Myofibrillar Cardiomyopathy due to a Novel Desmin Gene Mutation: Complementary Role of Echocardiography, Cardiac Magnetic Resonance, and Genetic Testing in Delineating Diagnosis

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INTRODUCTION

Myofibrillar myopathy (MFM) is a rare and genetically heterogeneous condition first described in a case report by Fardeau *et al.*[1] in 1978. MFM is characterized by slowly progressive muscle weakness that predominantly involves skeletal muscle but is also associated with various forms of cardiomyopathy (dilated, restrictive, and hypertrophic), arrhythmia, and atrioventricular conduction abnormalities.[2] This case of an 18-year-old male patient with MFM with a novel gene mutation highlights the complementary roles of early echocardiography and cardiac magnetic resonance imaging (cMRI), combined with genetic testing, in the diagnostic workup of a rare cardiomyopathy.

CASE PRESENTATION

An 18-year-old male patient was found to have abnormal electrocardiographic findings with extensive anterolateral T-wave inversion during screening before receiving anesthesia for elective nasal surgery (Figure 1). At time of presentation, there were no symptoms or clinical examination signs to suggest cardiac or neurologic disease. There was no medical or surgical history, and the patient described an active childhood, participating in soccer, swimming, and other athletics with no difficulty.

The patient had a significant family history of premature cardiac conduction disease: his grandmother required a permanent pacemaker at 36 years of age (cause unknown), and his mother had undergone permanent pacemaker placement at 26 years of age and was under investigation for myopathy at the time of our patient's presentation. There was no family history of sudden cardiac death.

The patient was referred for urgent echocardiography before his surgery. Transthoracic echocardiography demonstrated moderate concentric left ventricular (LV) hypertrophy with preserved systolic function (LV ejection fraction 67%) (Figure 2). LV diastolic filling parameters were as follows: E/A ratio 2.6, mitral E-wave deceleration time 180.3 msec, LV e′ septal velocity 0.052 m/sec, LV e′ lateral velocity 0.045 m/sec, septal E/e′ ratio 17, mild left atrial dilatation with left atrial volume index 34.7 mL/m^2, pulmonary vein S/D ratio 0.75, pulmonary vein A reversal velocity 0.33 m/sec, pulmonary vein A reversal duration 170.7 msec, and pulmonary A duration–mitral A duration difference 90 msec (Figure 3). Although the assessment of diastolic dysfunction was complicated by the fact that young patients in this age bracket have mitral inflow patterns with high E/A ratios and pulmonary vein D-wave dominance as a normal finding, the presence of reduced e′ velocity was regarded as abnormal, suggesting abnormal relaxation, an early hallmark of diastolic dysfunction. Moreover, the pulmonary vein A reversal signal was interpreted as abnormal, with an increased velocity as well as prolonged duration resulting in a pulmonary A reversal duration–mitral A duration difference of 90 msec, all of which were suggestive of LV end-diastolic dysfunction. However, the left atrium was not dilated, suggesting that filling pressures were not sufficiently elevated at this stage of his disease trajectory to cause left atrial dilatation because of chronic LV filling pressure elevation. There was also mild mitral regurgitation secondary to chordal systolic anterior motion of the anterior mitral leaflet but no LV outflow tract obstruction. Global longitudinal strain using speckle-tracking was −13.5% and notably did not exhibit the typical apical sparing pattern that can be seen in amyloid cardiomyopathy. Exercise stress echocardiography demonstrated above-average exercise tolerance (20 metabolic equivalents), normal augmentation of all LV wall segments, and no inducible arrhythmias.

Following echocardiography, cMRI was requested and demonstrated LV wall thickness up to 18 mm, involving the septum and the anterior and lateral walls. Delayed enhancement imaging revealed extensive midwall and right ventricular apical insertion point fibrosis, with increased signal intensity in these areas on T2-weighted imaging, suggesting coexisting edema (Figures 4 and 5). Laboratory cardiomyopathy screening was negative, including normal serum α- and β-galactosidase levels. Holter monitoring showed sinus rhythm with multiple asymptomatic sinus pauses (the longest 3.4 sec), predominantly during nocturnal hours.

During the time the patient was being investigated, his mother was diagnosed with MFM on the basis of a skeletal muscle biopsy carried out for investigation of peripheral myopathy. Because of this, MFM was suspected in this case, and our patient underwent quadriceps muscle biopsy. Biopsy revealed widespread subsarcolemmal accumulation of a granulofilamentous material and strong staining of these accumulations for antidesmin antibody on immunohistochemistry, consistent with a diagnosis of MFM (Figure 6).

