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CASE REPORT

Chronic kidney disease caused by maternally inherited diabetes and deafness: a case report

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Abstract

Maternally inherited diabetes and deafness (MIDD) is a mitochondrial genetic disorder with variable clinical presentations, which can delay its diagnosis. Herein, we report the case of a 57-year-old Japanese man with MIDD who developed chronic kidney disease. He developed proteinuria long before his diabetes and deafness; at the age of 36 years, a renal biopsy showed minor glomerular abnormality and electron microscopy showed mild mitochondrial degeneration in the distal tubular epithelial cells. Twenty years later, a second renal biopsy showed nephrosclerosis with interstitial fibrosis and arteriolar hyaline thickening, despite the absence of hypertension and relatively good glycemic control. Granular swollen epithelial cells were found in the medullary collecting duct epithelium. Electron microscopy showed accumulating mitochondria in podocytes and tubular cells, leading to the diagnosis of MIDD. A muscle biopsy also showed ragged-red fibers, despite the absence of muscle weakness. Mitochondrial DNA analysis revealed an m.3243A > G mutation, and taurine supplementation was initiated. Our findings suggest that mitochondrial dysfunction is mainly associated with progressive renal damage.

Keywords Maternally inherited diabetes and deafness · Mitochondrial disease · Chronic kidney disease

Introduction

Maternally inherited diabetes and deafness (MIDD) is a mitochondrial genetic disorder characterized by type 2 diabetes mellitus (DM) and hearing impairment. Abnormality in the mitochondrial (mt) DNA causes MIDD caused by defects in oxidative energy production. MIDD has variable clinical presentations, which can delay its diagnosis [1]. The m.3243A > G mutation in the mt $tRNA^{Leu(UUR)}$ gene is the most common mutation found in MIDD, but this mutation is also found in mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome [2].

Mitochondria are abundant in the kidney, especially in proximal tubules and glomerular epithelial cells [3]; mitochondrial dysfunction can cause renal damage. Renal diseases associated with mitochondrial cytopathy include focal segmental glomerulosclerosis (FSGS) and tubulointerstitial nephropathy [4, 5]. Such complications lead to the progression of chronic kidney disease (CKD) and end-stage kidney disease, which require renal replacement therapy [6, 7]. However, the mechanisms that underlie kidney heterogeneity and CKD progression in patients with mitochondrial disease are not well understood.

Here we report a case of MIDD in a 57-year-old man with a m.3243 A > G mutation, who developed CKD. For this patient, two renal biopsies were conducted 20 years apart to confirm the progression of renal damage. A muscle biopsy also showed subclinical myopathy.

Case report

A 57-year-old Japanese man was referred to our Nephrology Department by his primary physician with gradually

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progressive renal dysfunction and proteinuria. He was born at the term of a normal pregnancy from nonconsanguineous parents. Since age 22, mild urine protein from ± to 1 + (dipstick test) had been noted in his general health checkups. His first renal biopsy was performed at 36 years of age. Light microscopy of that specimen revealed 12 glomeruli, with no global sclerosis; two showed mildly increased mesangial matrix, and the others were almost intact (Fig. 1a). In the interstitium, fibrosis comprised less than 5% of the area and no infiltration cells were seen. IgG, IgA, IgM, C3, C4, and C1q were not detected with immunofluorescence. Electron microscopy showed that some mitochondria in the distal tubular epithelial cells had cristae that had lost their normal structures (Fig. 1b). Diagnosis of mitochondrial disease was difficult at this point. Treatment with angiotensin-converting-enzyme inhibitor was initiated.

The patient's primary physician followed the man's progress over the next two decades (Fig. 2). In a medical checkup at 40 years of age, he was found to have type 2 DM and bilateral sensorineural hearing loss. Five years later, medication for DM was started and he was using a hearing aid. Thereafter, serum hemoglobin A1c (HbA1c) levels remained in the range of 6–8%. Urine protein had increased from − to 2 +, and renal function gradually decreased. He had no symptoms of myopathy or encephalopathy and no history of stroke-like episodes. His mother had received hemodialysis for end-stage renal disease (etiology unknown) and his younger brother was suffering from hearing loss and renal dysfunction (Fig. 3), although no family member had undergone genetic examination. His current medications were glimepiride, saxagliptin, metformin, enalapril, and pravastatin. He had a history of smoking 20 cigarettes per day for 10 years before quitting at the age of 27.

