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【 CASE REPORT 】

Kidney Histology Findings in a Patient with Autosomal Dominant Tubulointerstitial Kidney Disease Subtype Hepatocyte Nuclear Factor 1β

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Abstract:
We evaluated kidney histology in a 43-year-old woman with autosomal dominant tubulointerstitial kidney disease subtype hepatocyte nuclear factor 1β. Magnetic resonance imaging showed multiple cysts in the renal medullary area, and computed tomography showed hypoplasia of the pancreatic body and tail. A kidney biopsy showed thinning of the cortex, size reduction of glomerular tuft area, proximal tubule clustering, fibrosis around the tubules, loss of peritubular capillaries, and multilayered epithelial cells of cortical collecting ducts; this last finding was consistent with so-called medullary dysplasia specific to congenital disease, in which the renal pelvic epithelial cells enter the collecting duct.

Key words: autosomal dominant tubulointerstitial kidney disease (ADTKD), medullary dysplasia, hepatocyte nuclear factor 1β (HNF1B)

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Introduction

Autosomal dominant tubulointerstitial kidney disease (ADTKD) is a group of autosomal dominant disorders characterized by progressive kidney disease, tubulointerstitial nephropathy, and bland urinary sediment (1). Various gene mutations can cause ADTKD, including the genes encoding uromodulin (*UMOD*), mucin-1 (*MUC1*), hepatocyte nuclear factor 1β (*HNF1B*), renin (*REN*), and the alpha subunit of the SEC61 complex (*SEC61A1*).

The HNF1B gene is located on chromosome 17q12 and is a DNA-binding transcription factor associated with kidney development (2). Patients with the *HNF1B* mutation show clinical features including type 2 diabetes, pancreatic hypoplasia, and hyperuricemia, as well as developmental abnormalities of the kidney, including kidney cysts, unilateral kidney agenesis, and hypoplasia. An *HNF1B* mutation is also known to be responsible for maturity-onset diabetes of the young type 5 (MODY5). However, few reports have included histological evaluations of the kidney in patients with an *HNF1B* mutation (3).

We herein report the kidney biopsy findings in a patient with a clinical picture typical of ADTKD-HNF1B.

Case Report

A 43-year-old Japanese woman was admitted to our hospital for the evaluation of worsening renal dysfunction. At 30 years old, this patient's serum creatinine had been 1.1 mg/dL, and her estimated glomerular filtration rate (eGFR) had been 48.7 mL/min/1.73 m^2 at workplace medical checkups. She did not have diabetes. Her mother was 70 years old and was being treated for type 2 diabetes mellitus (DM) with oral hypoglycemic agents. At the present time, her serum creatinine level was 1.85 mg/dL, and her eGFR was

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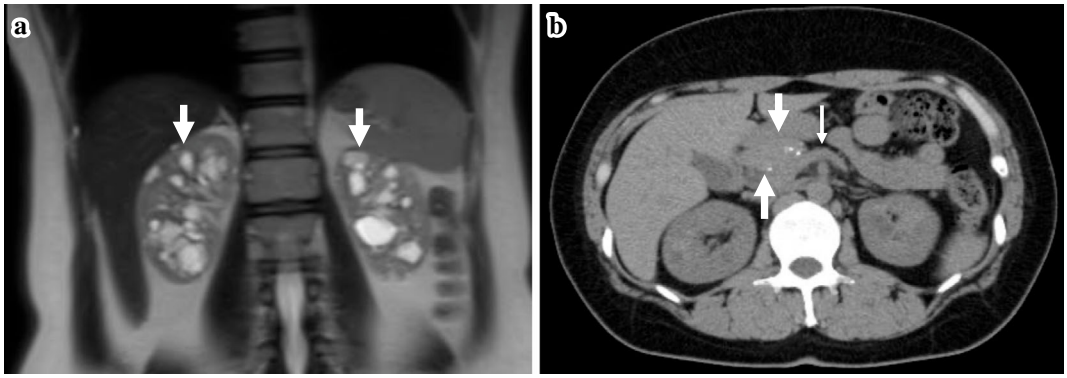

Figure 1. Magnetic resonance imaging and computed tomography findings. a: T2-weighted image of magnetic resonance imaging showed multiple cysts with hyperintensity (arrows) compared to the adjacent fat area in the renal medullary area. b: Computed tomography showed calcification of the pancreatic head (large arrows) but hypoplasia of the pancreatic body or tail (small arrow).

