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CASE REPORT

Features of myocardial injury detected by cardiac magnetic resonance in a patient with desmin-related restrictive cardiomyopathy

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Abstract

Myocardial fibrosis detected by cardiac magnetic resonance (CMR) has been reported in patients with desmin-related myopathy, although its characteristics remain unclear. Here, we describe a case of desmin-related restrictive cardiomyopathy wherein CMR imaging revealed myocardial oedema, ischaemia, and fibrosis in the left ventricle; the different types and processes of myocardial injury were detected by CMR. Middle wall left ventricular enhancement may be a feature of late gadolinium enhancement, and the lateral wall is often involved in cases of myocardial injury. CMR is useful for the early detection of cardiac involvement and the prediction of prognosis in patients diagnosed with desmin-related myopathy.

Keywords Desmin; Restrictive cardiomyopathy; Cardiac magnetic resonance

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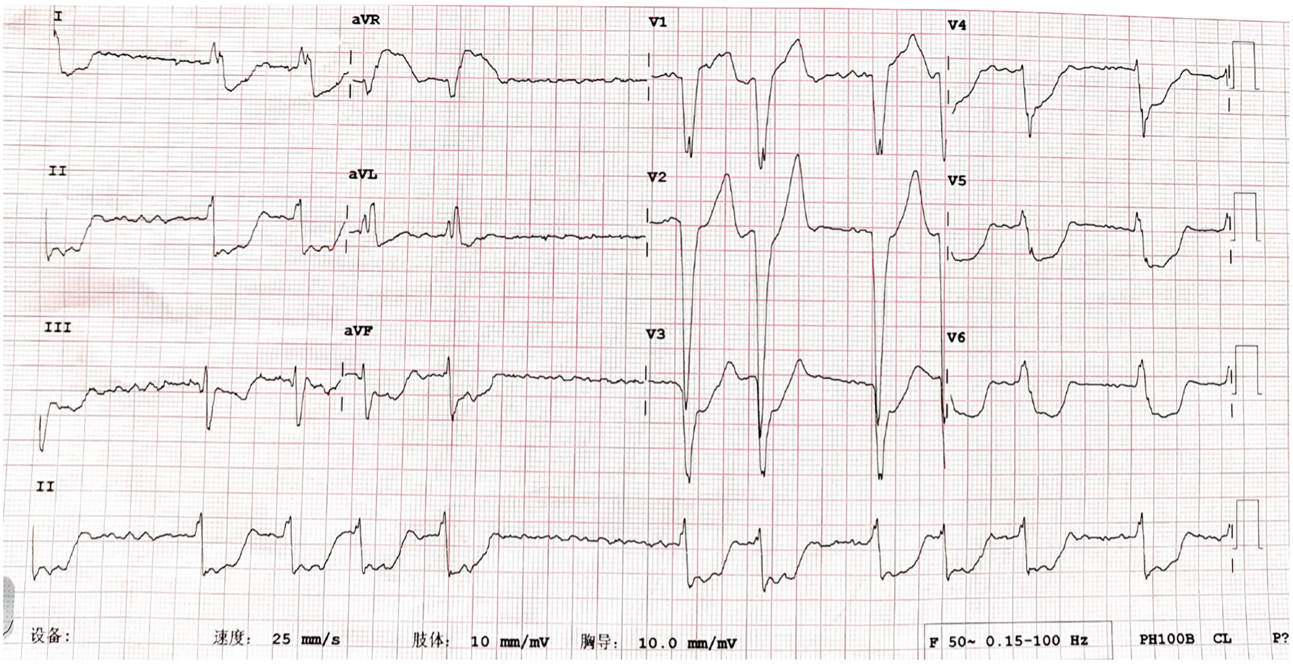
Introduction

Desmin-related myopathy (DRM) is an autosomal hereditary skeletal and/or myocardial myopathy primarily caused by mutations in the desmin (DES) gene.[1] DRM is generally characterized by progressive distal skeletal muscle weakness, cardiac arrhythmias, and different types of cardiomyopathies.[2] Cardiac diseases are the leading cause of death in patients worldwide,[3] and the early detection of cardiac involvement is essential for the diagnosis and prognosis of patients with heart disease. Cardiac magnetic resonance (CMR) has been used to differentiate different types of myocardial injury, including myocardial oedema, ischaemia, and fibrosis, by multi-parameter and multi-sequence imaging.[4] Here, we describe a case of DES-related restrictive cardiomyopathy with different types of myocardial injury detected by CMR.

