Mitochondrial disease can be caused by defects in either mitochondrial or nuclear DNA, but mtDNA mutations are the most common cause in adult. Among these mutations, m.3243A>G mutation (MTTL) was first identified in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome. The mutation is located in the gene encoding tRNA^{Leu} and results in impaired protein synthesis and electron transport chain dysfunction. Cardiomyopathy is seen in 40% of the symptomatic individuals, usually left ventricular hypertrophy with hypokinesis, which however is often overlooked when the patients show few phenotypes typical for mitochondrial disease.

The patient (case 1) was a 60-year-old man admitted to Nara Medical University Hospital because of dyspnea due to congestive heart failure. He had hypertension and diabetes mellitus for nearly 10 years and had been hard of hearing for 2 years. His mother also had diabetes mellitus and was diagnosed with an A-to-G transition at position 3243 of her mtDNA (m.3243A>G). Echocardiographic examination of the patient revealed diffuse hypertrophy and hypofunction of the left ventricle. Left heart catheterization showed no significant coronary artery disease. Endomyocardial biopsy showed marked vacuolar degeneration of the cardiomyocytes (Figure 1). Electron microscopic examination of the biopsy specimen by one of the authors (G.T. at Gifu University) revealed mitochondrial abnormalities that included a marked increase in mitochondrial or nuclear DNA, but mtDNA mutations were nearly overlooked because of the less typical phenotype. Genetic analysis performed by the staff of Niigata University Hospital revealed that the same mtDNA abnormality seen in case 1 was also present in case 2, that is, m.3243A>G.

In the present cases, we first observed ultrastructural alteration of the mitochondria in an endomyocardial biopsy of case 1 who presented a relatively typical phenotype of mitochondrial disease (deafness, diabetes mellitus, and the family history). Six years later, we found similarly altered mitochondrial ultrastructure in case 2, in whom mitochondrial disease was nearly overlooked because of the less typical phenotype (diabetes mellitus only). Vacular degeneration of cardiomyocytes is one of the characteristic pathological features of mitochondrial cardiomyopathy when visualized under a light microscope. However, routine light microscopic examination cannot reveal precise mitochondrial structure. In case 2, the electron microscopic findings, which closely resembled the mitochondrial phenotype in case 1, were a critical clue for diagnosis of mitochondrial disease. Morphological alterations of the mitochondria in cardiomyopathy with mt.3243A>G or other mutations have been described as case reports but have not been characterized in a systemic manner. We speculate that there is a morphological phenotype specific for each mtDNA genotype, which warrants future investigation. In addition, we
recommend collecting a tissue sample for electron microscopy during endomyocardial biopsy procedures.

Disclosures

None.

References


Key Words: cardiomyopathy ■ diabetes mellitus ■ heart failure ■ phenotype

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**Figure 1.** Light micrographs showing hematoxylin-eosin-stained endomyocardial biopsy specimens from case 1 (left) and case 2 (right). Vacuolar degeneration of the cardiomyocytes is conspicuous in both cases. Scale bars, 20 μm.
Figure 2. Electron micrographs of endomyocardial biopsy specimens from case 1 (left panels: 1A to 1C) and case 2 (right: 2A to 2C). 1A and 2A, Frequent dropout of mitochondria in the presence of mitochondriosis. 1B and 2B, Partially degenerated cristae. 1C and 2C, Irregular and shrunken cristae. A close resemblance is noted between the 2 cases. Scale bars, 1 μm in 1A and 2A; 200 nm in 1B, 1C, 2B, and 2C.
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