

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

Karen Koitka, MBBS, Arun Dahiya, MBBS, FRACP, FCSANZ, Ada Lo, BSc, M App Sc, Gregory M. Scalia, MBBS, MSc, FRACP, FCSANZ, FASE, FAHA, John J. Atherton, MBBS, PhD, FRACP, FCSANZ, and Sandhir B. Prasad, MBBS, FRACP, FCSANZ, Brisbane, Australia

## INTRODUCTION

Myofibrillar myopathy (MFM) is a rare and genetically heterogeneous condition first described in a case report by Fardeau *et al.*<sup>1</sup> 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.<sup>2</sup> 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<sup>2</sup>, 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  $\alpha$ - and  $\beta$ -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).

From the Cardiology Department, Royal Brisbane and Women's Hospital (K.K., A.D., A.L., J.J.A., S.B.P.); and Cardiology Department, The Prince Charles Hospital, Brisbane, Australia (G.M.S.).

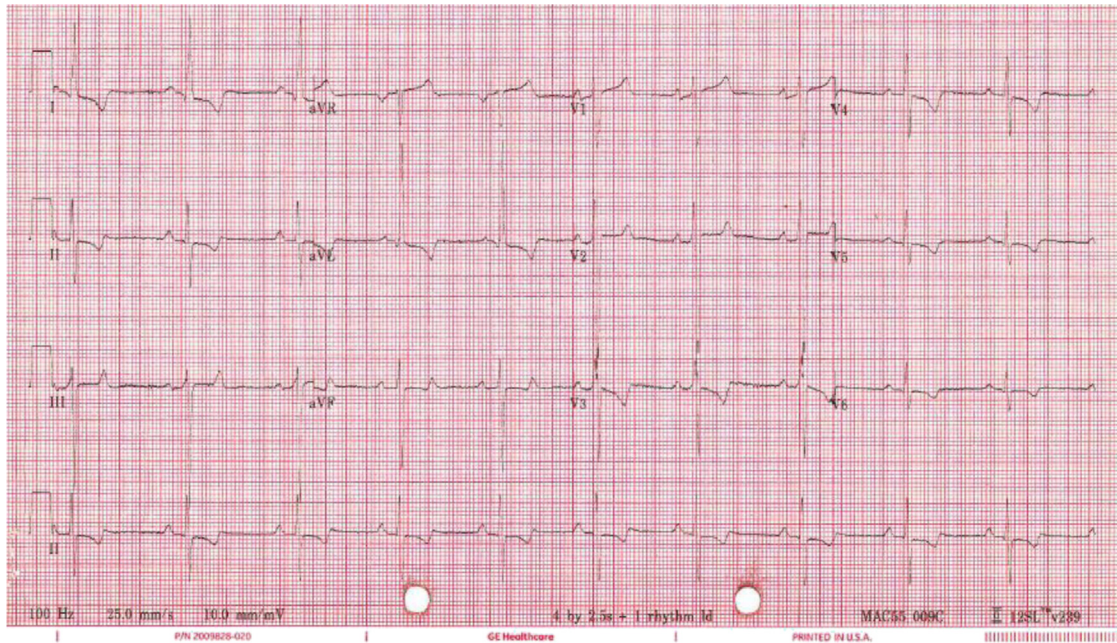
Keywords: Myofibrillar cardiomyopathy, Desminopathy

Conflicts of Interest: The authors reported no actual or potential conflicts of interest relative to this document.

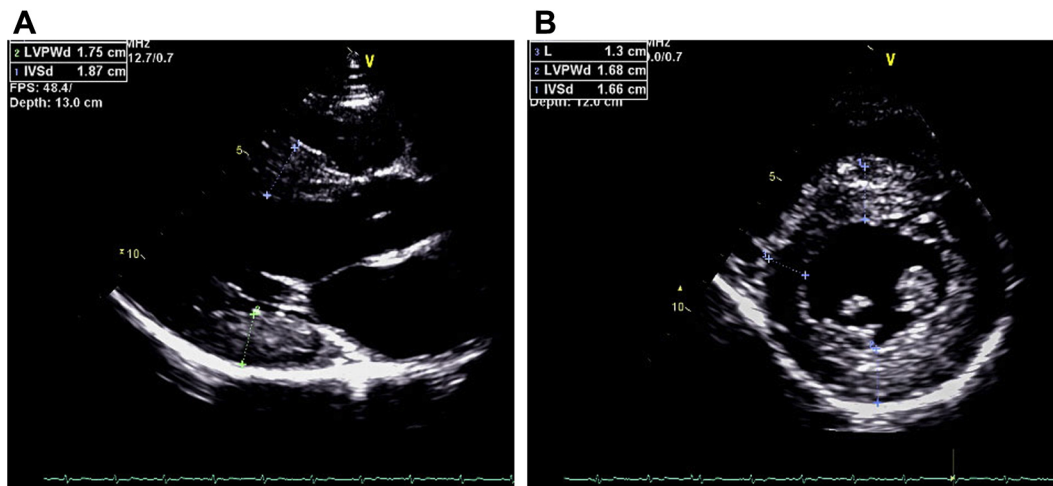
Copyright 2017 by the American Society of Echocardiography. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