Case report

A 22-year-old female patient presented to our cardiac department with chest tightness, shortness of breath, fatigue, and multiple episodes of syncope over a period of approximately 8 years. Three years prior to that, she was diagnosed with restrictive cardiomyopathy (RCM). Laboratory data showed increased N-terminal pro-B-type natriuretic peptide levels (2580 ng/mL; normal range: 300–450 ng/mL). Creatine kinase activity (8.6; normal range: 2.0–7.2 ng/mL) was increased, although troponin I levels (maximum value $<$0.01 ng/mL; normal range: $<$0.01 ng/mL) were normal. The patient was negative for all rheumatic immune antibodies. Electrocardiography showed sustained atrial fibrillation and a complete left bundle branch block (*Figure 1*). Moreover, echocardiography showed that the left atrium had moderate enlargement

Figure 1 Electrocardiography showed sustained atrial fibrillation and complete left bundle branch block.

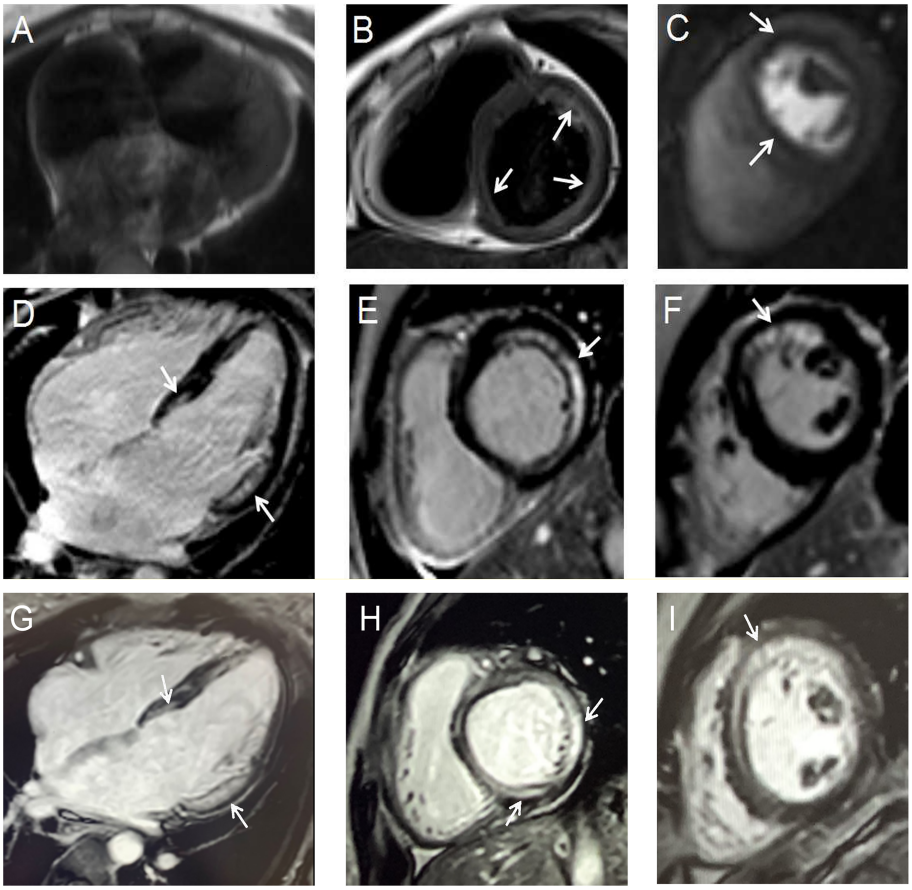


with a diameter of 49 mm, the left atrial volume index was 65 mL/m^2, and the average E/e′ ratio was 8.7 with a moderate decrease in left ventricular (LV) diastolic function. The LV ejection fraction was 40%, indicating that it was moderately decreased, and mild tricuspid and mitral regurgitation was present.

