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CASE REPORT: CLINICAL CASE

Ambiguous Clinical Presentations and Imaging Findings in Genetic Dilated Cardiomyopathy

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ABSTRACT

This case series underscores the crucial role of genetic testing and a multidisciplinary approach to the management of genetic dilated cardiomyopathy. It also highlights the importance of distinguishing dilated cardiomyopathies from other cardiomyopathies to personalize patient care. (JACC Case Rep. 2024;29:102821) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Dilated cardiomyopathy (DCM) is a heterogeneous disease linked to pathogenic variants in myocardial genes. Genetic DCM is an underrecognized subset of cardiomyopathies, accounting for at least one-third of all DCM cases.[1] Despite technological advancements, diagnosis and management remain challenging due to overlapping clinical and imaging features with other cardiomyopathies. We present a series of 4 cases that highlights these complexities and underscores the role of genetic testing and multidisciplinary team (MDT) management.

TAKE-HOME MESSAGES

- This case series highlights the ambiguous presentation and the role of advanced cardiac imaging techniques in the evaluation of genetic dilated cardiomyopathy.
- A multidisciplinary approach that integrates clinical evaluation with imaging findings and genetic testing is vital to provide personalized patient care.

PATIENT 1

A 49-year-old male presented with exertional dyspnea, bilateral lower extremity edema, and abdominal distension following a viral illness. Initial echocardiography and subsequent cardiac catheterization demonstrated biventricular dysfunction with a left ventricular ejection fraction (LVEF) of 26% and no obstructive coronary disease. Cardiac magnetic resonance (CMR) revealed a nonischemic pattern of late gadolinium enhancement (LGE) (**Figure 1**). He was initiated on guideline-directed medical therapy (GDMT) and discharged with a wearable external defibrillator.

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

CS = cardiac sarcoidosis

DCM = dilated cardiomyopathy

FDG = ^{18}F-fluorodeoxyglucose

GDMT = guideline-directed medical therapy

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

LVEF = left ventricular ejection fraction

MDT = multidisciplinary team

PET = positron emission tomography

RV = right ventricular

VT = ventricular tachycardia

Following discharge, a cardiac positron emission tomography (PET) scan showed improvement in LVEF to 56% and basal myocardial ^{18}F-fluorodeoxyglucose (FDG) uptake consistent with inflammation (Figure 1). Concern for cardiac sarcoidosis (CS) prompted immunosuppressive therapy. A PET scan repeated 4 months later demonstrated resolution of myocardial inflammation; immunosuppression was discontinued. Genetic testing revealed a heterozygous pathogenic *LMNA* gene variant consistent with genetic DCM.