On physical examination, his height was 160 cm, weight 47.8 kg, and BMI 18.6 kg/m^2. His blood pressure was 136/85 mmHg. He showed no peripheral edema or muscle weakness in his extremities. An ophthalmologic examination detected neither diabetic retinopathy nor hypertensive retinopathy. Electrocardiogram and echocardiogram were within normal limits. Laboratory data obtained from the patient on admission (Table 1) showed elevated serum creatinine levels (1.10 mg/dL) with an estimated glomerular filtration rate of

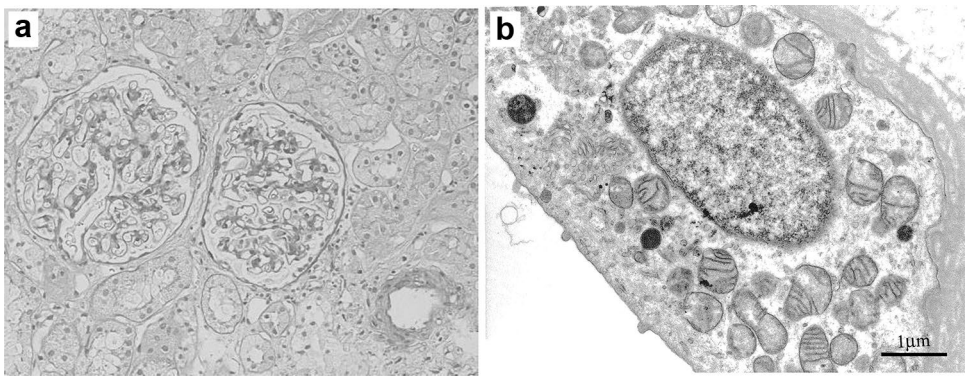

Fig. 1 Initial renal biopsy findings taken at 36 years of age. **a** Light microscopy shows most glomeruli were intact (periodic acid-Schiff stain, ×200). **b** Electron microscopy shows some mitochondria in distal tubular epithelial cells had cristae that had lost normal structures

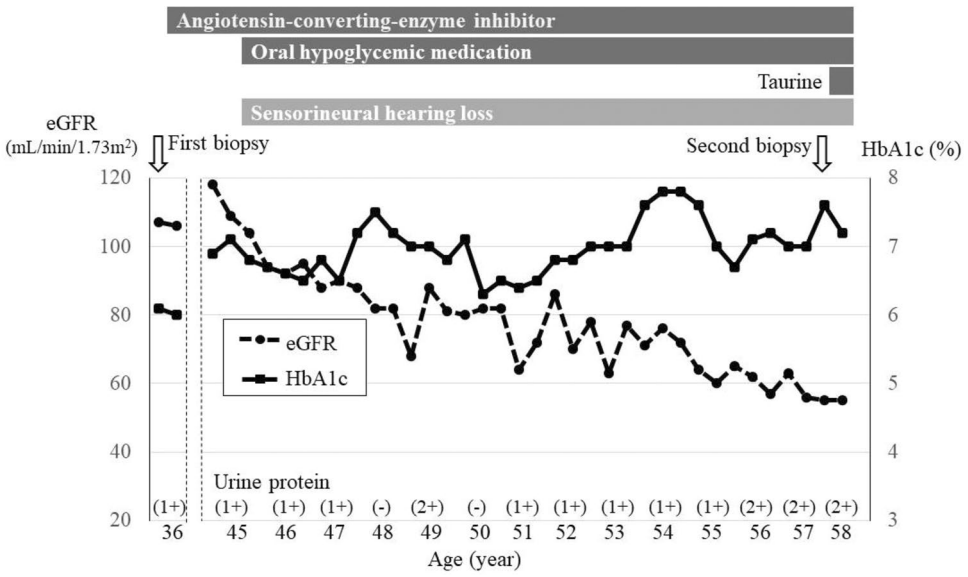

Fig. 2 Clinical course. Serum HbA1c levels remained in the 6–8% range; however, urine protein was 1 + –2 +, and renal function gradually decreased. *eGFR* estimated glomerular filtration rate, *HbA1c* hemoglobin A1c

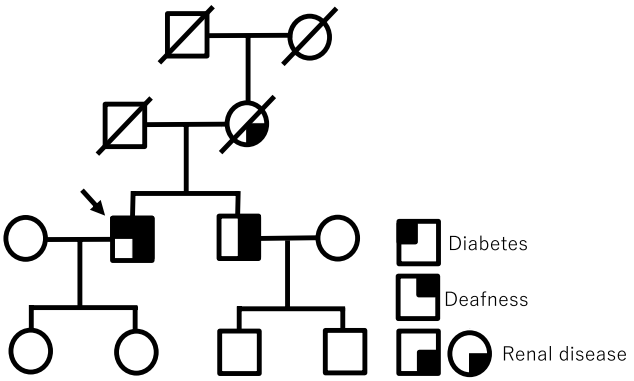

Fig. 3 Family tree. Arrow indicates the patient described in this report. His mother had received hemodialysis for the end-stage renal disease of unknown etiology, while his younger brother exhibited hearing loss and renal dysfunction