CMR was performed using a 3.0 T scanner (MAGNETOM Skyra, Siemens Healthineers, Erlangen, Germany). A half-Fourier acquisition single-shot turbo spin-echo sequence demonstrated severe enlargement in both the left and right atria, with an anteroposterior diameter of 52 and 59 mm, respectively (*Figure 2A*). A true steady-state free precession sequence showed that the biventricular end diastolic diameter was normal, but the global LV wall motion, especially the late gadolinium enhancement (LGE) segments, had moderately decreased LV ejection fraction (35%). T2-weighted imaging showed hyperintense lesions in the anterior, lateral, and inferoseptal LV walls, indicating myocardial oedema (*Figure 2B*). For myocardial tissue characterization, CMR first-pass perfusion and LGE imaging were performed with gadolinium-diethylenetriamine pentaacetic acid (0.1 mmol/kg body weight, Gadovist, Bayer Schering Pharma, Berlin, Germany), and the LGE images were captured using an inversion recovery sequence 10 min after injection. First-pass perfusion revealed a subendocardial perfusion defect in the left ventricle, indicating myocardial ischaemia (*Figure 2C*). The LGE images showed marked intramyocardial enhancement in the anterior, lateral, and septal LV walls (*Figure 2D–2F*), indicating myocardial fibrosis. When compared with the LGE images captured 3 years earlier, these images indicated that the scope of delayed enhancement had been reduced (*Figure 2G–2I*).

To screen for disease-related mutations, genomic DNA was extracted from peripheral blood samples of patient by DNA extraction kit (TIANGEN, DP332, Beijing, China). Whole-exome capture was performed with IDT xGen Exome research panel v1.0 kit. The captured library was then sequenced on Illumina NovaSeq 6000 System. Raw data from sequencing were put under quality control by FastQC. The Burrows–Wheeler Alignment tool was using sequencing data alignment to the Human Reference Genome (National Center for Biotechnology Information build 37, hg 19). Single-nucleotide variants were identified by GATK. All variants were saved in variant callformat and uploaded to the Ingenuity Variant Analysis and Translational Genomics Expert platform for biological analysis and variant interpretation. Next-generation sequencing confirmed the DES variant c.1216 (exon 6) C > T (p.R406W) (Supporting Information, *Table S1*). To determine whether point mutations are harmful, we used the online tool PolyPhen2 to predict the effects of R406 point mutations on DES proteins; a score of 0.999 indicates that R406 point mutations possibly have detrimental effects. Variants were interpreted according to the 2015 American College of Medical Genetics and Genomics guidelines. The missense mutation c.1216 (exon 6) C > T (p.R406W) was considered to be potentially pathogenic based on the following evidence: (PS1 + PM1 + PM2 + PP3)

Figure 2 Cardiac magnetic resonance imaging of the patient. Half-Fourier acquisition single-shot turbo spin-echo imaging (A, horizontal-axis view) shows left and right atrium enlargement. T2-weighted imaging (B, short-axis view) reveals myocardial oedema (arrow). First-pass perfusion imaging (C, short-axis view) demonstrates myocardial ischaemia (arrow). Four-chamber and two short-axis views (D–F) show fibrosis involving the middle layer of the left ventricle anterior, lateral, and inferoseptal walls. Late gadolinium enhancement images (G–I) from 3 years ago show a wider range of delay enhancement in the same segments of the left ventricle compared with the present late gadolinium enhancement images.



(i) strong pathogenic evidence PS1: the same missense mutations as the identified pathogenic variants by ClinVar database and Human Gene Mutation Database; (ii) moderate pathogenic evidence PM1: missense variants are located in the well-studied exon functional domain without benign variation (ClinVar without benign variant) and in pathogenic hotspots; (iii) moderate pathogenic evidence PM2: the single-nucleotide polymorphism c.1216 (exon 6) C > T (p.R406W) minimum allele frequency was <0.05, which belongs to a low-frequency variant; and (iv) supporting pathogenic evidence PP3: two statistical methods (MutationTaster and PolyPhen2) predict the influence of variants on the gene (gene product). Sequence alignment showed that R406 mutations are highly conserved and should therefore be important for protein function. To evaluate skeletal muscle symptoms, a detailed physical examination performed by expert neurologists confirmed that there were no abnormalities in the skeletal muscle strength of the patient.

Discussion

We identified different types of myocardial injury and CMR features in a patient with DRM.