2468-6441

<http://dx.doi.org/10.1016/j.case.2016.11.001>



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



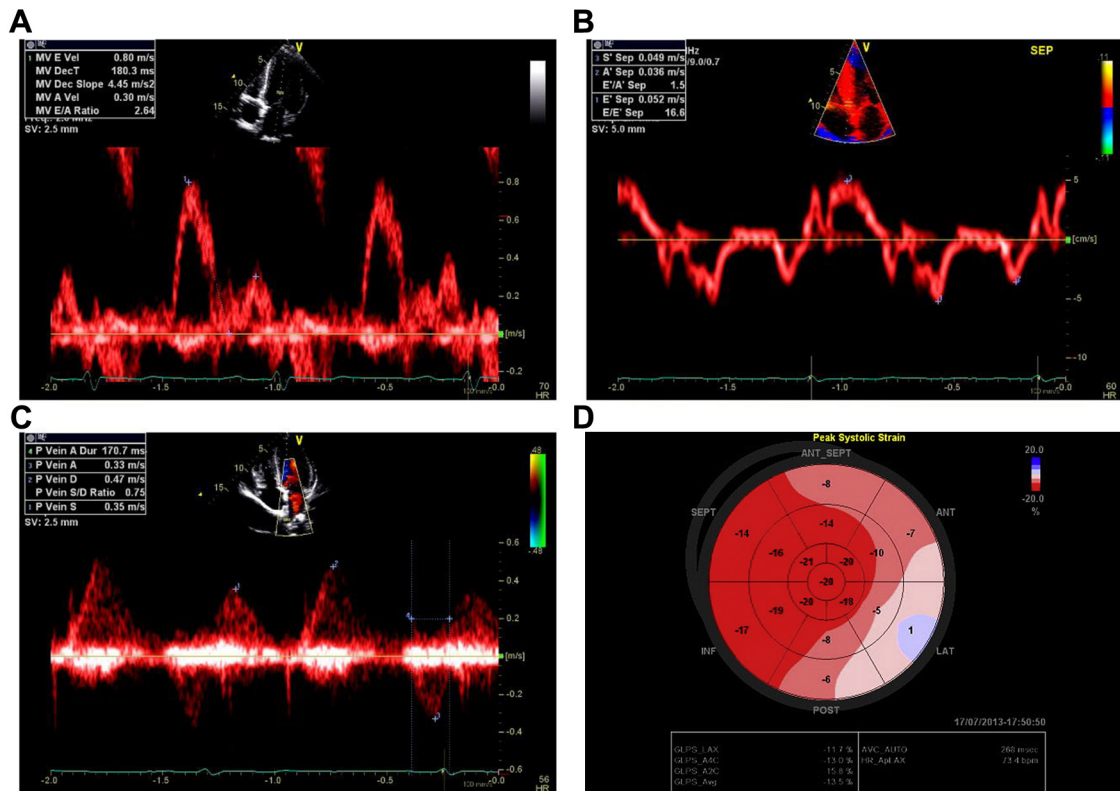
**Figure 2** Baseline transthoracic echocardiogram demonstrating concentric LV hypertrophy. **(A)** Interventricular septal thickness 18.7 mm, LV posterior wall thickness 17.5 mm. **(B)** Concentric hypertrophy.

