Sudden Death in an Infant With Angina, Restrictive Cardiomyopathy, and Coronary Artery Bridging
An Unusual Phenotype for a β-Myosin Heavy Chain (MYH7) Sarcomeric Protein Mutation

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The patient, a female infant aged 9 months, presented to a community hospital emergency room with fever and was referred for cardiac evaluation because of an abnormal chest radiograph. Her ECG showed biatrial enlargement and inferolateral ST depression. An echocardiogram showed a dilated left atrium and a mildly dilated and thickened left ventricle. Systolic function was preserved but diastolic filling showed restrictive physiology. A clinical diagnosis of restrictive cardiomyopathy (RCM) with associated myocardioc hypertrophy was made.

The patient underwent a comprehensive metabolic screen, as well as genetic testing (Hypertrophic Cardiomyopathy [HCM] Panel, Laboratory for Molecular Medicine, Cambridge, MA), which revealed a mutation (A1157G) in exon 13 of the β-myosin heavy chain (MYH7) gene, resulting in a nonsynonymous amino acid change from tyrosine to cysteine at position 386. This mutation has not been reported in the literature but had been seen previously by the Laboratory in an infant with de novo HCM. The mutation was categorized as being likely pathogenic.

The child was asymptomatic, and she was started on metoprolol to limit her maximal heart rate and acetylsalicylic acid for thromboprophylaxis. At 16 months of age, the patient presented with episodes of grunting and crying, with generalized discomfort and diaphoresis. A Holter monitor showed significant, rate-related ST depression with an increase in troponin T to 0.01 μg/L (normal <0.01 μg/L). These episodes were presumed to be related to myocardial ischemia, and the child was treated with oral morphine, increased metoprolol, and was listed for cardiac transplantation. At 18 months of age, the child became ill with vomiting, lethargy, and diaphoresis and presented to a local emergency room with absent vital signs and died after an unsuccessful attempt at resuscitation. An external cardiac defibrillator placed with the family was deployed at the time of her death.

An autopsy was performed, and the findings are summarized below.

Cardiac Pathology

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Autopsy revealed normal ventricular wall thicknesses. In retrospect, the abnormal trabeculations of the left ventricle may have contributed to the echocardiographic diagnosis of hypertrophy (Figure A). The left atrium was severely dilated and thick walled, whereas the right atrium was only mildly dilated. There was minimal endocardial fibroelastosis of the ventricles but diffuse, marked endocardial fibroelastosis of the left atrium (Figure A). There was myocardial bridging of the left anterior descending coronary artery (Figure B). Microscopically, there was extensive, patchy interstitial fibrosis in both ventricles and multiple areas of patchy replacement fibrosis, most prominent in the interventricular septum (Figure C) but also present in the free wall of the left ventricle. There was only minimal myocardial fiber disarray in the posterior interventricular septum. The left anterior descending was surrounded by replacement fibrosis (Figure C) with stenosed left anterior descending branch vessels because of intimal thickening (Figure D). In the interventricular septum, there were multiple foci of contraction band necrosis, some with early dystrophic calcification, indicating ongoing ischemic injury. The autopsy findings point to a restrictive, not hypertrophic, cardiomyopathy.

MYH7 mutations are most commonly associated with HCM but have been reported in RCM.1 Phenotypic and genotypic diversity is increasingly recognized in HCM and RCM, with varying degrees of hypertrophy and fibrosis perhaps representing a continuum of disease. A greater hazard for death in patients with combined RCM and HCM than for HCM alone has been described,2 and early listing for transplantation is advocated by some.3 Our practice has been to await some evidence of symptoms in patients who come to notice incidentally, as for this infant.

The finding of myocardial bridging was surprising. To our knowledge, this is the first report of a patient with an MYH7 mutation, RCM, and myocardial bridging. Diagnostic angiography in such patients is not routine, and the management of myocardial bridging when present in classical HCM remains controversial.4 Nevertheless, this case suggests that the presence of myocardial bridging should be considered with RCM and, when implicated by unexplained symptoms, should be ruled out with coronary angiography. In the absence of...
effective therapy, listing for cardiac transplantation should be considered very soon after diagnosis in this high-risk patient population.

Disclosures

None.

References


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Figure. A, The left side of the heart shows a severely dilated and thick-walled left atrium (LA) with diffuse, marked endocardial fibroelastosis and the abnormally trabeculated left ventricle (LV) with normal wall thicknesses for age. B, The locations of consecutive tissue blocks along the left anterior descending (LAD) are shown, and the arrows indicate the intramural course of the artery. C, The intramural LAD (arrow) is surrounded by fibrosis (green staining), and patchy but extensive fibrosis is seen throughout the ventricular septum. D, Branches from the intramural LAD show luminal narrowing by fibrointimal thickening.
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