22.0 mL/min/1.73 m^2. Renal cysts were noted, but pancreatic involvement was unknown. The patient's grandmother also had a history of diabetes, but no further details were available.

On admission, the patient was 161 cm tall and weighed 68.5 kg. Her blood pressure was 101/61 mmHg, and her body temperature was 36.6°C. Heart and breath sounds were normal. Edema was not present in the lower extremities. Blood chemistry tests showed a total protein level of 6.7 g/dL; albumin, 3.6 g/dL; urea nitrogen, 17 mg/dL; creatinine, 1.2 mg/dL; estimated glomerular filtration rate, 39.2 mL/min/1.73 m^2; uric acid, 7.3 mg/dL; magnesium, 1.5 mg/dL (normal; 1.7-2.3 mg/dL); and hemoglobin A1c, 5.4%. Total urinary protein excretion was 0.03 g/day, and urine sediment contained <1/ erythrocyte per high-power field. Magnetic resonance imaging showed multiple cysts in the renal medullary area (Fig. 1a), and computed tomography showed calcification of the pancreatic head and hypoplasia of the pancreatic body and tail (Fig. 1b).

A glucose tolerance test using an oral glucose dose of 75 g (OGTT) was performed. Fasting plasma glucose (measured before the OGTT begins) was 117 mg/dL (normal: <100 mg/dL), and the 2-h glucose value of the OGTT was 162 mg/dL (normal: <140 mg/dL). Impaired glucose tolerance was diagnosed according to the diagnosis criteria of the World Health Organization (WHO).

Kidney biopsy findings

A kidney biopsy was performed to evaluate renal dysfunction. A light microscopic examination of a biopsy specimen contained 20 glomeruli. Global sclerosis was seen in five glomeruli, which were clustered on the cortical capsular side (Fig. 2a), and thinning of the cortex was noted. The preserved glomeruli were almost intact, but the size of the glomerular tuft area was reduced in most of them (Fig. 2b). Mesangium cell proliferation, mesangium matrix expansion, and crescentic formation were not observed. Usually, proximal and distal tubules are mixed together in biopsy material from the cortical region; however, in our patient we found clusters of proximal tubules. Fibrosis was prominent around the tubules, and few peritubular capillaries were detected (Fig. 2c, d). Normally, epithelial cells are found in a single layer in the cortical collecting ducts, but in this patient, multilayered epithelial cells were prominent (Fig. 2e, f). Immunofluorescence was negative for IgG, IgM, IgA, C3, C4, and C1q. Electron microscopy showed no abnormalities in the glomerular or tubular basement membrane (Fig. 2g, h) - which are seen in cases of adult-onset nephronophthisis (4) - but did show swelling and shortening of mitochondria in tubular epithelial cells (Fig. 2i), although the mitochondria differed slightly from those described by Oba et al. (3).

Genetic analyses

Because the patient's mother had type 2 diabetes and multiple renal cysts, a genetic test was performed in the laboratory of one of the co-authors (Kandai Nozu) according to a previously published method (5). A comprehensive analysis was performed by next-generation sequencing, and the identified mutations were confirmed by the Sanger method. A potentially pathogenic heterozygous mutation variant of *HNF1B* (NM_000458: c.544C>A, p.Gln182*) was identified in exon 2 of *HNF1B* (Fig. 3). C.544 is the last nucleotide of Exon 2, and the next nucleotide is the first nucleotide of Exon 3. This nucleotide change (c.544C>T) changes the sequence from CAA to TAA, which then leads to an amino acid change of p.Gln182* (Fig. 3 Supplementary Material). This mutation was previously reported as a pathogenic variant of MODY5 (6).

Discussion

We presented the kidney histology findings of a 43-year-old woman with ADTKD-HNF1B diagnosed by genetic testing.