PATIENT 2

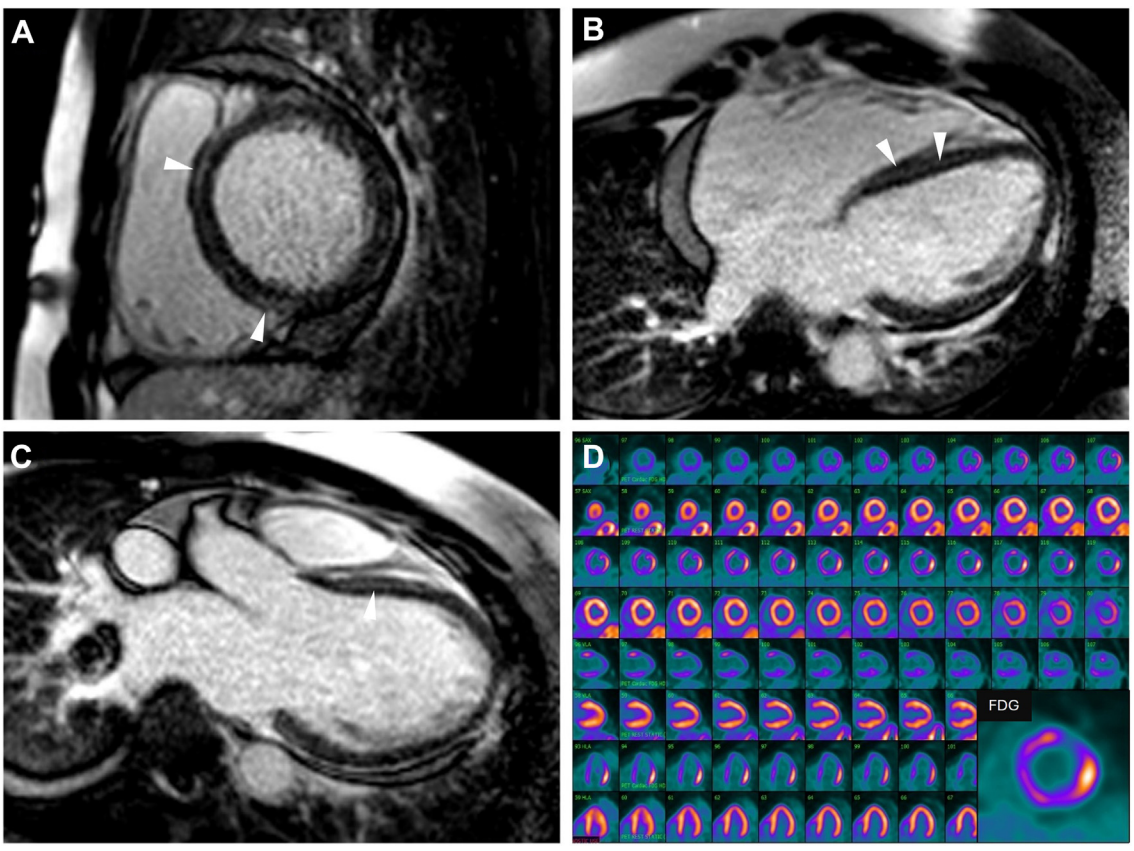
A 50-year-old male with a family history of sudden cardiac death was admitted due to acute ischemic stroke. ECG demonstrated high-degree atrioventricular block and slow monomorphic ventricular tachycardia (VT). CMR revealed severe left ventricular (LV) dilatation and dysfunction, mediastinal lymphadenopathy, left atrial appendage thrombi, and extensive LGE in a nonischemic pattern (Figure 2). Given the concern for CS, a biventricular implantable cardioverter-defibrillator (ICD) was implanted and immunosuppression was initiated.

Cardiac PET showed diffuse, homogeneous myocardial uptake suspected to represent inadequate myocardial suppression (Figure 2). Endobronchial and endomyocardial biopsies yielded no significant findings. Genetic testing identified a heterozygous pathogenic variant in the *LMNA* gene, consistent with genetic DCM. Immunosuppression was discontinued and he was maintained on GDMT.

