Severe obstructive hypertrophic cardiomyopathy occurring secondary to mitochondrial disease

Mitokondri hastalığına bağlı ciddi tıkayıcı hipertrofik kardiyomiyopati

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Mitochondrial disorders have been recognized as important secondary causes of cardiomyopathies. Differentiation of these cases from primary cardiomyopathies is important since the pathogenesis, accompanying systemic manifestations, and prognosis may be different. The typical cardiac manifestation of mitochondrial disorders is hypertrophic cardiomyopathy. We report on an 11-year-old girl with severe obstructive hypertrophic cardiomyopathy and mild myopathy of the lower extremities. Surgical left ventricular septal myectomy was performed and ragged red fibers typical of mitochondrial disorders were detected on histological examination of the resected myocardial sample. Subsequent electron microscopic examination revealed ultrastructurally abnormal mitochondria in the skeletal muscle biopsy, though respiratory chain enzyme analysis was normal. Cardiomyopathy may be the presenting or the sole manifestation of a mitochondrial disorder. Nonobstructive hypertrophic cardiomyopathy has been considered to be the typical cardiac phenotype of mitochondrial disorders, and cases with left ventricular outflow tract obstruction have only rarely been reported.

Key words: Cardiomyopathy, hypertrophic/etiology; child; echocardiography; ventricular outflow obstruction/pathology; mitochondrial diseases/complications.

Mitokondri bozuklukları ikincil kardiyomiyopatilerin önemli nedenlerindendir. Patogenez, eşlik eden sistemik belirtiler ve prognozun farklı olabilmesi nedeniyle, mitokondri bozukluğuna bağlı kardiyomiyopatilerin birincil kardiyomiyopatilerden ayrımı önemlidir. Mitokondri bozukluklarının tipik kardiyak belirtisi hipertrofik kadiyomiyopatidir. Bu yazıda, ciddi tıkayıcı hipertrofik kardiyomiyopati ve alt ekstremitelerde hafif miyopati saptanan 11 yaşında bir kız hasta sunuldu. Hastaya cerrahi olarak sol ventrikül septal miyektomisi uygulandı ve çıkarılan miyokart örneğinin histolojik incelenmesinde mitokondri bozukluğu için tipik olan kırmızı düzensiz fibriller gözlendi. Takiben, iskelet kası biyopsisinin elektron mikroskobisi ile değerlendirilmesinde ultrayapısal olarak anormal mitokondriler saptandı; respiratuvar zincir enzim analizi ise normal bulundu. Kardiyomiyopati, mitokondri bozukluklarının başvuru ve hatta tek belirtisi olabilir. Tıkayıcı olmayan hipertrofik kardiyomiyopati mitokondri bozukluklarının tipik kardiyak fenotipi olarak sayılagelmiştir; bu bozukluklarda sol ventrikül çıkım yolunda darlık olan olgular nadiren bildirilmiştir.

Anahtar sözcükler: Kardiyomiyopati, hipertrofik/etyoloji; çocuk; ekokardiyografi; ventrikül çıkış yolu tıkanıklığı/patoloji; mitokondri hastalığı/komplikasyon.

Hypertrophic cardiomyopathy primarily occurs due to sarcomere protein gene mutations; however, on rarer instances, it may occur secondary to several genetic and metabolic disorders.[1] Mitochondrial disorders which affect the energy metabolism and free radical production have been recognized as important secondary causes of cardiomyopathies.[2,3] We describe a young girl who presented with obstructive hypertrophic cardiomyopathy occurring secondary to mitochondrial cytopathy.

CASE REPORT

An 11-year-old girl was brought to the Cardiology Department of Kartal Koşuyolu Heart and Research Hospital for evaluation of a cardiac murmur and decreased effort capacity. She had developmental delay