As described above, ADTKD is caused by mutations in various genes. The organization Kidney Disease: Improving Global Outcomes (KDIGO) proposed adoption of a new terminology for this group of diseases using the term 'ADT-

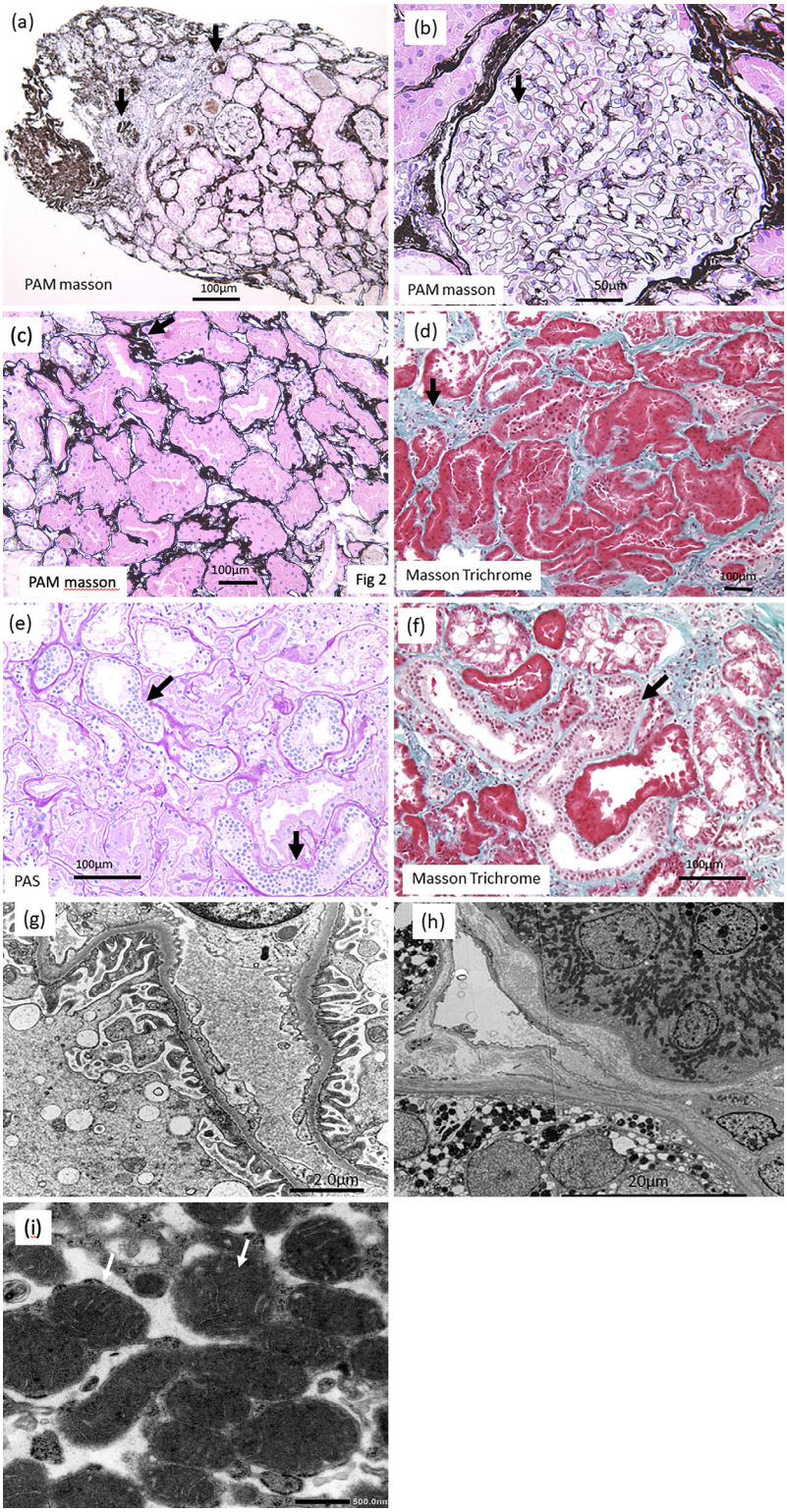

Figure 2. **Kidney biopsy findings. a: Global sclerosis (arrows) was seen in 5 glomeruli, which were clustered on the cortical capsular side (original magnification×100). b: The preserved glomeruli were almost intact, but a reduced glomerular tuft area (arrow) was a characteristic finding (original magnification×400). c and d: Clusters of proximal tubules were more prominent than those of distal tubules. Fibrosis was prominent around the tubules (arrows), and few peritubular capillaries were detected (original magnification×200). e and f: Multilayered epithelial cells were prominent in the cortical collecting ducts (arrows) (original magnification×400). g and h: Electron microscopy showed no abnormalities in the glomerular (g) or tubular basement membrane (h). i: Electron microscopy showed swelling and shortening of mitochondria (arrow) in the tubular epithelial cells.**

