Letter

Focal glomerulosclerosis expanding from the glomerular vascular pole in a Japanese male with mitochondrial-DNA mutation

Sir,

Recently mitochondrial DNA mutations have been detected in patients with various diseases, in particular, mitochondrial encephalomyopathies. With regard to renal involvement, renal tubular dysfunction resulting in renal tubular acidosis and de-Toni-Debre-Fanconi syndrome were reported for the first time in 1977 [1]. In addition, recent studies reveal that focal glomerulosclerosis (FGS) and chronic renal failure are accompanied by mitochondrial abnormality [2–5]. Little is known, however, about the mechanism and progression of glomerular injury induced by mitochondrial mutations. We report a case of a FGS patient with mitochondrial DNA mutation whose clinical course has been followed for 8 years before starting haemodialysis (HD).

Case. In 1983, a 13-year-old male was first hospitalized for proteinuria. Physical examination revealed a short stature, a leptosomatic body (132 cm, 33 kg) and bilateral perceptive deafness. Urinalysis showed proteinuria of 0.96 g/day, with normal renal function. A renal biopsy (see below) was performed, and he received prednisolone (60 mg/day) for 2 weeks which was discontinued due to an adverse reaction.

In 1985, he was hospitalized for the second time because of an increase in urinary protein excretion (3.71 g/day). His renal function was still normal (serum creatinine 0.8 mg/dl). In addition, the renal tubular function remained relatively unaffected. In particular tubular reabsorption of phosphorus and Fishberg concentration test were normal. On the other hand, diabetes mellitus was diagnosed, using a 75 g oral glucose tolerance test. Methylprednisolone pulse therapy (500 mg/day, 3 days) was tried, but discontinued because of hyperglycaemia.

Renal function gradually decreased after he had a sudden onset of diabetic ketoacidosis in 1986. In 1990, a second renal biopsy (see below) was performed. Cyclosporin was given for 10 consecutive months. This treatment failed to improve the clinical course. At the onset of end-stage renal failure in 1992, HD was started. The patient had no episodes of limb paralysis or convulsions during the course of the disease.

The first renal biopsy in 1983 showed a deposition of a hyaline-like substance at the vascular pole in one of 60 glomeruli; however, the tubules and interstitium were almost
intact. Immunohistochemical analysis revealed focal and segmental deposits of IgM. Electron microscopic analysis of the vascular pole demonstrated a marked increase in the number of mitochondria with abnormal cristae in the smooth muscle cells of the arteriole (Figure 1a, b). In addition, subendothelial deposits of hyaline-like substance were found near the vascular pole (Figure 1c). The subsequent renal biopsy in 1990 revealed segmental sclerosis with hyalinosis involving the vascular poles in 4 of 16 glomeruli.

A DNA sample extracted from the patient’s leukocytes and renal biopsy tissue was analyzed for the typical point mutation associated with mitochondrial diseases (an A-to-G transition mutation at nucleotide pair 3243 in the mitochondrial tRNA LEU(UUR)) by PCR method using endonuclease Apol [6]. The mutation was detected in both leukocytes and renal tissue.

Comment. Recent studies revealed several patients of FGS with mitochondrial mutation (A-to-G 3243) preceding renal tubular dysfunction as our case [3,4]. Note that we performed serial renal biopsies twice and could confirm glomerular sclerosis expanding from the vascular pole prior to Cyclosporin administration. Furthermore, it is notable that increased numbers of abnormal mitochondria were observed in the smooth muscle cells of the arteriole at the glomerular vascular pole for the first time. Mochizuki et al. [5] likewise reported a 14-year-old female with mitochondrial encephalomyopathy and segmental sclerosis at the vascular pole and the leimyocytes of a small renal artery in the interstitium, containing numerous abnormally enlarged mitochondria, but they did not mention renal outcome. Rennke et al. [7] reported that haemodynamic changes might lead to glomerular capillary hypertension and hyperperfusion resulting in FGS. Therefore, changes induced by a dysfunction of the arteriole at the vascular pole might have led to the FGS lesions observed in our case. Moulonguet-Doleris et al. [3] also found hyaline lesions in afferent arterioles and small arteries in two of four such cases and speculated that intraglomerular haemodynamic changes might explain the FGS lesions. They did not, however, directly prove the presence of abnormal mitochondria in the lesions. On the other hand, Hotta et al. [4] found severely damaged, multinucleated podocytes containing extremely dysmorphic abnormal mitochondria in their patients.

From these findings, we speculate that various mechanisms may underlie FGS with mitochondrial mutation. Further investigations will be necessary to explore the mechanism and prognosis of FGS accompanied by mitochondrial abnormality.

In conclusion, we report a 21-year-old male with FGS accompanied by mitochondrial DNA mutation required intermittent haemodialysis treatment despite a close follow-up for 8 years and intensive immunosuppressive treatment regimens. Serial renal biopsies revealed glomerulosclerosis expanding from the glomerular vascular pole, and electron microscopic analysis showed abnormal mitochondria in the smooth muscle cells of the arteriole of the pole. This observation suggests that pathological changes of the vascular pole may be associated with FGS formation in patients with abnormal mitochondria.

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1. Van Biervliet JBGM, Bruinvis L, Ketting D et al. Hereditary mitochondrial myopathy with lactate acidemia, a de-Toni-Debre-Fanconi syndrome and a defective respiratory