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.<sup>3,4</sup>

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



**Figure 3** Significant diastolic dysfunction in an asymptomatic 18-year-old male patient. **(A)** E/A ratio 2.6. **(B)** Low tissue velocities with septal E' 0.052. **(C)** Pulmonary venous Doppler D-dominant pattern with prominent A reversal velocity. **(D)** Abnormal global longitudinal strain  $-13.5\%$  without apical sparing.

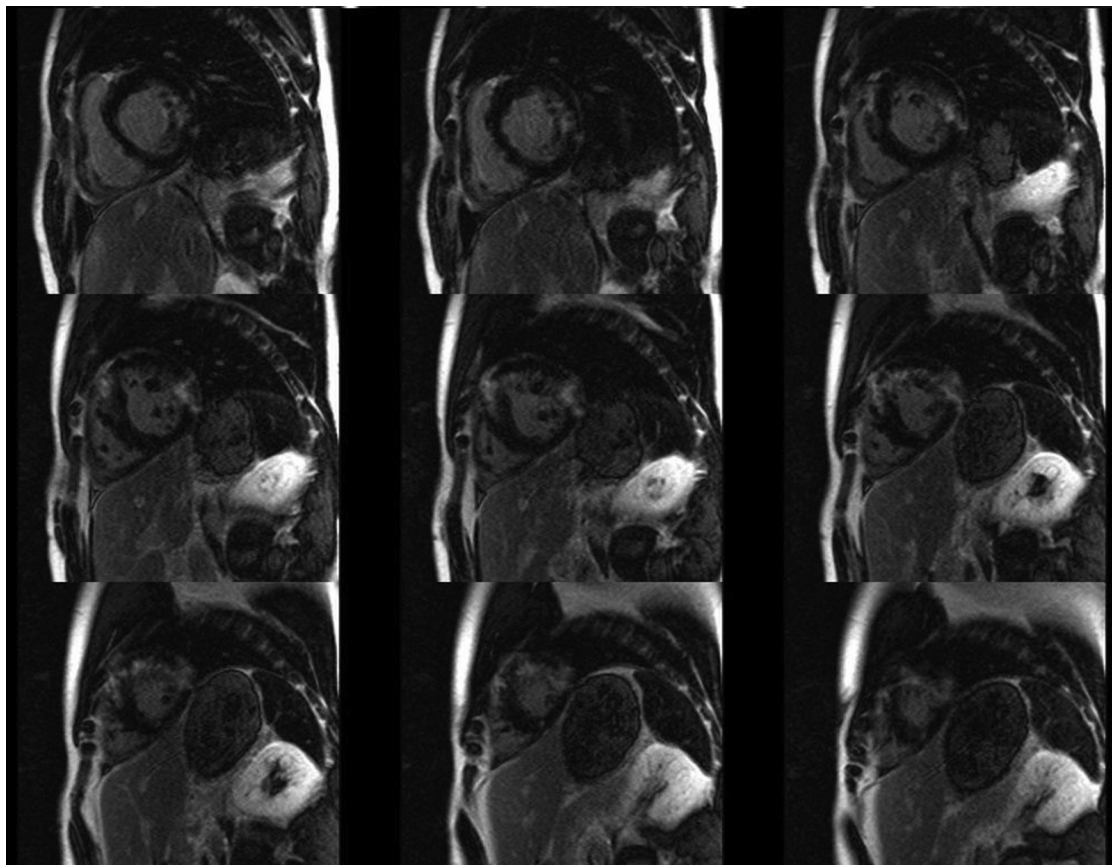
sparing pattern on strain imaging, that can refine and guide further investigation.

The patient in our case presented with asymptomatic, concentric, increased LV wall thickness at 18 years of age, with no history of hypertension or valvular heart disease. The primary differential diagnoses considered at this point included atypical hypertrophic cardiomyopathy, an infiltrative condition such as Fabry disease, cardiac amyloidosis, and storage diseases (i.e., glycogen storage disease and mitochondrial myopathies). Primary myopathies were not considered initially, because the patient had no neurologic symptoms or signs, but important other diseases associated with cardiac involvement include myotonic dystrophy, Duchenne muscular dystrophy, Barth syndrome, and laminopathies.<sup>5</sup> The red flag in this case was the patient's strong family history of premature cardiac conduction disease, which makes the sarcomeric causes of LV hypertrophy less likely and raises the possibility of other genetic cardiomyopathies, such as glycogen storage disorders (adenosine monophosphate kinase mutations) and, less commonly, desminopathies.<sup>6</sup>

