Hypertrophic Cardiomyopathy Attributable to Mitochondrial DNA Mutation Diagnosed by Pathology and Gene Sequencing

Young Choi, MD; Jeong-Hwa Lee, MD, PhD; Mei Nu Cui, MD; Young Su Lee, MD; Mi-Hyang Jung, MD; Jeong-Eun Yi, MD; Hae Ok Jung, MD, PhD; Ho-Joong Youn, MD, PhD

A 46-year-old man presented with exertional dyspnea that had gradually progressed for 2 years. He had a 10-year history of hearing impairment. There was no other medical history including hypertension, diabetes mellitus, coronary artery disease, or arrhythmia. On admission to our hospital, vital signs and physical examination results were nonspecific. Serum lactic acid, creatine kinase-MB, troponin T, and N-terminal probrain natriuretic peptide were elevated to 32.2 mg/dL, 11.37 ng/mL, 2.287 ng/mL, and 2404 pg/mL, respectively. A transthoracic echocardiogram demonstrated severe concentric left ventricular hypertrophy (septal wall thickness of 15 mm, left ventricle posterior wall thickness of 15 mm, relative wall thickness of 0.55, and left ventricular mass index of 261.9 g/m²) with a diffusely speckled pattern of the myocardium (Figure 1A and 1B). Global hypokinesia of the left ventricle was evident, with an ejection fraction of 36%. Right ventricular hypertrophy and decreased systolic function were also noted (right ventricle free wall thickness, 8 mm; tricuspid annular plane systolic excursion, 14 mm). Coronary angiography showed normal coronary arteries. Cardiac MRI demonstrated diffuse biventricular hypertrophy and decreased left ventricle systolic function. T2-weighted imaging revealed focal increased signal in the midventricle and apex of the left ventricle. Late gadolinium enhancement imaging revealed focal increased signal in the midventricle and apex of the left ventricle. T2-weighted imaging revealed hyperplasia of mitochondria with variable size and shapes. Mitochondrial swelling and abnormal cristae were also noted (Figure 2). These findings suggested that the underlying mitochondrial disease had resulted in hypertrophic cardiomyopathy. Sequencing of mitochondrial DNA from leukocytes collected from the peripheral blood showed mutation m.3243A>G in the MT-TL1 gene (Figure 3), confirming the diagnosis of mitochondrial cardiomyopathy. We prescribed angiotensin II receptor blocker, diuretics, vitamin, and the antioxidant drugs. Exertional dyspnea gradually resolved and he was followed up in the outpatient clinic. However, he died after 6 months from the diagnosis because of acute refractory heart failure.

Mitochondrial myopathy is a diagnosis of a heterogeneous group of multisystemic diseases. The prevalence is estimated to be >1 in 5000 births. Mitochondrial dysfunction that develops consequent to the mutation in the nuclear or mitochondrial DNA causes impairment of energy production. Tissues with high-energy demands, such as brain, heart, and skeletal muscle, are usually more susceptible and severely affected in mitochondrial disorders. The most common cardiac presentation is hypertrophic cardiomyopathy, but variable manifestations can include heart failure, arrhythmia, left ventricular myocardial noncompaction, and sudden death. The most common pathogenic mitochondrial tRNA mutations related to cardiomyopathy are m.3243A>G, m.4300A>G, and m.8344A>G. Muscle biopsy is considered to be the gold standard for the diagnosis of mitochondrial disease. Light microscopy with modified Gomori trichrome stain would show ragged red fibers arising from the subsarcolemmal accumulation of mitochondria. Electron microscopy can reveal subsarcolemmal, enlarged, and swollen mitochondria with irregular cristae and paracrystalline inclusions. Presently, we do not perform modified Gomori trichrome stain from endomyocardium. However, this case met 2 of the previously proposed major diagnostic criteria, allowing the definite diagnosis of mitochondrial disease. There is still no cure for mitochondrial disease, and the mainstay of management is standard heart failure treatment with various dietary supplements of antioxidants. However, there is no clear evidence of the efficacy of these treatments.

In conclusion, mitochondrial disease has a diverse presentation, and the diagnosis of mitochondrial cardiomyopathy can be easily overlooked if there is no suspicion. Considering mitochondrial disease as a differential diagnosis is important when evaluating unexplained hypertrophic cardiomyopathy.
Disclosures

None.

References


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**Figure 1.** Transthoracic echocardiogram and cardiac MRI. Two-dimensional echocardiogram in parasternal long axis (A) and parasternal short axis (B) showed concentric LV hypertrophy with a diffusely speckled pattern of the myocardium. Late gadolinium enhancement cardiac MRI revealed multifocal and curvilinear patchy enhancement in the subepicardial and midmyocardial layers on the long axis (C) and short axis (D), denoted by the white arrows. LV indicates left ventricle.

**Figure 2.** Endomyocardial biopsy findings. A, Light microscopy demonstrated cardiomyocyte hypertrophy and perinuclear vacuolization (black arrows; hematoxylin and eosin, x40 original magnification). B, Electron microscopy revealed proliferation of polymorphic mitochondria causing displacement of myofibrils (x10000). C, Electron microscopy images of variable-sized swollen mitochondria with abnormal cristae (x20000).
**Figure 3.** Sequencing chromatogram of mitochondrial DNA mutation of leukocytes. **Top,** Shows the wild-type nucleotide G at the position 3243 in the *MT-TL1* gene. **Bottom,** Shows the heteroplasmic mutant allele A.
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