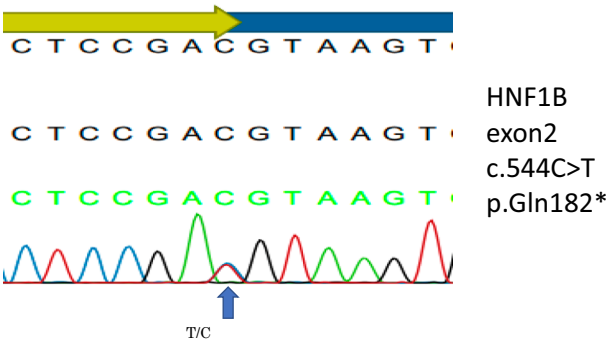

Figure 3. Results of genetic analyses.

KD', with a gene-based subclassification appended for previously used terminology, including 'Medullary Cystic Kidney Disease (MCKD) type 2'. Common clinical features of patients with ADTKD include autosomal dominant inheritance, progressive loss of the kidney function, bland urinary sediment, and absent or mild albuminuria and proteinuria. Common histological findings include interstitial fibrosis, tubular atrophy, thickening and lamellation of tubular basement membranes, tubular dilatation (microcysts), and negative immunofluorescence for complement and immunoglobulins (7).

HNF1B, a DNA-binding transcription factor, is involved in the development of the kidney, particularly differentiation of the tubules, by regulating the expression of other genes. Massa et al. showed that inactivation of HNF1B in the murine metanephric mesenchyme leads to a severe tubular defect characterized by the absence of proximal, distal, and Henle's loop segments (8). Clissold et al. reported the following findings as the renal histology of patients with ADTKD-HNF1B: hypoplastic glomerulocystic kidney disease; oligomeganephronia; cystic renal dysplasia; interstitial fibrosis; and enlarged glomeruli, which are thought to arise from abnormal nephron development (9). Devuyst et al. proposed a mechanism by which mutated *HNF1B* causes tubulointerstitial fibrosis: deletion of *HNF1β* in renal tubular epithelial cells leads to activation of a twist-related protein 2-dependent transcriptional network, which induces epithelial-mesenchymal transition pathways and aberrant transforming growth factor-β signaling (10). Casemayou et al. reported that inhibition of *HNF1B* significantly reduced the expression of peroxisome proliferator-activated receptor γ coactivator 1α and altered the mitochondrial morphology and respiration in proximal tubule cells (11). Oba et al. reported that mitochondrial morphological abnormalities, including small size and swelling, were seen on a kidney biopsy of a patient with ADTKD-HNF1B (3). Our kidney biopsy also showed findings similar to the mitochondrial abnormalities reported by Oba et al. (3), supporting the findings of Casemayou et al. (11).

Although we cannot be sure that the findings obtained in one patient are specific to this disease, we believe that this report will lead to a better understanding of the renal involvement in ADTKD-HNF1B and the pathogenesis of the renal function decline.

In conclusion, we evaluated the kidney histology in a patient with ADTKD-HNF1B diagnosed by genetic testing. We found thinning of the cortex, size reduction in the glomerular tuft area, proximal tubule clustering, fibrosis around the tubules, loss of peritubular capillaries, and multilayered epithelial cells in the cortical collecting ducts. Given that epithelial cells of the renal pelvic ureter are usually multilayered, this anomaly in which renal pelvic epithelial cells enter the collecting duct may be referred to as medullary dysplasia specific to congenital disease.

This investigation was conducted in accordance with the Declaration of Helsinki. The patient gave her informed consent for this case report to be published.

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

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