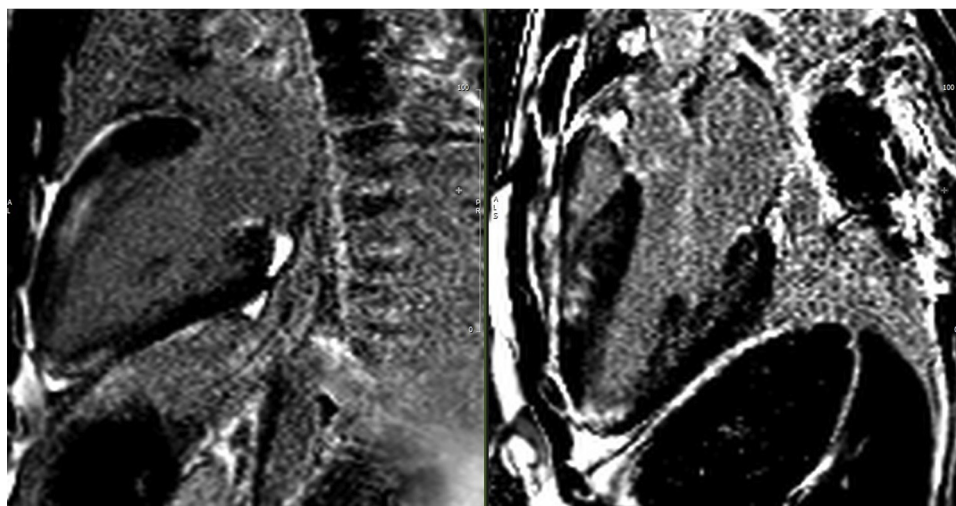
Diagnosis of MFM can be difficult because of the heterogeneity of clinical and histologic features. In those presenting with neurologic abnormalities, electromyography is important to exclude other causes of myopathy, and muscle biopsy is essential in the diagnostic pathway. To investigate for cardiac involvement, electrocardiography can reveal arrhythmias or conduction abnormalities. Serum creatine kinase is not reliably elevated in those with MFM.<sup>7,8</sup> Echocardiography plays an important role in the workup of these patients and is useful for defining the morphologic and functional fea-

tures of any associated cardiomyopathy. True isolated restrictive cardiomyopathy, as seen in this case, is rare and usually characterized by normal LV size and systolic function, with evidence of pathologic diastolic stiffening and atrial enlargement.<sup>9</sup> Doppler evaluation is essential in the diagnosis of a restrictive cardiomyopathy: early in the disease course, mitral inflow shows a delayed relaxation pattern. Progressive disease will reveal a pathologically elevated E/A ratio ( $>2.0$ ), a shortened deceleration time (usually  $<160$  msec), and low tissue velocities.<sup>9</sup> It is important to note that fit young individuals ( $<40$  years of age) may have E/A ratios  $>2.0$ . In this group of patients, other signs of diastolic dysfunction (such as reduced tissue Doppler velocities at the mitral annulus) must be present to make the diagnosis.<sup>9,10</sup>

Cardiovascular magnetic resonance has been used to demonstrate myocardial wall fibrosis on late gadolinium enhancement imaging in various cardiomyopathies. In the hypertrophic cardiomyopathy group, for example, myocardial fibrosis is related to patient prognosis. Strach *et al.*<sup>11</sup> carried out cardiovascular magnetic resonance in 11 desmin gene mutation carriers and found mid-myocardial wall fibrosis on late gadolinium enhancement imaging in four patients. Additionally, they found that two patients had focal hypertrophic changes that were missed on echocardiography. Cardiovascular magnetic resonance is the only noninvasive method to identify myocardial fibrosis and for this reason is a vital tool to detect early cardiac involvement and document the extent of fibrosis in patients with desminopathies.<sup>11</sup> It is important to note that although multimodality imaging provides vital information, the phenotypic expression can be nonspecific, and endomyocardial biopsy may be necessary to determine the