PATIENT 3

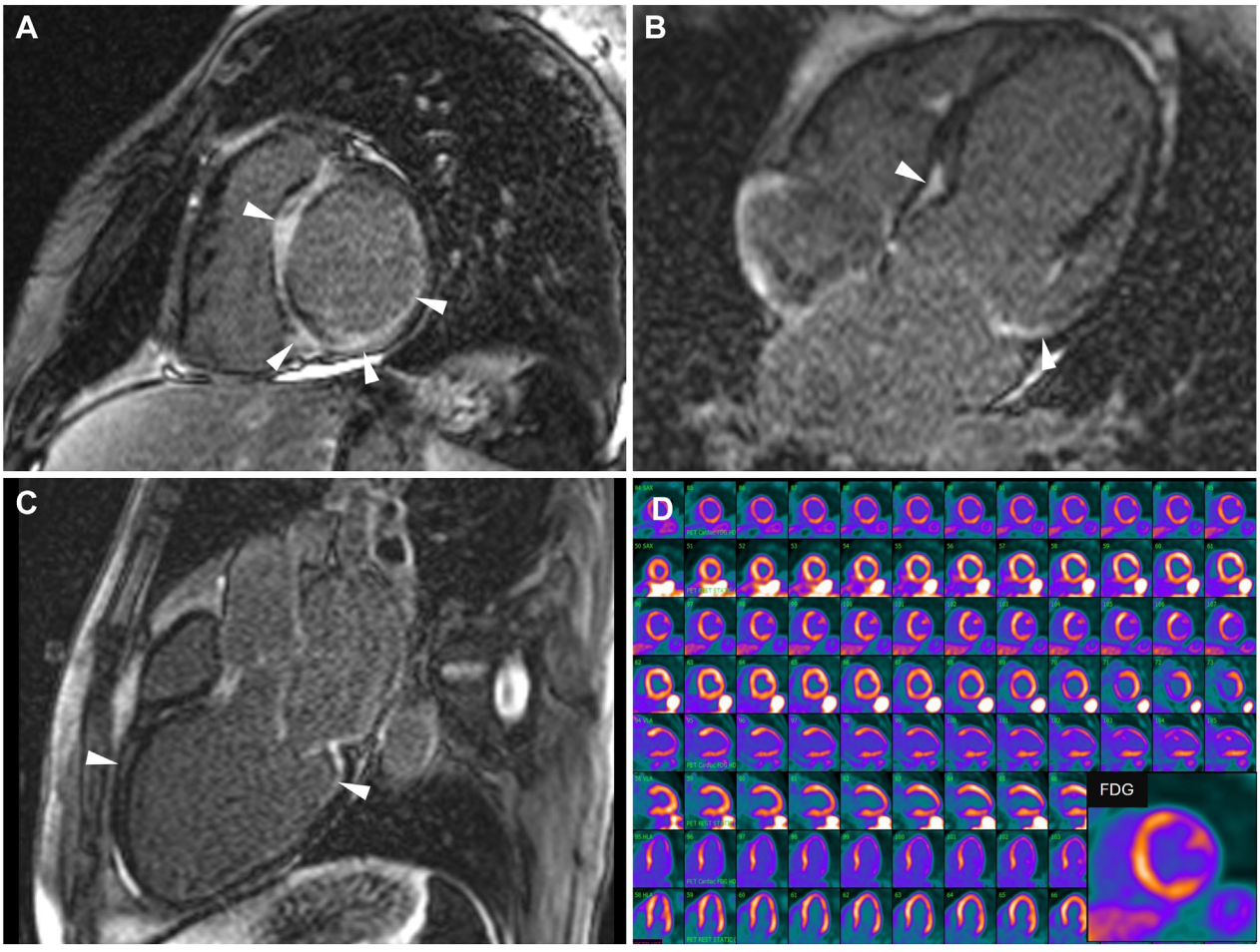
An 18-year-old male with a family history of sudden cardiac death experienced progressive palpitations

FIGURE 1 Case 1: Cardiac Magnetic Resonance and Positron Emission Tomography Images



Late gadolinium enhancement (LGE) imaging on cardiac magnetic resonance in the (A) short-axis, (B) 4-chamber, and (C) 3-chamber views demonstrating focal LGE along the anterior and inferior right ventricular insertion sites as well as faint midwall LGE along the septal segments. (D) Positron emission tomography imaging demonstrating focal ^{18}F-fluorodeoxyglucose (FDG) uptake along the lateral and septal segments (odd rows) with normal perfusion (even rows) indicating active inflammation.

FIGURE 2 **Case 2: Cardiac Magnetic Resonance and Positron Emission Tomography Images**