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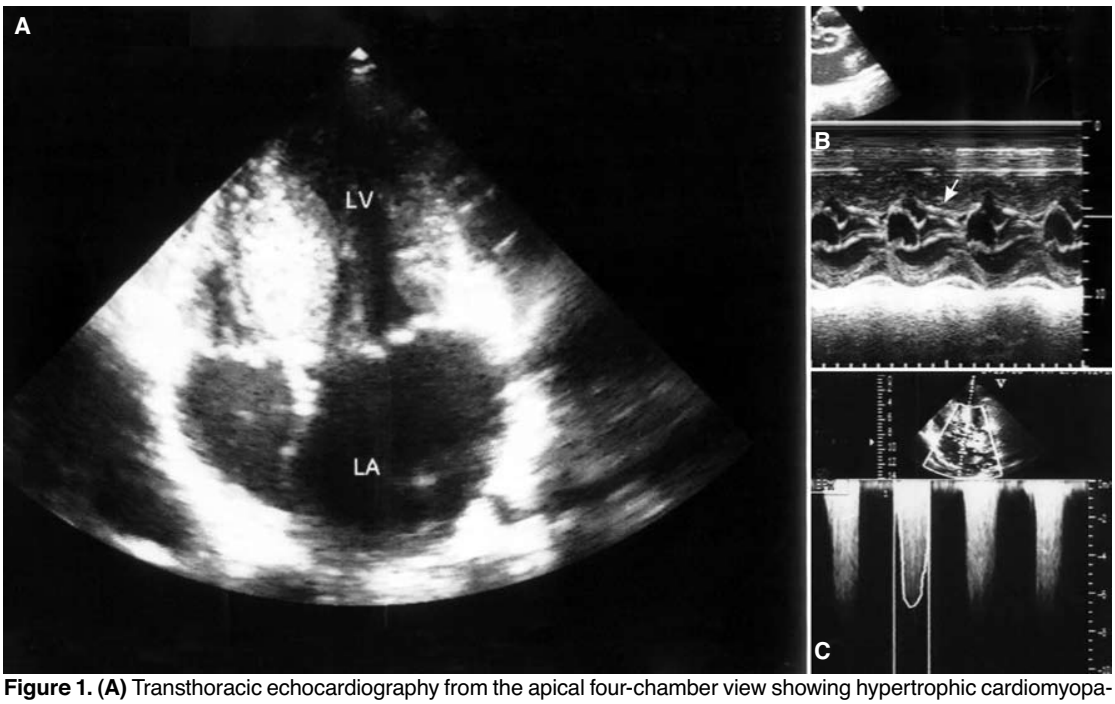

Figure 1. (A) Transthoracic echocardiography from the apical four-chamber view showing hypertrophic cardiomyopathy. **(B)** M-mode parasternal long-axis view at the mitral valve level showing septal hypertrophy and systolic anterior motion of the mitral leaflets (arrow) causing outflow tract obstruction. **(C)** A peak velocity of 6.7 m/sec and a mean of 110 mmHg gradient were detected at the outflow tract with Doppler echocardiography. LA: Left atrium; LV: Left ventricle.

and had started walking only four years before. She was alert and her mental status was normal. Growth retardation was apparent; weight and height for age were both below the third percentile. The muscles of the lower extremities were slightly atrophic and weak. Cardiac examination revealed a harsh crescendo-decrescendo systolic murmur with a prominent S_4 at the apical region. Electrocardiography showed high voltage and secondary ST changes in the lateral leads that were suggestive of left ventricular hypertrophy. Echocardiographic examination revealed hypertrophic cardiomyopathy (Fig. 1a) with left ventricular outflow tract (LVOT) obstruction, mainly involving the septal, anteroseptal, and anterior segments. Mitral valves were elongated and typically displayed anterior motion during systole (Fig. 1b). Severe LVOT obstruction (mean 110 mmHg pressure gradient) (Fig. 1c) and severe mitral regurgitation were detected by Doppler echocardiography. Left ventricular systolic function was normal. A family history of cardiomyopathy was not reported and echocardiographic examinations of the parents were normal.

The patient underwent septal myectomy to relieve the obstruction. The mean LVOT gradient dropped to 10 mmHg postoperatively. Histologic examination of the resected heart muscle with modified Gomori trichrome stain revealed ragged red appearance of cardiomyocytes, typical of a mitochondrial disorder (Fig. 2). Cardiomyocyte disarray, a characteristic of sarcomeric hypertrophic cardiomyopathy that is expected to be absent in secondary forms of hypertrophic cardiomyopathy,[1] was not evident. Immunostaining of the samples for succinate dehydrogenase and cytochrome c oxidase was negative. After the detection of ragged red fibers that were highly suggestive of a mitochondrial disorder, the

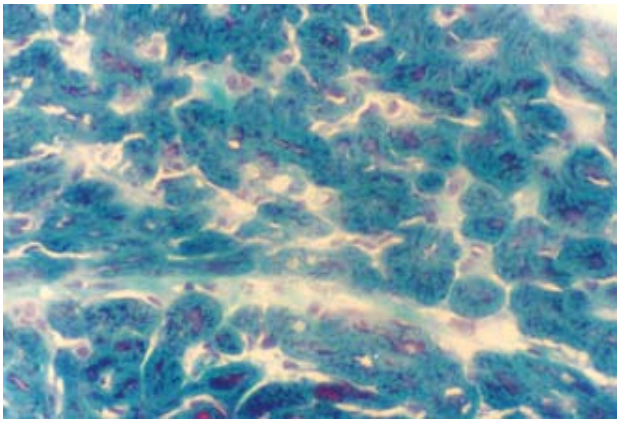

Figure 2. Modified Gomori trichrome stain of the myocardial sample showing ragged red appearance of cardiomyocytes. Intracellular red-purple staining areas represent abnormal mitochondrial aggregates causing the typical ragged red appearance of mitochondrial cytopathy (x400).