55 ml/min/1.73 m^2. Proteinuria was observed at 0.64 g per gram of creatinine (g/gCre); no hematuria was detected (1–4 red blood cells/high-power field). Notable serum levels were HbA1c: 7.2%; lactic acid: 18.0 mg/dL (normal, 3.7–16.3 mg/dL); pyruvic acid: 0.93 mg/dL (normal, 0.3–0.9 mg/dL), and lactic acid/pyruvic acid ratio: 19 (normal, < 10).

A second renal biopsy was performed because hereditary kidney disease was suspected from his family history. Light microscopy revealed 4 glomeruli, all of which showed global glomerulosclerosis. In the interstitium, chronic fibrosis was observed over almost 40% of the area. Local chronic inflammatory cell infiltration and dilated tubules that contained proteinaceous material were also observed (Fig. 4a, b). The artery and arterioles showed moderate fibrous intimal thickening and hyalinization with enlarged vascular smooth muscle cells (Fig. 4c). Granular swollen epithelial cells (GSEC)—which are reportedly a specific change associated with mitochondrial cytopathy [8]—were found in the medullary collecting duct epithelium (Fig. 4d). As with his first renal biopsy, IgG, IgA, IgM, C3, C4, and C1q were not detected with immunofluorescence. Electron microscopy showed moderate foot process effacement. Accumulating mitochondria were observed in the cytoplasm of some podocytes (Fig. 4e) and proximal tubular cells (Fig. 4f), a portion of which were enlarged.

Based on these findings, the mitochondrial disease was suspected, and a muscle biopsy was performed from his bicep. Modified Gomori trichrome stain showed ragged-red fibers (Fig. 5a). Ragged-red fibers that are positive for succinate dehydrogenase (SDH) stain indicate deficient fiber activity on cytochrome c oxidase stain; strongly SDH-reactive blood vessels were observed (Fig. 5b). These findings were consistent with mitochondrial dysfunction. A subsequent genetic test from the muscle specimen revealed a mitochondrial gene with a m.3243A > G mutation, with 69.9% heteroplasmy. Thus, the diagnosis of MIDD was considered

Table 1 Laboratory data for blood and urine on admission

Blood test		Sodium	143 mEq/L	ANA	–
WBC	5300/mL	Potassium	4.9 mEq/L	PR3-ANCA	–
RBC	4.4×10^4/mL	Chloride	107 mEq/L	MPO-ANCA	–
Hemoglobin	11.9 g/dL	Calcium	8.8 mg/dL	ASO	–
Platelet	17.7×10^4/mL	Phosphorus	2.6 mg/dL	ASK	–
PT-INR	0.9	LDL-cho	79 mg/dL	HBs antigen	–
APTT	26.5 s	Hemoglobin A1c	7.2%	HCV antibody	–
Total protein	6.7 g/dL	CRP	0.78 mg/dL	Urinalysis	
Albumin	4.2 g/dL	IgG	780 mg/dL	pH	5.5
AST	18 U/L	IgA	200 mg/dL	Gravity	1.024
ALT	17 U/L	IgM	77 mg/dL	Protein	0.64 g/gCre
LDH	158 U/L	Complement 3	122 mg/dL	Sugar	–
ALP	353 U/L	Complement 4	32.1 mg/dL	RBC	1–4/HPF
CK	80 U/L	CH50	48 U/mL	WBC	1–4/HPF
BUN	16.8 mg/dL	Lactic acid	18.0 mg/dL	β2-MG	84 mg/L
Creatinine	1.1 mg/dL	Pyruvic acid	0.93 mg/dL	NAG	5.5 U/L
Uric acid	6.2 mg/dL	L/P ratio	19	BJP	–

WBC white blood cells, *RBC* red blood cells, *PT-INR* prothrombin time international normalized ratio, *APTT* activated partial thromboplastin time, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *CK* creatine kinase, *BUN* blood urea nitrogen, *LDL-cho* low-density lipoprotein cholesterol, *CRP* C-reactive protein, *Ig* immunoglobulin, *CH50* 50% hemolytic complement activity, *L/P* Lactic acid / Pyruvic acid, *ANA* antinuclear antibody, *PR3-ANCA* proteinase 3-anti-neutrophil cytoplasmic antibody, *MPO* myeloperoxidase, *ASO* antistreptolysin-O, *ASK* antistreptokinase, *HBs* hepatitis B surface, *HCV* hepatitis C virus, *Ccr* creatinine clearance, *HPF* high-power field, *MG* microglobulin, *NAG* N-acetylglutamate, *BJP* Bence Jones protein