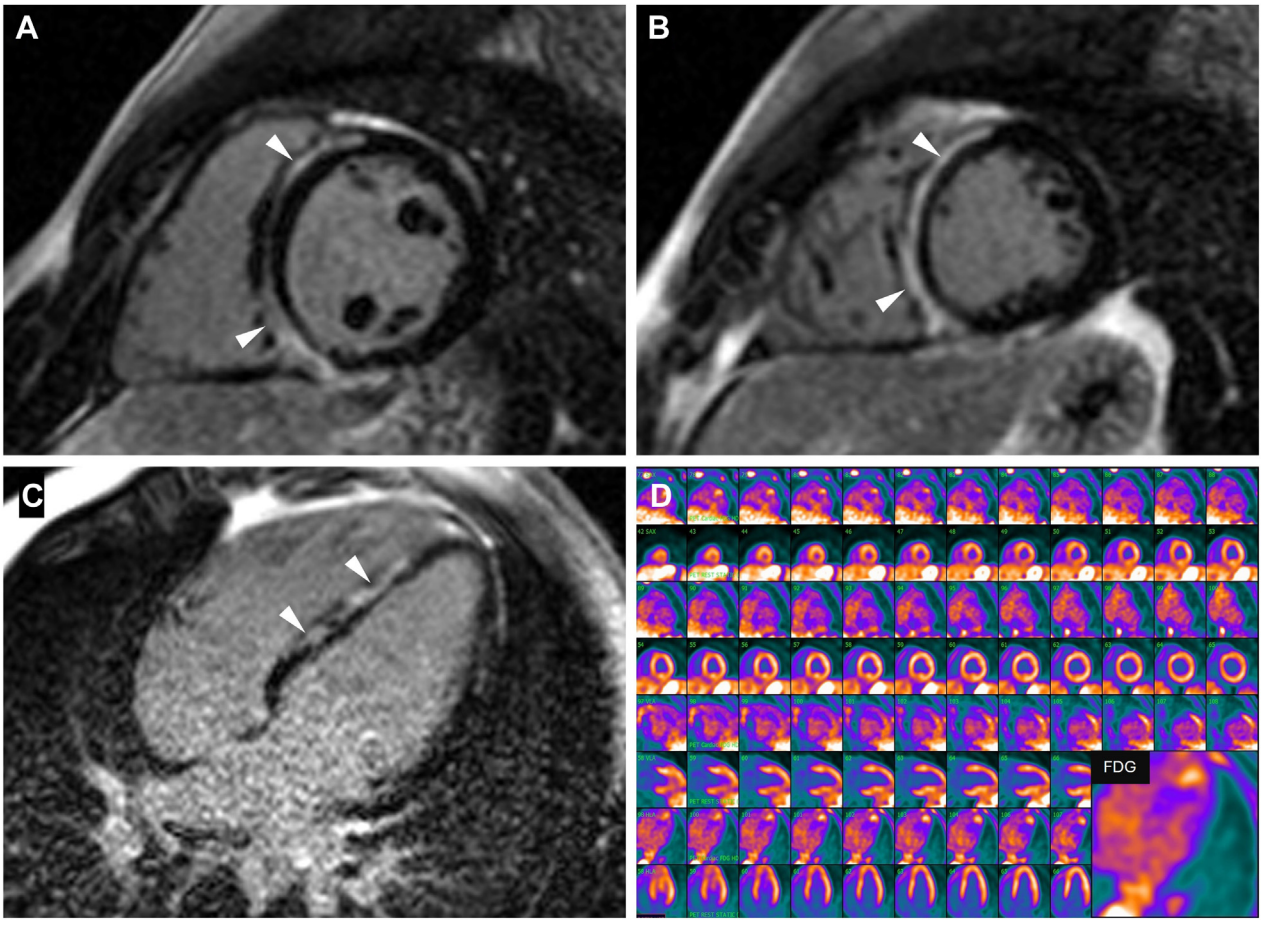
LGE imaging on cardiac magnetic resonance in the (A) short-axis, (B) 4-chamber, and (C) 3-chamber views demonstrating extensive LGE along the septal, lateral, and inferior segments. (D) Positron emission tomography imaging demonstrating diffuse FDG uptake throughout the myocardium (odd rows) with normal perfusion (even rows) initially suggesting poor myocardial suppression. Abbreviations as in Figure 1.

leading to syncope. Initial evaluation revealed monomorphic VT and LVEF of 57%. CMR demonstrated moderate LV dilation and extensive subepicardial LGE (Figure 3). A cardiac PET scan showed focal myocardial FDG uptake at the apex and apical septal wall, suggesting an inflammatory process (Figure 3). Endomyocardial biopsy was nondiagnostic. An ICD was implanted for secondary prevention.