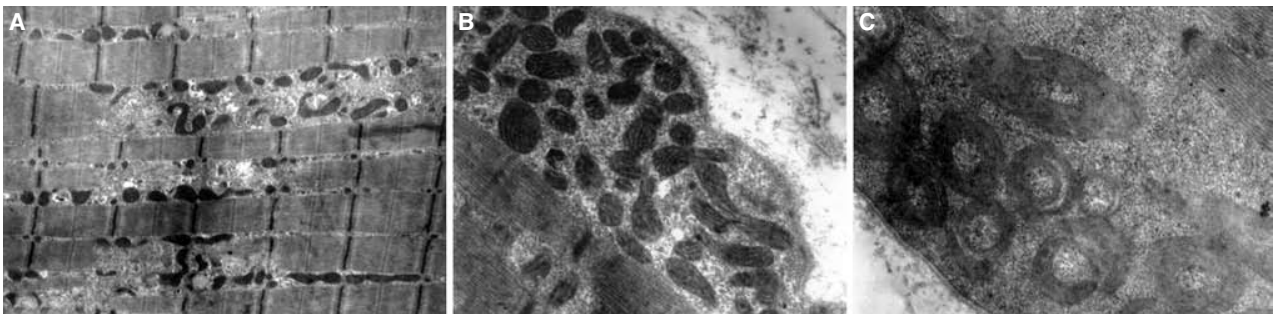

Figure 3. Electron micrographs of skeletal muscle showing typical ultrastructural abnormalities of mitochondrial cytopathy: **(A)** abnormal, disarrayed, pleomorphic mitochondria filling the intermyofibrillar space (x4500); **(B)** subsarcolemmal mitochondrial aggregates (x9500); **(C)** spheric abnormal mitochondria with concentric cristae (x9500).

patient was examined further for other manifestations of mitochondrial diseases. She did not have lactic acidosis (lactic acid 12.9 mg/dl, normal range 5-22 mg/dl; pyruvate 0.6 mg/dl, normal range 0.3-1 mg/dl). Neurological examination was normal except for the myopathic involvement of the lower extremities. There was no history of an encephalomyopathy attack or coma and findings of cranial magnetic resonance imaging were normal. Ophthalmologic and audiologic examination excluded ophthalmoplegia, optic neuropathy, cataract, and hearing loss. Sequence analysis of the entire mitochondrial DNA obtained from the myocardial sample showed no known mutations. The myocardial sample was inappropriate for a detailed mitochondrial enzyme and ultrastructural analysis. Informed consent was obtained and a skeletal muscle biopsy was performed from the affected calf muscle. Ultrastructural analysis of the skeletal muscle revealed abnormal mitochondria located in the intermyofibrillar and subsarcolemmal areas (Fig. 3). In spectrophotometric analysis, activity of all the respiratory chain enzyme complexes and their ratios were normal to slightly increased. The patient was diagnosed as having mitochondrial cytopathy primarily affecting the skeletal and cardiac muscle; however, the precise biochemical and genetic defect could not be defined. The patient was well after two years from her first diagnosis; recurrence of the obstruction or impairment of left ventricular systolic function did not occur.

DISCUSSION

The major function of the mitochondria is to generate cellular energy in the form of ATP through oxidative phosphorylation. Oxidative phosphorylation is mediated by five enzyme complexes of the electron transport chain embedded in the inner mitochondrial membrane; several subunits of these enzyme complexes are encoded by the mitochondrial DNA and others by the nuclear DNA.[2] Mitochondrial diseases are a heterogeneous group of clinical disorders caused by mitochondrial or nuclear DNA mutations that impair enzyme complexes of oxidative phosphorylation or mitochondrial transmembrane transporter proteins, resulting in decreased energy production.[2,4,5] Multisystemic involvement is typical and central nervous system, heart and skeletal muscle are the most commonly involved organs, generally in a syndromic fashion.[4] Isolated organ involvement may also occur.[4] Mitochondrial disorders may manifest at any age from infancy to elderly.[4] The typical cardiac manifestation of mitochondrial cytopathies is cardiomyopathy; atrioventricular conduction abnormalities may also occur and are typical of Kearns-Sayer syndrome.[4]