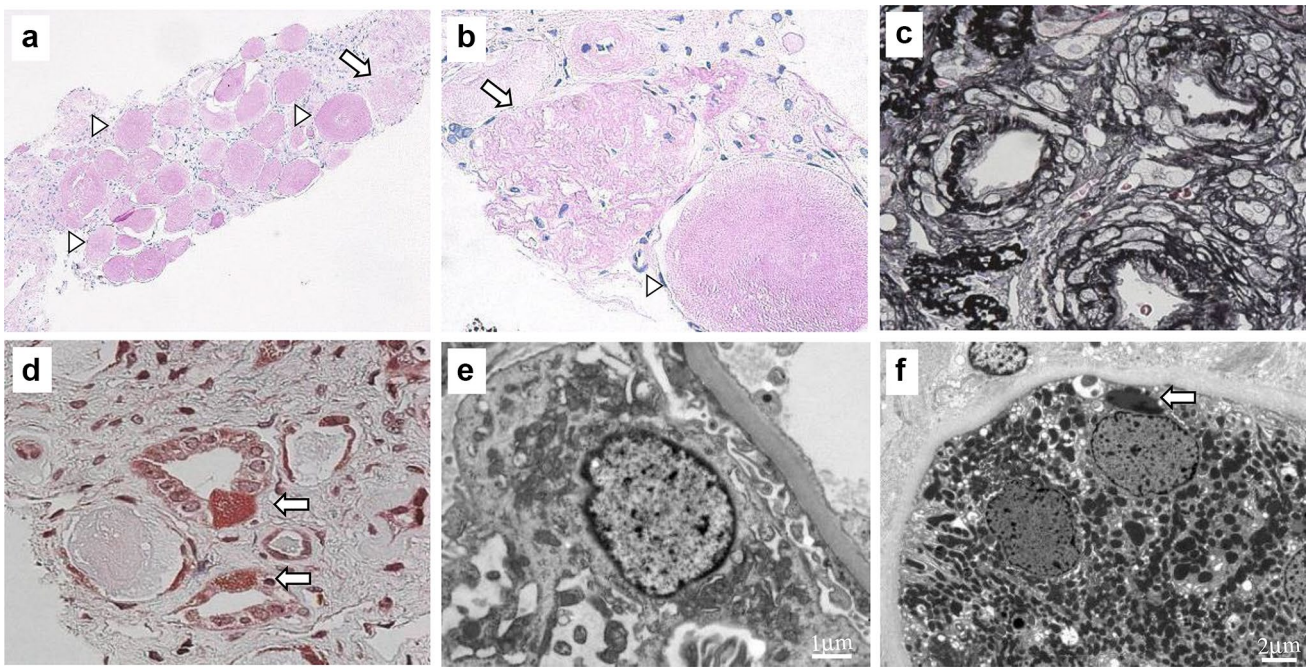

Fig. 4 Renal biopsy findings at 57 years of age. **a**, **b** Light microscopy shows global glomerulosclerosis (arrows), local chronic inflammatory cell infiltration and dilated tubules that contain proteinaceous material (arrowheads, periodic-acid-Schiff stain, **a**: × 40, **b**: × 200). **c** Vascular smooth muscle cells are enlarged (periodic acid silver-methenamine stain, × 400). **d** Granular swollen epithelial cells in medulla collecting duct epithelium (arrows, Masson-trichrome stain, × 400). Electron microscopy shows accumulated mitochondria in cytoplasm of some podocytes (**e**) and proximal tubular cells (**f**), some of which were enlarged (arrow)