One week postdischarge, he presented with left-sided chest pain. Coronary angiography and ICD interrogation ruled out obstructive coronary disease and arrhythmia, respectively. The case was reviewed at an MDT CS conference, where his presentation was deemed more consistent with myocarditis than arrhythmogenic right ventricular (RV) cardiomyopathy or CS. He was treated with nonsteroidal anti-inflammatory drugs, colchicine, and beta-blockers for suspected myopericarditis with frequent ectopy.

Following 2 admissions for ICD shocks due to VT despite escalation of medical therapy and a non-diagnostic repeat endomyocardial biopsy, a trial of steroid therapy was initiated for potential recurrent myocarditis or atypical CS. Treatment was eventually adjusted to quinidine monotherapy with successful suppression of VT. Persistent symptoms prompted genetic testing, revealing a pathogenic *DSP* gene variant consistent with arrhythmogenic LV cardiomyopathy.

FIGURE 3 Case 3: Cardiac Magnetic Resonance and Positron Emission Tomography Images



LGE imaging on cardiac magnetic resonance in the (A, B) short-axis and (C) 4-chamber views demonstrating extensive LGE along the septal segments as well as subepicardial LGE along the distal lateral segment. (D) Positron emission tomography imaging demonstrating focal FDG uptake along the apical septal segment (odd rows) consistent with active inflammation. Abbreviations as in Figure 1.

PATIENT 4

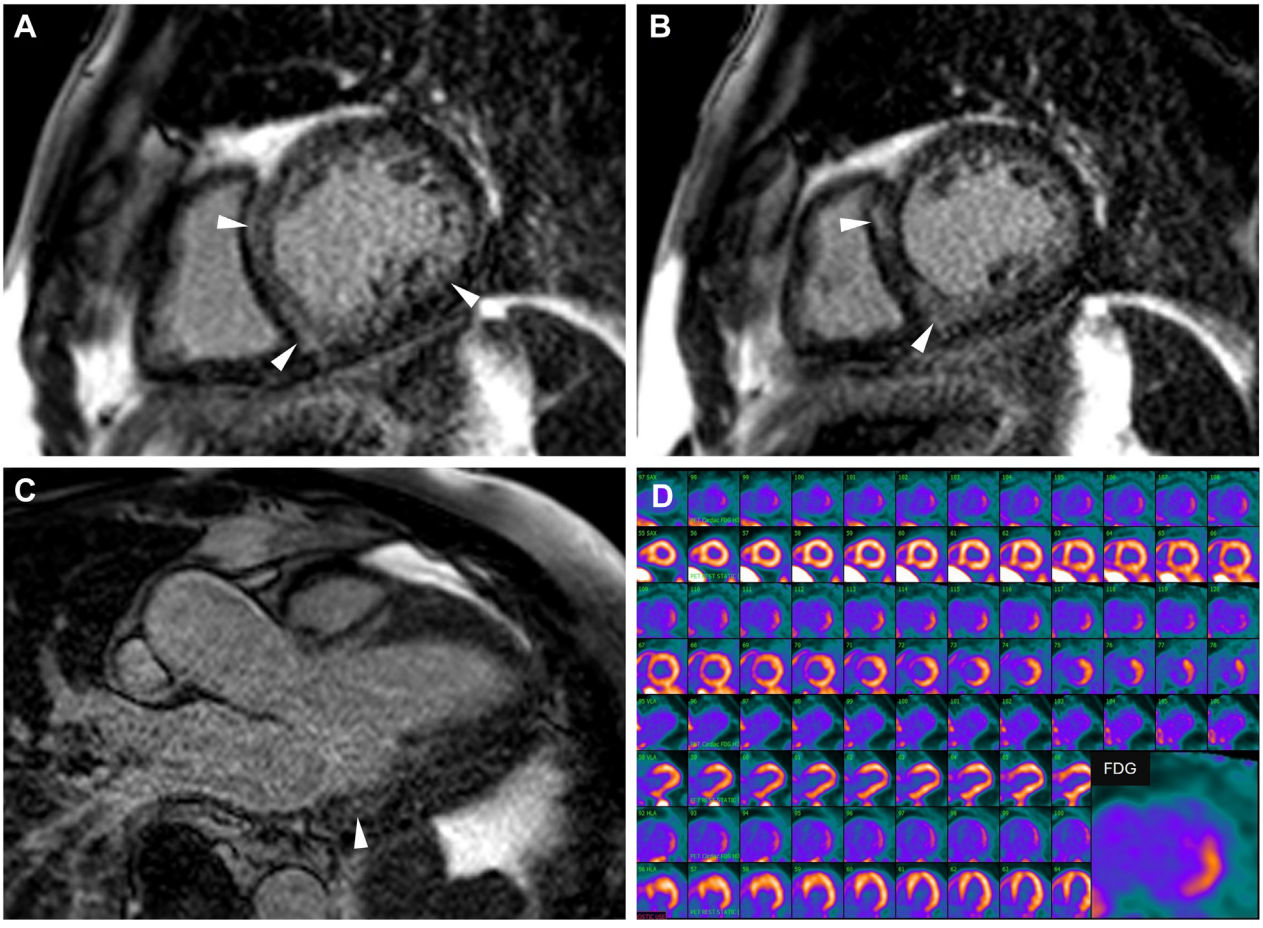
A 66-year-old man was admitted with respiratory failure with bilateral airspace consolidation along with mediastinal and hilar lymphadenopathy suggesting multifocal pneumonia. Initial echocardiography revealed a moderately dilated LV and moderate global hypokinesis, with a LVEF of 37%. Diuretics and antibiotics were initiated, and he was discharged on GDMT with plans for outpatient workup. Outpatient stress CMR demonstrated midwall LGE and a severely reduced LVEF of 28% with normal RV size and function (Figure 4). Cardiac PET showed FDG uptake along the LV lateral wall (Figure 4). Outpatient troponin levels were within normal limits.

