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Hypertrophic cardiomyopathy as the initial presentation of mitochondrial disease in an infant born to a diabetic mother

Jun Chul Byun and Hee Joung Choi

Department of Pediatrics, Keimyung University School of Medicine, Keimyung University Dongsan Medical Center, Daegu, Republic of Korea

Brief Report

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Author for correspondence:
Hee Joung Choi, MD, Department of Pediatrics, Keimyung University School of Medicine, 1095 Dalgubeol-daero, Dalseo-gu, Daegu 42601, Republic of Korea. Tel: +82 53 258 7312; Fax: +82 53 258 7319.
E-mail: joung756@dsmc.or.kr

Abstract

In contrast to hypertrophic cardiomyopathy caused by maternal diabetes, neonatal mitochondrial cardiomyopathy is rare and has a poor prognosis. We report an infant born to a mother with maternal diabetes with persistent ventricular hypertrophy, who was diagnosed with mitochondrial disease associated with m.3243A>G mutation in a mitochondrial tRNA leucine 1 gene. The hypertrophic cardiomyopathy was his initial and only clinical presentation.

Neonatal hypertrophic cardiomyopathy is a rare disease. Maternal diabetes mellitus is the common cause of neonatal myocardial hypertrophy, and the other causes of this disorder in children include genetic and metabolic diseases, maternal hyperthyroidism, and steroid use.[1,2] Among the various genetic causes of mitochondrial cardiomyopathy, m.3243A>G mutation in a mitochondrial tRNA leucine 1 variant is the well-characterized pathogenic gene, and it is found in approximately 80% of patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome.[3] The clinical onset of cardiac involvement differs, and cardiomyopathy has been rarely observed in the infantile period. Nevertheless, early-onset cardiomyopathy has a poor prognosis.[3,4]

Herein, we report an infant born to a mother with maternal diabetes who presented with persistent ventricular hypertrophy, and finally diagnosed as mitochondrial cardiomyopathy.

Case

A male baby was born to a 34-year-old G2P1 mother with gestational diabetes via caesarean section. His birth weight was 3080 g at 38 + 1 weeks of gestation. The mother was receiving insulin injection during pregnancy, and her haemoglobin A1c level was 5.9% before delivery.

Because the mother had a high-risk pregnancy with diabetes mellitus, the baby underwent two-dimensional echocardiography 21 days after birth. The results revealed hypertrophied interventricular septum (an end-diastolic interventricular septal thickness of 9.9 mm with a Z score of 4.66 and an end-systolic interventricular septal thickness of 11.2 mm with a Z score of 4.52) and left ventricular free wall (end-diastole left ventricular posterior wall thickness of 6.7 mm with a Z score of 4.24 and an end-systolic left ventricular posterior wall thickness of 8.1 mm with a Z score of 2.35) (Fig. 1*a*). Electrocardiography showed T wave inversion in precordial leads (Fig. 1*b*).

Laboratory examination revealed that the patient's lactate, bicarbonate, and ammonia levels and pH were within normal range. Brain magnetic resonance imaging showed no definite abnormalities.

Follow-up echocardiography at 49 days after birth revealed sustained hypertrophied interventricular septum (end-diastolic interventricular septal thickness of 13.8 mm with a Z score of 5.96 and end-systolic interventricular septal thickness of 13.2 mm with a Z score of 5.49) and left ventricular free wall (LVPWd of 7.5 mm with a Z score of 4.61 and LVPWs of 7.6 mm with a Z score of 1.66). With ventricular hypertrophy progression, the left ventricular capacity decreased gradually. However, there was no obstruction in the left ventricular outflow tract. During the regular follow-up, the patient's physical activity and feeding were good on β-blocker medication. However, at the age of 4 months, he suddenly died after severe irritability at home.

The mitochondrial panel test revealed m.3243A>G mutation in a mitochondrial tRNA leucine 1 gene. Further, based on familial genetic survey, his mother and older brother had m.3243G>A mutation, and his father had normal test results. His mother and older brother had no abnormal finding on brain imaging study, echocardiogram, electrocardiography, hearing test, and eye examinations.

