Case 5

Focal segmental glomerulosclerosis with an ACTN4 mutation in two siblings

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[Background]

Mutations in the ACTN4 gene were known to cause autosomal dominant form of human focal segmental glomerulosclerosis (FSGS). Most of the patients with ACTN4 mutations show mild proteinuria of non-nephrotic range in the teenage years or later and slow progression of the renal dysfunction. We report two siblings with S262F mutation in ACTN4 mutations showed early-onset full-blown nephrotic syndrome and rapid progression to end-stage renal disease (ESRD). Their father, who was clinically silent, had germ-line mosaicism of the mutation.

[Cases]

A 3-year-old boy was referred to our hospital due to newly-onset nephrotic syndrome with positive family history. Initial laboratory tests on admission were as follows. His serum urea nitrogen 14 mg/dL, creatinine 0.8 mg/dL, total protein 4.3 g/dL, albumin 1.6 g/dL, and cholesterol 614 mg/dL. Urinalysis showed (++++) proteinuria without hematuria. Urinary protein excretion was 9.6 g/day.

He was treated with oral steroid (2 mg/kg/day #3) for 16 days, but nephrotic syndrome persisted. Kidney biopsy was done on 36th hospital day, and showed collapsing variant form of FSGS with segmental sclerosis in 30% of the glomeruli and global sclerosis in 11%.

His elder sister, at the age of 3.7 years, was diagnosed as nephrotic syndrome at other hospital.

She didn't respond to any treatment (oral or intravenous pulsed steroid, cyclosporin, cyclophosphamide or mycophenolate mofetil) and rapidly progressed to ESRD. Her renal biopsy revealed FSGS. She underwent kidney transplantation from her mother at age 5.7 years, but she expired on the ninth post-operative day due to sepsis/DIC.

The urinalysis of their parents and an elder brother showed no abnormality.

Because of positive family history of steroid-resistant nephrotic syndrome, NPHS2 (podocin) and ACTN4 gene study was done with peripheral blood genomic DNAs of the family members and genomic DNA from biopsy tissue of the deceased sister, and a ^{262}Ser(TCC) > Phe(TTC) heterozygous mutation was detected at ACTN4 gene in both affected siblings only, but not in the parents and the unaffected brother. These findings suggested germ-line mosaicism of the mutation in one of the parents, because ACTN4 mutations are known to be associated with autosomal dominant form of FSGS. Thus, a linkage study with an intragenic DNA microsatellite marker (D19S422) was done, which revealed that the mutation was of paternal origin and excluded false paternity. Finally, mosaicism of the mutation was confirmed in DNA from father's sperm.

[Renal pathologic findings]

In his biopsy specimen, total 126 glomeruli were observed, and 11% (14/126) of the glomeruli showed global sclerosis. The remaining glomeruli were normal in size and mildly hypercellular. About 30% (38/126) of the glomeruli exhibited segmental sclerosis with segmental collapse of the tuft and hypertrophy or hyperplasia of podocytes. The tubules revealed focal mild atrophy or loss, and focal mild infiltration of mononuclear cells and focal mild fibrosis were noted in the interstitium. The electron microscopic examination revealed segmental wrinkling of the glomerular basement membranes. There were no electron-dense deposits in the glomeruli. Epithelial foot processes are widely effaced.

One glass slide of the elder sister's renal biopsy tissue stained with H&E was available to review. The specimen contained 10 glomeruli. The glomeruli were normal in size was and mildly hypercellular. Two glomeruli showed segmental sclerosis, but the hypertrophy or hyperplasia of podocytes was not found. Focal tubular atrophy and interstitial fibrosis were also noted.

[Points of discussion]

1. This is the first report of ACTN4 mutation-associated FSGS in Korean as well as in Asian.

2. Germ-line mosaicism of the ACTN4 mutation has never been reported, and it makes genetic counseling more difficult.

3. The difference of renal pathologic findings between two siblings with same mutation suggests new understanding of the pathologic variants of FSGS.

4. These siblings showed unusual clinical features (early-onset, full-blown, and rapidly progressing nephrotic syndrome) of ACTN4 mutation-associated FSGS. To confirm the possible association of a second mutation in other gene, which modifies the clinical course, NPHS1 (nephrin) and TRPC6 gene study is ongoing.