**Figure 4** cMRI: Delayed enhancement short axis showing extensive midwall fibrosis.

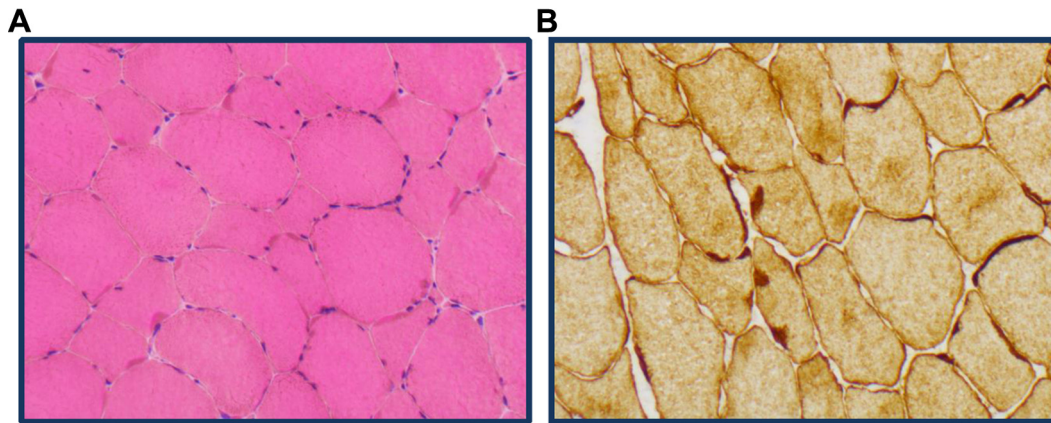


**Figure 5** cMRI: Delayed enhancement long-axis images, two chamber and three chamber views demonstrating multiple areas of mid-wall fibrosis.

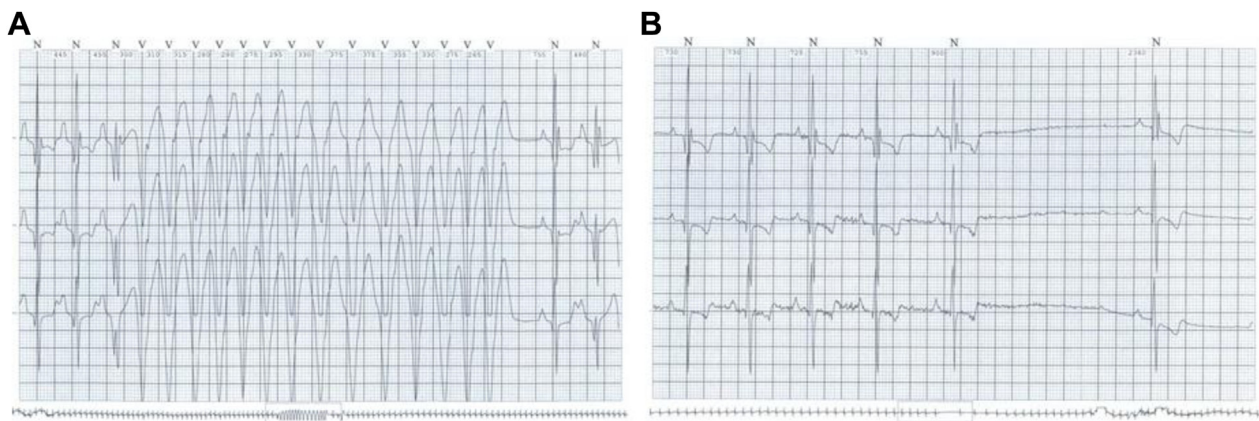
etiology. Additionally, troponin levels were not assessed in this patient, but if elevated in combination with T2-weighted magnetic resonance imaging showing myocardial edema would have suggested active myocardial protein deposition.

In this case, the genetic abnormality leading to the pathology presented was a desmin gene mutation. Disease related to desmin gene

mutations is often termed “desminopathy” and is a type of MF. Desmin is encoded by the DES gene, located on chromosome 2q35, and is the main intermediate filament protein expressed in skeletal, cardiac, and smooth muscle.<sup>7</sup> The desmin protein supports the myofibrils at the level of the Z-disk by forming a three-dimensional scaffold around the Z-disk and connecting the contractile apparatus



**Figure 6** (A) Quadriceps biopsy histopathology showing widespread subsarcolemmal accumulation of a granulo-filamentous material. (B) Immunohistochemistry revealed strongly positive staining for antidesmin antibody.