Desmin is the main intermediate filament protein of skeletal and cardiac muscles and maintains the integrity of the structure and function of myofibril.[5] DES gene mutation leads to the accumulation of insoluble protein in the intracellular area, which causes myofibril dysfunction and eventually leads to cell death and replacement fibrosis.[6] DES mutations can affect the integrity of intercalated discs, thereby inducing conduction defects and malignant arrhythmias.[7]

Desminopathy primarily occurs in adulthood, and the main manifestations are skeletal myopathy and cardiomyopathy. Skeletal lesions progressively occur in the distal lower and lateral areas of the body and are accompanied by upper limb muscle weakness; additionally, truncal, respiratory, and facial muscle weakness could occur.[8]

The DES was classified as a definitive evidence for dilated cardiomyopathy and isolated LV hypertrophy.[9,10] Also, DES had moderate evidence for arrhythmogenic right ventricular cardiomyopathy causality.[11] So cardiac diseases present different types of cardiomyopathy and cardiac arrhythmias, including dilated cardiomyopathy, hypertrophic cardiomyopathy, RCM, and arrhythmogenic right ventricular cardiomyopathy.[2] Non-compaction cardiomyopathy has also been reported in patients with cardiac disease.[12] Arrhythmic manifestations include atrioventricular conduction defects, bundle branch blocks, atrial fibrillation, and ventricular tachycardia.[8]

Conventional examination methods, such as echocardiography, electrocardiography, and biomarkers, cannot directly determine the form and degree of myocardial injury. CMR has been confirmed to differentiate an injured myocardium from a normal one. The T2-weighted imaging sequence myocardial hyperintensity reflects myocardial oedema, and a perfusion sequence can detect myocardial ischaemia. LGE is the only direct and non-invasive imaging technique that can identify myocardial fibrosis and is consistent with pathology. However, studies on DRM assessed using CMR have rarely been reported. Only one study systematically used CMR to evaluate myocardial involvement in patients with desminopathies. This study revealed that out of 13 patients with desminopathy, 11 underwent CMR and LGE was found in four patients with cardiac symptoms. LGE was located in the LV lateral walls, anterolateral wall, and inferoseptal wall. However, the common LGE feature was detected in the middle LV wall.[8] In another case of DES-related hypertrophic cardiomyopathy, focal LGE in the middle layer of the LV lateral wall was further observed.[2] In this study, LGE was also detected in the middle layer of the anterior, lateral, and inferoseptal LV walls in both CMR examinations, indicating changes in the process of myocardial injury and severe myocardial fibrosis. Furthermore, myocardial oedema and ischaemia were observed, revealing the process of myocardial injury. Previous studies have reported that DRM is generally not accompanied by global or focal systolic wall motion abnormalities, especially in the LGE segments.[13] However, our patient presented with global LV systolic wall motion abnormalities, especially in the LGE segments, revealing an advanced disease stage. It was further confirmed that the extent of myocardial fibrosis was related to poor prognoses, including worsening of LV function and adverse outcomes.[14]

In China, cardiac involvement was the most common type of desminopathy, which may be accompanied by skeletal muscle disease.[15] Our patient had no definite skeletal muscle symptoms and only showed an elevation in creatine kinase. This finding is consistent with the characteristics of Chinese patients. The poor rate of cardiac involvement may be related to the mutation site of the DES gene. The DES molecule is organized into three domains: a highly conserved alpha-helical core and N-terminal and C-terminal ('head' and 'tail'). The alpha-helical core is organized into four consecutive helical segments, namely, 1A, 1B, 2A, and 2B, which are connected by short non-helical linkers. The 2B helical segment has more than 50% of known DES mutations; therefore, structural analysis of this region has attracted immense attention.[16] Recent studies have shown that the R406W mutation in the 2B helical region prevents DES filaments from being anchored to desmosomes, thereby destroying the structural and functional integrity of intercalated discs, which is the main reason for the early development of cardiac disease.[17] Our patient was confirmed to have a mutation in the R406W gene, which further explains the cause of severe cardiac involvement.

In conclusion, desminopathies should be considered in patients presenting with RCM combined with conduction block, and genetic testing is essential for such patients. CMR can detect different myocardial injuries in patients with DES-related restrictive cardiomyopathy. Middle wall LV enhancement may be an LGE feature, and the lateral wall may often be involved in such cases. CMR is a useful imaging technique to detect early cardiac involvement and predict patient prognosis in DRM.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. NHm1e gene lists.

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