Cardiomyopathic involvement in the course of mitochondrial cytopathy may accompany or precede other organ involvement[6] or mitochondrial defect may be confined to the heart without extracardiac involvement.[3] Cardiomyopathy occurs in 25-40% of patients with mitochondrial diseases and usually dominates the clinical picture.[6-8] Nonobstructive hypertrophic cardiomyopathy is considered the typical cardiac phenotype of mitochondrial cytopathies.[6,7] Interestingly, in contrast to patients with primary hypertrophic cardiomyopathy, LVOT obstruction is a very rare finding in these patients.[7] Dilated cardiomyopathy phenotype is also common and is assumed to reflect terminal dilatation of the hypertrophic ventricle.[7,8] Left ventricular noncompaction is another cardiac presentation.[8] There is no specific imaging characteristic to aid differentiation of cardiomyopathy occurring secondarily to mitochondrial diseases, which is phenotypically indistinguishable from primary cardiomyopathies. While multisystemic involvement accompanying cardiomyopathy may be a clue for a mitochondrial disease, mitochondrial disorders confined only to the heart have been increasingly reported.[3,8] Mitochondrial cardiomyopathies generally have a poor prognosis especially when they occur earlier, dur-

ing infancy, and when they are caused by cytochrome c oxidase deficiency.[6,8] Arrhythmic and sudden cardiac death do not appear to be the major concern in these cases, but most cases are lost due to abrupt transition of hypertrophic cardiomyopathy to dilated cardiomyopathy phenotype and progressive circulatory failure.[3,6,8] Unfortunately, other than supportive measures, at present, there is no specific treatment for mitochondrial diseases or their cardiac involvement. However, successful cardiac transplantation has been reported in patients with mitochondrial cytopathy when cardiac involvement is predominant or isolated.[9]

Mitochondrial disorders should be suspected in any patient presenting with unrelated symptoms of different organ systems.[4] Common manifestations of mitochondrial disorders are encephalomyopathy, seizures, stroke, growth and developmental delay, lactic acidosis, myopathy, cardiomyopathy, ophthalmoplegia, sensorineural hearing loss, renal diseases, and diabetes mellitus.[4] Morphological abnormalities of the mitochondria detected as intense subsarcolemmal staining with Gomori trichrome stain and/or distinctly abnormal shape and number of mitochondria by electron microscopic examination of an affected tissue are highly suggestive of a mitochondrial disorder.[2] The next step is to define the biochemical and genetic defect, but this may not be possible in all patients.[4,8] Biochemical assays generally identify decreased activity of one or more of the enzyme complexes of oxidative phosphorylation and the genetic defect may be on either the mitochondrial or the nuclear DNA.[2,4] Occasionally, the activity of the enzyme complexes may be normal or even compensatively increased, in which case a mitochondrial transporter protein may be the cause of mitochondrial cytopathy,[5] or a compensatory amplification of mitochondrial DNA may be associated with normal respiratory chain activity.[10] Hence, findings of clinical, histopathologic, biochemical and genetic evaluations are complementary for the diagnosis of mitochondrial disorders. While the diagnosis is clearly established with the detection of a significant respiratory chain defect or a pathogenic mutation, in many cases, the diagnosis still depends on histochemical and ultrastructural evaluation of an affected tissue.[2,11] In a large study of 113 pediatric patients with a definite diagnosis of mitochondrial disease, a significant respiratory chain defect and a mitochondrial DNA mutation were found only in 71% and 11.5%, respectively.[8]

Our patient presented with obstructive hypertrophic cardiomyopathy, myopathy, and growth and developmental retardation as the manifestations of a mitochondrial disorder. Similar to the clinic presentation of our patient, cardiomyopathy combined with myopathy, rather than well-defined mitochondrial syndromes, was shown to be one of the most common clinical presentations of mitochondrial diseases.[8] At first, we erroneously attributed growth and developmental retardation to the severe LVOT obstruction that was probably causing a low cardiac output state. Histologic and ultrastructural analyses, however, strongly exhibited signs of a mitochondrial cytopathy. Although a mitochondrial DNA abnormality and the precise biochemical defect were not detected, and a secondary mitochondrial disorder of undefined origin could not be completely excluded, we considered the diagnosis of mitochondrial cytopathy in our patient based on typical clinical presentation and the appearance of typical histologic ragged red fibers and ultrastructural mitochondrial abnormalities in two different affected tissues, heart and skeletal muscle, respectively. In the presence of normal enzyme activities, a mitochondrial transporter defect encoded by a mutated nuclear gene can still be suspected.[5] Of note, mitochondrial abnormalities have also been detected in the skeletal muscle of some patients with primary (sarcomeric) hypertrophic cardiomyopathy; however, these are in the form of a focal decrease in mitochondrial number and a subtle reduction in mitochondrial respiratory function[12] rather than the findings similar to those detected in our patient. Our patient represents one of the very few cases of hypertrophic cardiomyopathy occurring secondarily to mitochondrial cytopathy associated with a significant LVOT obstruction.

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