**Figure 7** Holter monitor findings. (A) Nonsustained ventricular tachycardia. (B) Sinus pauses up to 2.3 seconds.

to the plasma membrane and nuclear lamina, thus aligning the myofibrils.<sup>12,13</sup> The cardiac Purkinje fibers are rich in desmin, explaining the particular association with cardiac conduction disease. Approximately 15%-30% of those with desmin mutations will have associated cardiomyopathy with different cardiac phenotypes, including dilated (17%), restrictive (12%), and hypertrophic (6%) cardiomyopathy in one study.<sup>7,8</sup> In a meta-analysis of *DES* mutation cases, varying degrees of atrioventricular block were common (30% of cases). In contrast, life-threatening arrhythmias such as ventricular tachycardia were uncommon, occurring in only 4.5% of cases.<sup>7</sup> Twenty-six patients in the cohort died, with 26% of deaths being attributed to sudden cardiac death, emphasizing the importance of screening and aggressive treatment of arrhythmias. The age of onset of cardiac involvement is variable, but the majority of cases become clinically apparent in the third to fourth decades of life.<sup>7</sup>

### Genetics

An increasing number of associated genes are reported to be involved in the pathogenesis of MFM. Eight genes encoding Z-disk-associated proteins have been identified.<sup>7,12</sup> Six of these genes are particularly associated with cardiac involvement: mutations in the *DES* gene encoding desmin; *CYAB* gene, encoding  $\alpha$ -crystallin B chain; *MYOT* gene, encoding myotilin; *LDB3*, encoding LIM domain binding protein 3; *FLNC*, encoding filamin C; and *BAG3*, encoding BAG-family

molecular chaperone regulator 3.<sup>12</sup> Recent discoveries have been mutations in *FHL1* and *DNAJB6*.<sup>13</sup>

The number of known disease-causing desmin mutations is rapidly increasing: Goldfarb *et al.*<sup>12</sup> in 2009 described 45 disease-causing desmin mutations, and van Spaendonck-Zwarts *et al.*<sup>8</sup> in 2011 described 53 mutations. The Leiden Open Variation Database as of December 2015 listed 80 unique desmin deoxyribonucleic acid variants.<sup>14</sup> The inheritance pattern of desminopathies is most commonly autosomal dominant, with autosomal-recessive inheritance being rare.<sup>2,4</sup> Sporadic cases also account for a small proportion of cases.<sup>8,12</sup>

The genetic abnormality in this case report is to our knowledge a novel mutation. Park *et al.*<sup>4</sup> in 2000 were the first to report a splice-site mutation at exon 3; patients were found to have atrioventricular block requiring pacemaker placement in their third or fourth decade. A review by Abrustini *et al.*<sup>3</sup> detailed a number of mutations that affect the same splice site, and these resulted in skipping of exon 3 and deletion of 32 amino acids from the mature protein. The affected family members presented with restrictive cardiomyopathy and atrioventricular block.

### Management

Therapy for MFM is supportive and depends on the presenting phenotype. Those presenting with symptoms of heart failure should

be treated per the standard guidelines, as there is no evidence to support differing practice in the MFM population. Screening and treatment for conduction disease and arrhythmias are vital.<sup>7</sup> One study found that 36% of *DES* mutation carriers required pacemaker insertion, and 4% required ICD insertion.<sup>7</sup> No studies have looked at the risk for sudden cardiac death in the MFM group, and thus no information is available on what risk factors should be used to guide consideration or timing of ICD insertion.

In this case, the pros and cons of commencing  $\beta$ -blocker and angiotensin-converting enzyme inhibitor therapy were discussed. Although there is no evidence in favor of the use of medical therapies for heart failure in patients with MFM, the possibility of elevated filling pressures seen on our patient's transthoracic echocardiogram suggested that angiotensin-converting enzyme inhibitor therapy may be of benefit. After nonsustained ventricular tachycardia was witnessed on our patient's Holter monitoring, it was recommended that he commence  $\beta$ -blocker therapy.

Consideration for device implantation was not taken lightly. The clinical features that guided risk stratification for sudden cardiac death were similar to those for hypertrophic cardiomyopathy assessment, including the significant LV hypertrophy, extensive delayed enhancement on cMRI, and nonsustained ventricular tachycardia. In addition to this, we considered the patient's risk for developing symptomatic conduction system disease to be high given a family history of symptomatic conduction disease requiring pacing and his Holter results displaying sinus pauses. We contrasted the benefits of an intravascular system with pacing capabilities against that of a subcutaneous ICD, which would spare his vasculature of an intravascular device at a young age. He was screened for a subcutaneous ICD but did not meet the criteria because of his T-wave size. Particularly at higher heart rates, the large T-wave size would have placed him at increased risk for inappropriate shocks with the subcutaneous device. The long-term implications of intravascular ICD insertion were discussed in detail.