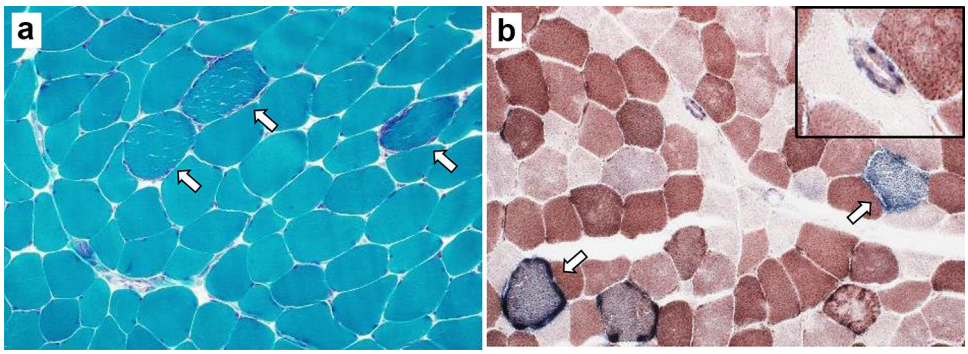

Fig. 5 Light microscopy of muscle biopsy. **a** Ragged-red fibers on modified Gomori trichrome stain (arrows, × 100). **b** Ragged-red fibers positive for succinate dehydrogenase (SDH) stain (blue) showed deficient fiber activity on cytochrome c oxidase stain (brown) (arrows, × 100). Strongly SDH-reactive blood vessel was highlighted (upper panel)

to be unequivocal. Oral taurine supplementation (12 g/day) was initiated. One year later, his renal function has remained unchanged with no apparent side effects.

Discussion

In this patient, proteinuria appeared prior to diabetes or deafness, making an early diagnosis of MIDD difficult. Pathological findings progressed to nephrosclerosis with interstitial fibrosis and arteriolar hyaline thickening over 20 years, despite the absence of hypertension or diabetic retinopathy, and relatively good glycemic control. Although we could not find any FSGS lesions in the glomeruli, accumulating mitochondria were seen in podocytes and tubular cells by electron microscopy. GSECs were found in the medulla collecting duct epithelium, which indicated mitochondrial cytopathy. In contrast, no pathological manifestations typical of diabetic nephropathy (e.g., glomeruli with nodules or hyalinotic lesions) were found. These observations implied that mitochondrial cytopathy is mainly associated with CKD progression, rather than diabetic nephropathy.

CKD has been reported previously in patients with MIDD [4, 5]. Although the long course of DM appears to have a major impact on renal damage, renal manifestations in patients with MIDD are not always the consequences of diabetic nephropathy [9]. Acquired mitochondrial dysfunction is reportedly associated with progression

of CKD [10, 11] and atherosclerosis [12]. The extent to which mitochondrial cytopathy is associated with the development of CKD in patients with MIDD is unclear. However, impairment of oxidative phosphorylation in podocytes and tubular cells can result in overgeneration of reactive oxygen species and in functional and structural alterations, resulting in proteinuria, tubular dysfunction and ultimately, development of glomerular sclerosis and interstitial impairment [3, 13, 14].

Clinical characteristics related to MIDD include early-onset DM with short stature, a normal or low BMI, and hearing loss that occurs at about the same time as the onset of DM [9, 15], as seen in this case. As the clinical manifestation depends on threshold levels of the mitochondrial mutation in each organ [2], patients with MIDD develop other mitochondria-related complications [15]. Our patient had no symptoms of a cardiac disorder or the neurological phenotype of MELAS syndrome, but his muscle biopsy showed ragged-red fibers despite the absence of muscle weakness. Although the clinical manifestations of mitochondrial diseases differ among individuals, histological changes due to mitochondrial abnormality may occur in some organs, even if no subjective symptoms are seen.

Treatment to prevent MIDD complications has not been established. Coenzyme Q_{10} therapy was reported to prevent progressive hearing loss and improve insulin secretory defect in patients with MIDD [16]. However, taurine modifies the first anticodon nucleotide mt $tRNA^{Leu(UUR)}$ [17] in normal humans, and taurine modification was absent in mt $tRNA^{Leu(UUR)}$ of cells derived from MELAS patients with the m.3243A > G mutation [18]. A recent multicenter, open-label trial in Japan showed that oral taurine supplementation can effectively reduce the recurrence of stroke-like episodes and increase taurine modification in mt $tRNA^{Leu(UUR)}$ in MERAS [19]. Taurine is expected to serve as a therapeutic drug for various organ disorders caused by mitochondrial diseases with m.3243A > G mutations. In this case, we initiated oral taurine supplementation in addition to renin-angiotensin system blockade therapy, to prevent exacerbating MIDD-related symptoms and CKD progression. Careful follow-up is required.

In conclusion, the findings from the present case suggest that mitochondrial cytopathy due to MIDD may be associated with progressive CKD. If kidney disease associated with mitochondrial cytopathy is suspected from the clinical course, a proactive renal biopsy may lead to satisfactory diagnosis and treatment.

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Compliance with ethical standards

Conflicts of interest The authors have declared that no Conflict of interest exists.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from the patient whose case is reported in this paper.

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