During review at the MDT conference, the hilar lymphadenopathy and noncoronary distribution of LGE raised suspicions of an inflammatory/infiltrative process, though overall concern for CS was low due to reassuring cardiac biomarkers, absence of conduction disease, and a weak pattern of inflammation on cardiac PET and CMR.

Three-month follow-up CMR demonstrated an improvement in LVEF to 35% but worsened RV function, systolic septal flattening, and further extension of midwall LGE concerning for disease progression. Subsequent cardiac PET showed increased FDG uptake, particularly in the basal-to-mid lateral wall segments.

Repeat MDT discussion raised concern for a progressive inflammatory nonischemic cardiomyopathy and advised performing a voltage-guided endomyocardial biopsy, empiric immunosuppression, genetic consultation, and consideration for ICD.

FIGURE 4 Case 4: Cardiac Magnetic Resonance and Positron Emission Tomography Images



LGE imaging on cardiac magnetic resonance in the (A, B) short-axis and (C) 4-chamber views demonstrating extensive midwall LGE along the septal segments as well as subendocardial LGE along the basal inferolateral segments. (D) Positron emission tomography imaging demonstrating focal FDG uptake along the inferolateral segments (odd rows) consistent with active inflammation. Abbreviations as in Figure 1.

Endobronchial and transbronchial biopsies were unremarkable. Before undergoing endomyocardial biopsy, genetic testing revealed a pathogenic heterozygous variant in the *RBM20* gene, consistent with genetic DCM. The patient had an ICD successfully implanted and was continued on GDMT.

DISCUSSION

These 4 cases of DCM are summarized in Table 1 and demonstrate the variability in presentation and lack of pathognomonic findings on routine diagnostic evaluation. Genetic DCM, representing more than one-third of DCM cases, arises from pathogenic variants in genes critical for cardiac myocyte structure and function. These conditions are associated with a broad spectrum of clinical presentations, ranging from asymptomatic to severe heart failure with or without rhythm abnormalities.[1] The phenotypic and temporal heterogeneity associated with these conditions varies according to the implicated genes: *LMNA*, *SCN5A*, *TTN*, and *RBM20*, among others.[1-3]

Echocardiography remains the cornerstone for the initial assessment of genetic cardiomyopathy. However, the variability in LV dilatation and dysfunction observed at presentation often necessitates further characterization through CMR. The European Society