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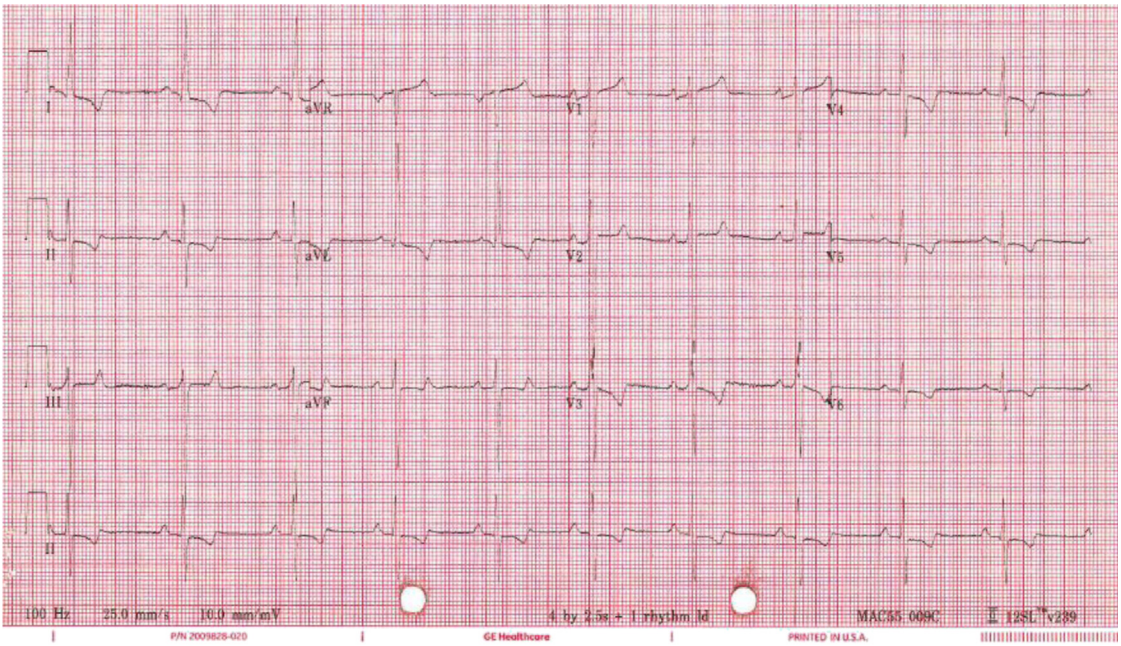

Figure 1 Baseline electrocardiogram demonstrating sinus rhythm, voltage criteria suggesting LV hypertrophy, and anterolateral T-wave inversion.

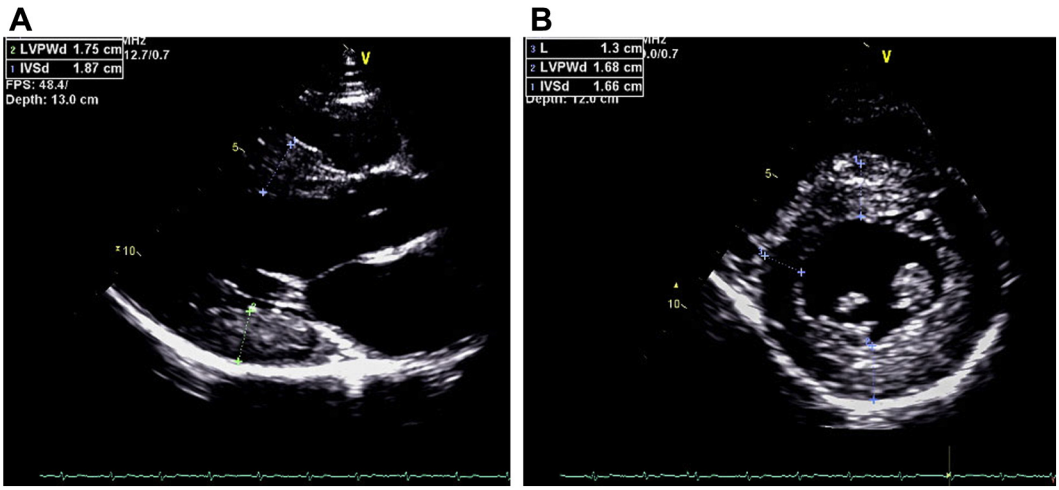

Figure 2 Baseline transthoracic echocardiogram demonstrating concentric LV hypertrophy. **(A)** Interventricular septal thickness 18.7 mm, LV posterior wall thickness 17.5 mm. **(B)** Concentric hypertrophy.

Genetic testing was subsequently requested and revealed a novel desmin (*DES*) gene mutation. Direct sequencing analysis of the entire coding region of the *DES* gene identified a heterozygous deletion of a single G nucleotide at position 735 + 1 in intron 3. This disrupts the invariant splice site at the end of exon 3 and is likely to result in skipping of the exon. This mutation has not been previously described, but a number of mutations that affect the same splice site have been published.[3,4]

Two years after presentation, the patient experienced two episodes of palpitations and presyncope at rest. Holter monitoring revealed symptomatic nonsustained ventricular tachycardia, the longest run being 17 beats, and asymptomatic sinus pauses up to 2.3 sec (Figure 7). The patient underwent insertion of an implantable cardioverter-defibrillator (ICD).

DISCUSSION

This case illustrates the sequential workup of a rare case of restrictive cardiomyopathy and highlights the central and complementary roles of echocardiography and cMRI in the diagnostic workup of inherited cardiomyopathies. Insights from cardiac imaging, coupled with important clues from history and tailored genetic testing, led to the successful delineation of a rare genetic diagnosis. Cardiac imaging has a dual role in restrictive cardiomyopathies: primarily to disclose morphology and function but also to provide clues about etiology. Although the phenotypic appearances of a number of different cardiomyopathies are similar, there are several subtle clues available from detailed analysis of the results of echocardiography and cMRI, such as an apical