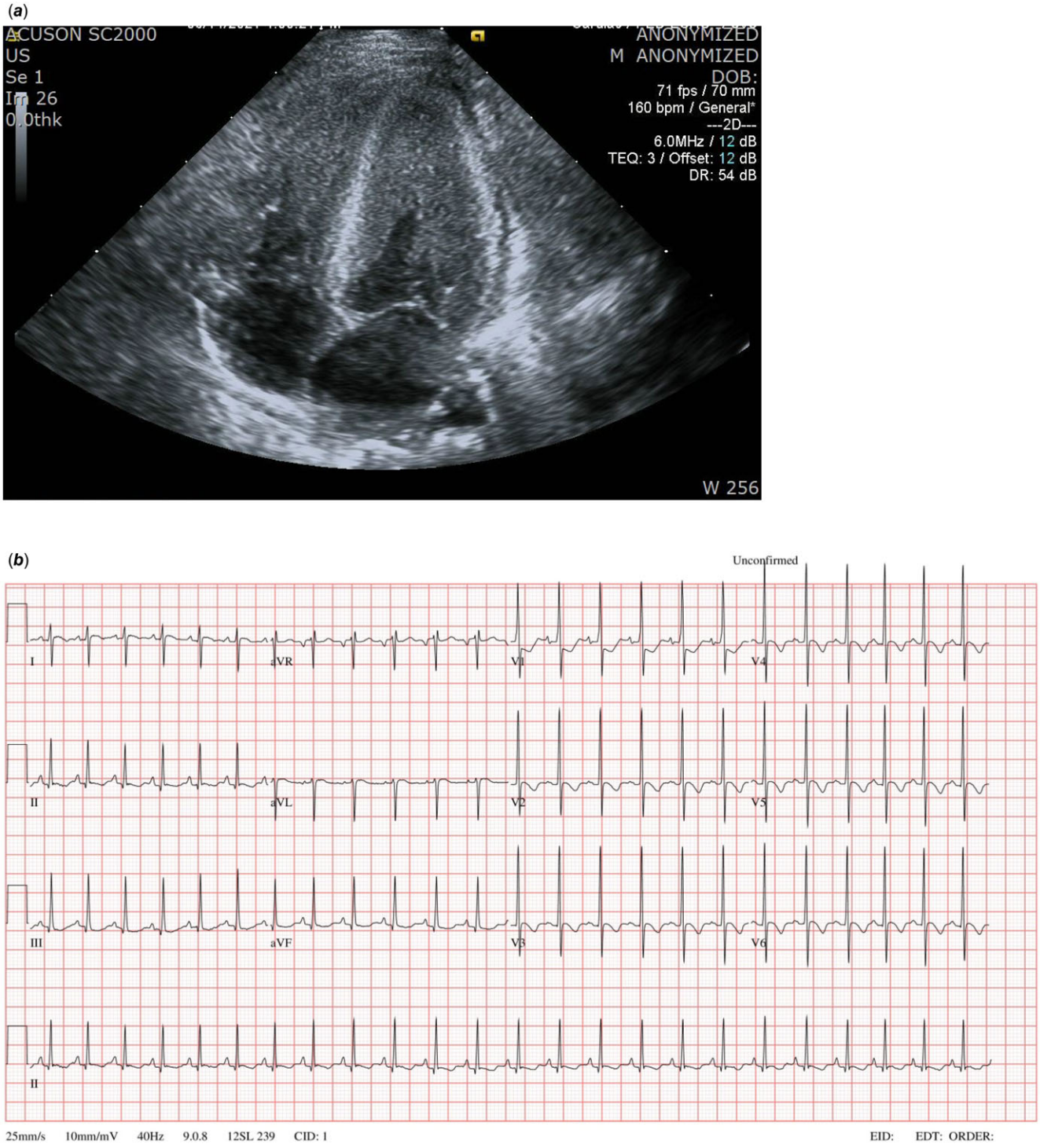

Figure 1. Echocardiographic (***a***) and Electrocardiographic (***b***) image of the patient 21 days after birth.

Discussion

Paediatric hypertrophic cardiomyopathy is distinguished from adult hypertrophic cardiomyopathy in terms of several aspects. The incidence of paediatric hypertrophic cardiomyopathy is relatively low. Moreover, its aetiology is limited to idiopathic conditions, and its signs and symptoms are relatively vague.[2] In a Korean study, the prevalence of hypertrophic cardiomyopathy was 0.51/100,000 children aged younger than 15 years, and the survival rates of children aged over 9 years was 90.3%.[5] In the infantile period, the prognosis of hypertrophic cardiomyopathy is relatively poor, with a mortality or transplantation rate of approximately 30%.[2]

Hypertrophic cardiomyopathy is frequently observed among neonates born to mothers with diabetes mellitus.[1] However, most infants with hypertrophic cardiomyopathy are clinically asymptomatic, and the condition spontaneously regresses within a few months and resolves at 1 year of age.[1] In our case, the patient

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underwent echocardiography due to a history of maternal diabetes mellitus and found the progressive left ventricular hypertrophy. Thus, genetic surveillance was performed to assess other genetic causes and found m.3243A>G mutation in a mitochondrial tRNA leucine 1 gene.

The m.3243A>G mutation in a mitochondrial tRNA leucine 1 gene, located at seven base pairs away from the D loop of the $tRNA^{Leu(UUR)}$ molecule, was the well-characterized pathogenic gene of mitochondrial cardiomyopathy. The m.3243A>G mutation is found in approximately 80% of patients with MELAS syndrome, and it is commonly a maternally transmitted mutation.[4] Up to 56–75% of adult patients with mitochondriopathy associated with m.3243A>G presented with hypertrophic cardiomyopathy.[6] In paediatric patients with mitochondrial disease, cardiomyopathy is observed in approximately 20% and its onset and severity remarkably vary. That is, some patients die at an early postnatal age, and others show gradual progression during the adolescent period. The paediatric-onset cardiomyopathy is associated with poor prognosis, with 10-year survival rates of 67%.[7,8] In our case, hypertrophic cardiomyopathy was related with m.3243A>G mutation. However, the patient was not definitely diagnosed with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome as he died before presenting with other clinical manifestations, such as developmental delay, muscle weakness, and epilepsy. The hypertrophic cardiomyopathy was the initial and only clinical presentation of his mitochondrial cardiomyopathy.

In conclusion, hypertrophic cardiomyopathy associated with m.3243A>G mutation in a mitochondrial tRNA leucine 1 gene is extremely rare among neonates. Nevertheless, due to cardiac involvement, the condition has a poor prognosis. Therefore, in patients diagnosed with neonatal hypertrophic cardiomyopathy, special surveillance must be performed for genetic diagnosis, and active intervention is required, even though the patient was born to a diabetic mother.

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Conflicts of interest. None.

Ethical standards. This study is a retrospective and observational study and does not contain any studies with human participants or animals. This study was approved by the institutional review board of the Keimyung University Dongsan Medical Center (approval number: 2022-05-025).

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