TGFBI-associated corneal dystrophy and nephropathy: a novel syndrome?

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Abstract

Transforming growth factor beta-induced (*TGFBI*)-associated corneal dystrophies are a group of inherited progressive corneal diseases. One of these *TGFBI*-associated corneal dystrophies is Avellino corneal dystrophy, an autosomal dominant corneal dystrophy characterized by multiple asymmetric stromal opacities that potentially impair vision. Recently, a case with corneal dystrophy complicated by nephropathy possessing a pathogenic variant of the *TGFBI* gene was reported for the first time. Here, we report the second case with the same condition and the same mutation in the *TGFBI* gene. The patient was an 18-year-old male. He and his father had already been diagnosed with corneal dystrophy. Proteinuria was revealed in the patient during urine screening at school. Since his serum creatinine level was raised, a percutaneous renal biopsy was performed. Light microscopy demonstrated oligomeganephronia. Electron microscopy demonstrated an irregular basement membrane. *TGFBI* was analyzed by direct sequencing. A heterozygous mutation c.371G > A in exon 4, which caused an amino acid substitution from arginine to histidine at codon 124, was identified in the patient and his father. Although only one case of *TGFBI*-associated corneal dystrophy and nephropathy has been reported, our case's clinical and pathological findings were almost identical to those in that reported case. Further investigations of this new disease entity should be reported to all nephrologists and ophthalmologists.

Keywords Avellino corneal dystrophy · *TGFBI* · Renal dysfunction · Electron microscopy

Introduction

In 1992, *TGFBI* (transforming growth factor beta-induced gene) was recognized in a study of genes whose expression was induced by TGF- β in a human adenocarcinoma cell line

derived from the lung [1]. The protein encoded by *TGFBI* is transforming growth factor beta-induced 68 kDa (TGFBI).

TGFBI-associated corneal dystrophies are a group of inherited progressive corneal diseases and which have been divided into two groups based on the anatomical location of the deposits: Bowman's layer or stroma. Mutations in *TGFBI* are responsible for three types of corneal stromal dystrophy: lattice corneal dystrophies (LCD), GCD type 1 (GCD1), and GCD type 2 (GCD2). Each of these dystrophies can usually be distinguished by slit-lamp biomicroscopy, histopathology, electron microscopy, and genetic testing to identify the mutations responsible for the different types of corneal dystrophy.

Granular corneal dystrophy type 2 (GCD2), also called Avellino corneal dystrophy (ACD), is one of the most common forms of autosomal dominant corneal dystrophy in Japan. The corneal opacities are the result of a specific mutation (R124H) in *TGFBI*. Bilateral corneal deposits can cause photophobia and reduce visual acuity. In one report,

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it was estimated that p.Arg124His is the most commonly reported mutation worldwide (~26%) and is the most frequently observed mutation among Asians with clinical corneal dystrophy (~88%) [2].

An epidemiological study on the frequency of the p.Arg124His mutation in a Korean population estimated that the overall prevalence rate is 11.5/10,000 individuals [3]. Moreover, previous Japanese studies reported that the p.Arg124His mutation was the most common, accounting for up to 72% of patients with corneal dystrophy [4].

The transforming growth factor beta-induced gene (*TGFBI*; *BIGH3*; *βigh3*) encodes transforming growth factor beta-induced protein (TGFBIp), a 68-kDa extracellular matrix protein composed of 683 amino acid residues. TGFBIp is known to be ubiquitous in various organs including kidney. Previously, the cornea was considered to be the only affected tissue in patients with *TGFBI* corneal dystrophy. However, recently, a case of nephropathy associated with a *TGFBI* mutation was reported [5].

We have also recently experienced a patient with ACD and nephropathy who had the same p.Arg124His mutation in the *TGFBI* gene. Our case showed a quite similar clinical and pathological presentation.

Case report

The patient was an 18-year-old male. At 13 years of age, he was revealed to have proteinuria by urine screening at school. At 17 years of age, he was referred to our hospital because of proteinuria, which was again identified by urine screening at school. He was born at a gestational age of 39 weeks with a birth weight of 2705 g. He had no particular pre- or postnatal history including acute kidney injury. He had no past history of urinary tract infection or fever of unknown origin, but he had suffered from ACD, since his time at junior high school. Regarding the family history, his father also had ACD, as well as hyperuricemia, but his renal function and urinalysis results were normal, as revealed by an annual medical checkup. The patient's serum creatinine level was 1.51 mg/dL (eGFR 34.4 mL/min/1.73 m²), so further examination was conducted. The physical findings on admission were almost normal. He had no abnormalities of the nails, knees, and elbows. On admission, laboratory findings were as follows: blood urea nitrogen level, 14.3 mg/dL; serum uric acid level, 7.9 mg/dL; albumin level, 4.1 g/dL; serum calcium, 9.5 mg/dL; phosphate, 3.5 mg/dL; and intact PTH, 32 pg/mL. Urinalysis showed a urinary protein level of 1.2 g/gCr, β2MG 109 μg/L, and NAG 3.3 U/L.

Renal ultrasonography revealed a diffuse increase of echogenicity and reduced size of the right kidney. The size of the right kidney was smaller than normal (left 11.5×4.6 cm, right 9.5×4.6 cm), as revealed by a CT scan. Tc-99m DMSA

images revealed no scarring, but decreased uptake in the right kidney (Fig. 1a).