## CONCLUSION

MFM should be considered in the differential diagnosis for patients presenting with cardiomyopathy or cardiac conduction disease at a young age with family histories of premature conduction disease. This case illustrates that the diagnosis of cardiomyopathies is complex, and multimodality cardiac imaging with echocardiography and cMRI is a key step in delineating the pathology and refining the diagnostic workup. Although the initial morphologic appearances of a number of cardiomyopathies on echocardiography and cMRI are similar, a number of subtle clues about etiology that are obtained from both modalities are crucial in guiding further investigation and diagnosis. In this case, several insights from a sequential workup, including first, echocardiography and then cMRI helped refine the diagnostic workup and, coupled with information from genetic testing, helped achieve a diagnosis in a rare case.

## ACKNOWLEDGMENTS

We thank Dr. Thomas Robertson, pathologist, Royal Brisbane and Women's Hospital, for providing histologic images and descriptions, and Mark Davis, PhD, FFSc (RCPA), Neurogenetics Unit, Department of Diagnostic Genomics, PathWest Laboratory Medicine, Western Australia, Australia, for advice on genetic abnormalities.

## REFERENCES

1. Fardeau M, Godet-Guillain J, Tome FM, Collin H, Gaudeau S, Boffety C, et al. IA new familial muscular disorder demonstrated by the intra-sarcomeric accumulation of a granulo-filamentous material which is dense on electron microscopy. *Rev Neurol (Paris)* 1978;134:411-25.
2. Selcen D, Engel AG. Myofibrillar myopathy. *GeneReviews*. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1499/>. Accessed December 13, 2016.
3. Abrustini E, Pasotti M, Pilotto A, Pellegrini C, Grasso M, Previtali S, et al. Desmin accumulation restrictive cardiomyopathy and atrioventricular block associated with desmin gene defects. *Eur J Heart Fail* 2006;8:477-83.
4. Park KY, Dalakas MC, Goebel HH, Ferrans VJ, Semino-Mora C, Litvak S, et al. Desmin splice variants causing cardiac and skeletal myopathy. *J Med Genet* 2000;37:851-7.
5. Finsterer J, Stöllberger C. Primary myopathies and the heart. *Scand Cardiovasc J* 2009;42:9-24.
6. Arad M, Benson DW, Perez-Atayde AR, McKenna WJ, Sparks EA, Kanter RJ, et al. Constitutively active AMP kinase mutations cause glycogen storage disease mimicking hypertrophic cardiomyopathy. *J Clin Invest* 2002;109:357-62.
7. Lilienbaum A, Vernengo L. Cardiomyopathies associated with myofibrillar myopathies. Available at: <http://www.desminopathy.info/pdf/27279.pdf>. Accessed December 13, 2016.
8. van Spaendonck-Zwarts K, van Hessem L, Jongbloed JD, de Walle HE, Capetanaki Y, van der Kooij AJ, et al. Desmin-related myopathy. *Clin Genet* 2011;80:354-66.
9. Armstrong WF, Ryan T. *Feigenbaum's Echocardiography*. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2010.
10. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;29:277-314.
11. Strach K, Sommer T, Grohé C, Meyer C, Fischer D, Walter MC, et al. Clinical, genetic and cardiac magnetic resonance imaging findings in primary desminopathies. *Neuromusc Disord* 2008;18:475-82.
12. Goldfarb LG, Dalakas MC. Tragedy in a heartbeat: malfunctioning desmin causes skeletal and cardiac muscle disease. *J Clin Invest* 2009;119:1806-13.
13. Paulin D, Li Z. Desmin: a major intermediate filament protein essential for the structural integrity and function of muscle. *Exp Cell Res* 2004;301:1-7.
14. Brodehl A, den Dunnen J. Leiden muscular dystrophy pages: desmin (DES). Leiden Open Variation Database. Available at: [http://www.dmd.nl/nmdb2/home.php?select\\_db=DES](http://www.dmd.nl/nmdb2/home.php?select_db=DES). Accessed June 11, 2016.