TABLE 1 Clinical Characteristics and Pathogenic Variants by Case

	Case 1	Case 2	Case 3	Case 4
Gene variant	*LMNA*, c.1444C>T;R482W	*LMNA*, c.961C>T;p.Arg321X	*DSP*, c.170+2dup	*RBM20*, c.1906C>T;p.R636C
Normal function	Encode proteins LAMIN A and LAMIN C for the nuclear lamina	Encode proteins LAMIN A and LAMIN C for the nuclear lamina	Encode desmosomes for intercellular junctions	Encode an RNA-binding motif that affects splicing of downstream genes affecting cardiac function
LV dysfunction on presentation	Yes	Yes	Yes	Yes
LV dilatation on presentation	Yes	Yes	Yes	Yes
RV dysfunction on presentation	Yes	Yes	No	No
LVEF, %	19	30	50	28
LGE pattern	Midwall LGE of the basal anteroseptal and basal to mid inferoseptal walls	Mid-wall LGE of basal to mid anteroseptal/inferosetpal segments and RV insertion sites; transmural LGE of basal to apical inferior segments; subendocardial LGE of basal to mid anterolateral/inferolateral segments and apical lateral segment	Subepicardial LGE of basal to mid anteroseptal, inferoseptal, distal septal, distal anterior, and distal inferior segments	Midwall LGE of basal to mid anteroseptal/inferoseptal and basal inferior segments as well as of the inferior RV insertion site
Conduction disease	No	Yes	No	No
Ventricular arrhythmias	No	Yes	Yes	No
ICD implanted	No	Yes	Yes	Yes

ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; RV = right ventricular.

of Cardiology affirms the value of CMR with a Class I recommendation for its use in the evaluation of a newly diagnosed cardiomyopathy.[4] This recommendation stems from the information that CMR provides on fibrotic, edematous, and inflammatory processes using T1-weighted, T2-weighted, and LGE techniques. Although patterns of LGE in genetic DCM are not pathognomonic, they typically involve the midwall and epicardium and less frequently the subendocardium.[2,4,5] More specifically, lamin gene variant-related DCM is often associated with septal midwall LGE, and desmosomal variants may show transmural RV and subepicardial mid-mural LV free wall LGE.[2,4]

The differential diagnosis for genetic DCM is broad and encompasses arrhythmogenic cardiomyopathy, CS, and myocarditis, all of which can present with similar CMR patterns of LGE.[3,6,7] Our institution utilizes cardiac PET imaging in select cases to evaluate the presence and pattern of FDG uptake as a marker of inflammation. Although this imaging modality does not differentiate genetic DCM from other etiologies, its sensitivity for inflammatory processes assists in diagnostic evaluation and therapeutic monitoring. Indeed, these cases highlight the common inflammatory process among these conditions. The overlap in imaging findings in DCM subtypes encourages appropriate interpretation of multimodality cardiac imaging, electrophysiologic abnormalities, genetic testing, and clinical evaluation.

Tailoring management strategies to patients is crucial in the treatment of genetic DCM. Patient 1 illustrates how a high clinical suspicion for CS leads to the initiation of empiric immunosuppression, highlighting the critical need to differentiate between genetic DCM and CS to avoid unnecessary treatment. Additionally, the potential for sudden cardiac death necessitates the consideration of device therapy, particularly in cases with ventricular arrhythmias or a concerning personal or family history, as demonstrated by patients 2 and 3.[8] The identification of pathogenic variants further complicates management, requiring a nuanced consideration of genetic counseling and targeted therapy.[9] This multifaceted approach underscores the complexity of managing genetic cardiomyopathies and the importance of an MDT to create a personalized treatment plan. Our institutional multidisciplinary CS team employs the expertise of a wide range of specialties, including advanced heart failure, electrophysiology, advanced cardiac imaging, pulmonology, and medical genetics for their valuable input in these complex cases.

CONCLUSIONS

These cases collectively highlight the need for an MDT approach to the diagnosis and management of genetic DCM, emphasizing the pivotal role of advanced imaging and early genetic testing. The integration of clinical findings with genetic insights

offers the potential to significantly improve patient outcomes through personalized care strategies.

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