Slit-lamp biomicroscopy revealed granular opacities with superficial stroma in both eyes (Fig. 1b). The results of dilated fundus examination were unremarkable. The patient's best corrected visual acuity was 20/50 in the right eye and 20/25 in the left eye.

A renal biopsy was performed on the left kidney. On light microscopy, the patient had four glomeruli with no crescent formation. The mean diameter of the glomeruli was about 200 μm, which was larger than normal (Fig. 1c). There was no increase in the size of the mesangial matrix, which exhibited a normal morphology. There was slight tubulus atrophy as well as interstitial fibrosis. Immunofluorescent findings of IgA, IgG, C3, and C1q were negative, while those of IgM and C4d were slightly positive in the mesangial area. The pathological features, consisting of a reduced number of enlarged glomeruli, were diagnostic of oligomeganephronia. Electron microscopy demonstrated a slightly irregular appearance, namely, a glomerular basement membrane with a moth-eaten appearance (Fig. 1d).

We conducted direct sequencing analysis and found that the patient was carrying a *TGFBI* monoallelic variant. The variant features a heterozygous G to A substitution at base position 371 in exon 4, which replaces the amino acid arginine with histidine at codon 124 (p.Arg124His) (Fig. 5). The patient's father carried this variant in heterozygous form. All of the laboratory and pathological analyses suggested ACD associated with *TGFBI* mutation complicated by nephropathy.

Discussion

This paper presents a case with ACD and nephropathy caused by *TGFBI* gene mutation. The *TGFBI* protein plays an important role in cell-collagen signaling interactions, including with extracellular matrix proteins that comprise the renal basement membrane. Immunohistochemical analysis of kidney, where the expression of *TGFBI* was moderate, localized *TGFBI* predominantly to epithelial cells of collecting ducts and distal and proximal tubules. A previous report showed various glomerular and tubular basement membrane changes including membrane widening in electron microscopic studies [5]. In our case, light microscopy demonstrated oligomeganephronia. However, electron microscopic studies showed the same basement membrane changes as was shown in the previous case. Because of his young age, our patient showed milder basement membrane changes, but we need to perform careful follow-up to monitor the development of nephropathy.

In our case, renal size and increased glomerular diameter were typical findings of oligomeganephronia. In contrast,

Fig. 1 **a** Dimercaptosuccinic acid scan. Tc-99m DMSA images showing no scarring. **b** Slit-lamp biomicroscopy. Granular deposits were viewed with diffuse illumination. **c** Periodic acid–Schiff stain ($\times 40$). Light microscopic examination showing enlarged glomeruli. Glo-

merular density was $0.3/\text{mm}^2$. **d** Electron microscopy. Higher magnification displaying irregular appearance of the GBM. **e** Gene analysis. *TGFBI* gene analysis showing a heterozygous G to A substitution at base position 371 in exon 4

in the above-mentioned previous report, it was shown that the patient had a normal kidney size and slightly enlarged glomeruli. We asked the authors of this report for additional information about this, which revealed that the glomerular diameter was 300 μm , involving remarkable enlargement. This might be suggestive of low glomerular density, as was shown in our case. The cause of the scarce glomeruli in oligomeganephronia is not yet clearly known. However, one proposed reason is the presence of the variant of a gene expressed in embryonic kidney that normally regulates kidney development but for which the variant form instead leads to inadequate embryonic development of nephrons. The role of *TGFBI* is not understood completely, but it has been suggested that it plays some role in kidney development.

TGFBI is known to be ubiquitous in various tissues and organs including heart, liver, pancreas, skin, bone, tendon, endometrium, kidney, and blood plasma. Its level of protein expression differs in each organ. However, its role is not completely understood. Previously, the cornea was considered to be the only affected tissue in patients with *TGFBI* corneal dystrophy, which may be due to its high concentration there [6]. Among 1679 proteins in the corneal stroma, *TGFBI* is the second most abundant ($17.6 \pm 3.3\%$). In line with these findings, we think that the symptoms may differ depending on the protein expression level.

Recently, CRISPR-Cas9-mediated genome editing for the correction of a *TGFBI* mutation in GCD patient-derived primary corneal keratocytes was reported [7]. Gene therapy for heredity corneal diseases may be possible in the future, it is important to accurately assess renal symptoms.

ACD with the p.Arg124His mutation is common in Japanese patients. However, this is only the second reported case of *TGFBI*-related oculorenal syndrome. We suggest the following three reasons for the fact that this syndrome has rarely been reported. First, more cases may have occurred but not been reported because of the difficulty in identifying them. Second, the severity of nephropathy may vary and in most cases be mild. Third, it is possible that, although our case is quite similar to that described in the previous report, the nephropathy was just coincidentally complicated by ACD. Therefore, further careful attention is needed to shed light on this rare syndrome.

We have reported a case of *TGFBI*-associated corneal dystrophy and nephropathy. The findings of electron microscopy showed an abnormal basement membrane, which seemed to be the result of *TGFBI* mutation. We think that

the accumulation of similar cases will help to elucidate the pathology of *TGFBI*-related oculorenal syndrome.

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Compliance with Ethical Standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of Kobe University Graduate School of Medicine (IRB approval number 301) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors have nothing to disclose.

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