/ml) | <7.0  | <9.9            |
| C1q-IC (Mg/ml) | <1.5  | <2.9            |

C3, complement component 3; C4, complement component 4; C1q-IC, C1q binding IgG immune complex; Cr, creatinine; eGFR, estimated glomerular filtration rate; HPF, per high-power field; MPO-ANCA, myeloperoxidase–antineutrophil cytoplasmic antibody; NGSP, National Glycohemoglobin Standardization Program; PR3-ANCA, proteinase3-antineutrophil cytoplasmic antibody; SS-A/Ro, anti-Ro/SS-5 syndrome A antigen; SS-B/La, anti-La/SS-6 syndrome B antigen; WF, whole field.

Table 1. Laboratory results on admission

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Castelletti et al. reported that all mutations occurred at the heparin-binding domains of fibronectin 1. However, Ohtsubo et al. reported that a mutation exists at an unreported site that regulates integrin binding.

Regarding treatment, steroid drugs or immunosuppressive agents are empirically used in patients with FNG in whom nephrotic syndrome has developed. It has been reported that mizoribine has a good treatment effect. However, in terms of pharmacological properties, it is possible that mizoribine exerts its effects indirectly rather than directly by its immunosuppressive effects, binding to chaperone proteins and

Figure 1. Histopathological findings of the renal biopsy specimen. (a) Deposits are observed in all glomeruli in a low-power view (periodic acid–Schiff staining; bar = 200 μm). There are no marked changes in the renal tubule. (b)–(d) Each image shows a glomerulus in a high-power view ([b] periodic acid–Schiff staining positive, [c] periodic acid–methenamine silver staining negative, and [d] stained red with the Masson trichrome staining). Each glomerulus is enlarged (bar = 50 μm). Spike formation was not seen in the glomerular basement membrane. In addition, the double contour of the glomerular capillary wall was not observed. (e) Immunofluorescent images on frozen sections. Ig, complements, and C1q were negative. The results of the immunostaining with Igs and other proteins were all negative. Electron microscopy shows that massive dense deposits are distributed across the mesangial areas and under the endothelium of the glomerular capillary wall. The deposits are distributed, especially under the endothelium of the glomerular capillary wall on its whole circumference. These deposits are not seen in the glomerular basement membrane or under the epithelium. No pathognomonic structures are seen at a high magnification (×12,000) ([f] left image, ×3000 [bar = 2 μm]; right image, ×12,000 [bar = 500 nm]). (g, h) Images showing the findings of specific staining with anti-fibronectin monoclonal antibodies. The results of IST-4 staining for serum fibronectin and tissue fibronectin are mostly positive, and the result of IST-9 staining for tissue fibronectin is slightly positive, proving the deposition of serum fibronectin (bar = 200 μm).
correcting defective nephrin biogenesis through the restoration of intracellular energy balance, and this medication is reportedly not always effective in patients with FNG. These teaching points are summarized in Table 2.

CONCLUSION

In our case, FNG was pathologically suspected, and thus, gene analysis was performed, which led to a definitive diagnosis of this disease. When a lobular pattern and the enlargement of glomeruli are observed and periodic acid-Schiff-positive deposits exist, FNG should be suspected and the presence of deposits and a fibrous structure should be confirmed using electron microscopy. Furthermore, immunostaining with anti-FN monoclonal antibodies (IST-4 and IST-9) and genetic diagnosis are considered useful when FNG is suspected. Currently, there are no efficacious treatment modalities for this condition.

DISCLOSURE

All the authors declared no competing interests.

Table 2. Fibronectin glomerulopathy: teaching points

| Teaching Points | Details |
|-----------------|---------|
| Fibronectin glomerulopathy (FNG) is characterized by massive glomerular deposits of fibronectin (FN), and it is an autosomal dominant disease that results in end-stage kidney disease. |
| FNG is characterized by globulin-negative results in immunostaining. |
| FN is considered to be blood derived (soluble plasma FN) and not produced in the glomerulus. |
| Mutations in the FN1 locus at 2q32 have been identified, but it was reported that various phenotypic patterns exist. |
| No standard treatment has been established for FNG. |

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