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CASE SERIES
Inherited cardiac conditions/cardiomyopathies

Nuclear envelope lamin-related dilated cardiomyopathy: a case series including histopathology

William O'Connor[1], Asma Arshia[1], Deipthan Prabakar[2], Vaishnavi Sabesan[2], and Jeffrey F. Spindel [3]*

[1]Department of Pathology and Laboratory Medicine, University of Kentucky, 800 Rose Street, Lexington, KY 40536-0298, USA; [2]Government Kilpauk Medical College, 822 Poonamallee High Road, Kilpauk, Chennai 600010, India; and [3]Division of Cardiovascular Medicine, University of Kentucky, 800 Rose Street, Lexington, KY 40536-0298, USA

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Background Lamin A/C gene (LMNA) mutations cause myocardial fibrosis manifesting as arrhythmogenic, non-compaction, or dilated cardiomyopathies. Fibro-fatty replacement largely involves the conduction system and conduction disease commonly occurs prior to contractile dysfunction.

Case summary Two young, unrelated Caucasian males, aged 34 and 25, were referred to our centre for treatment of advanced heart failure. Both patients had a family history of heart failure and sudden cardiac death among their first-degree relatives and were diagnosed with Lamin A/C mutations, but they had not been screened prior to disease onset. Although the initial phenotypes were dilated cardiomyopathy and left ventricular non-compaction cardiomyopathy, both patients' disease progressed rapidly to include ventricular arrhythmias, severe global left ventricular hypokinesis, and dependence on outpatient milrinone to complete activities of daily living. Both patients received heart transplantation within 2 years of initial disease onset. The surgical pathology of the explanted hearts revealed characteristic findings of fibro-fatty degeneration of the conduction system, and using light microscopy, they were found to have nuclear membrane thinning, bubbling, and convolution throughout all areas sampled.

Discussion Lamin A/C–related cardiomyopathy is associated with sudden cardiac death early in the disease course, warranting early consideration of implantable cardioverter defibrillator implantation, and rapid progression to end-stage cardiomyopathy refractory to standard medical therapies, necessitating early referral to an advanced heart failure centre. We report a newly observed and recorded finding of morphologic nuclear alterations in late-stage disease using high-power light microscopy. These alterations underscore the pathophysiology of Lamin A/C–related cardiomyopathy and provide a basis for future research into disease-specific therapies.

Keywords Lamin A/C • LMNA • Arrhythmogenic cardiomyopathy • Myocardial fibrosis • Dilated cardiomyopathy • Case series • Case report

ESC curriculum 6.2 Heart failure with reduced ejection fraction • 6.5 Cardiomyopathy

* Corresponding author. Tel: +1 859 323 8040, Fax: +1 859 257 9461, Email: jeffrey.spindel@uky.edu
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Learning points

- Lamin A/C mutations cause heritable cardiomyopathy with a range of phenotypes including non-compaction, arrhythmogenic, and dilated cardiomyopathies.
- Pathophysiology includes fibro-fatty infiltration of myocardium and electrical tissue, and we report a novel finding of late-stage nuclear derangements inherent to LMNA cardiomyopathy.
- Conduction system disease often occurs prior to contractile dysfunction and sudden cardiac death is a reported first presentation.
- There is a high risk of major ventricular arrhythmias, and the guidelines of the European Society of Cardiology suggest considering implantable cardioverter defibrillator implantation in patients with LMNA mutation based on risk stratification criteria specific to LMNA cardiomyopathy.

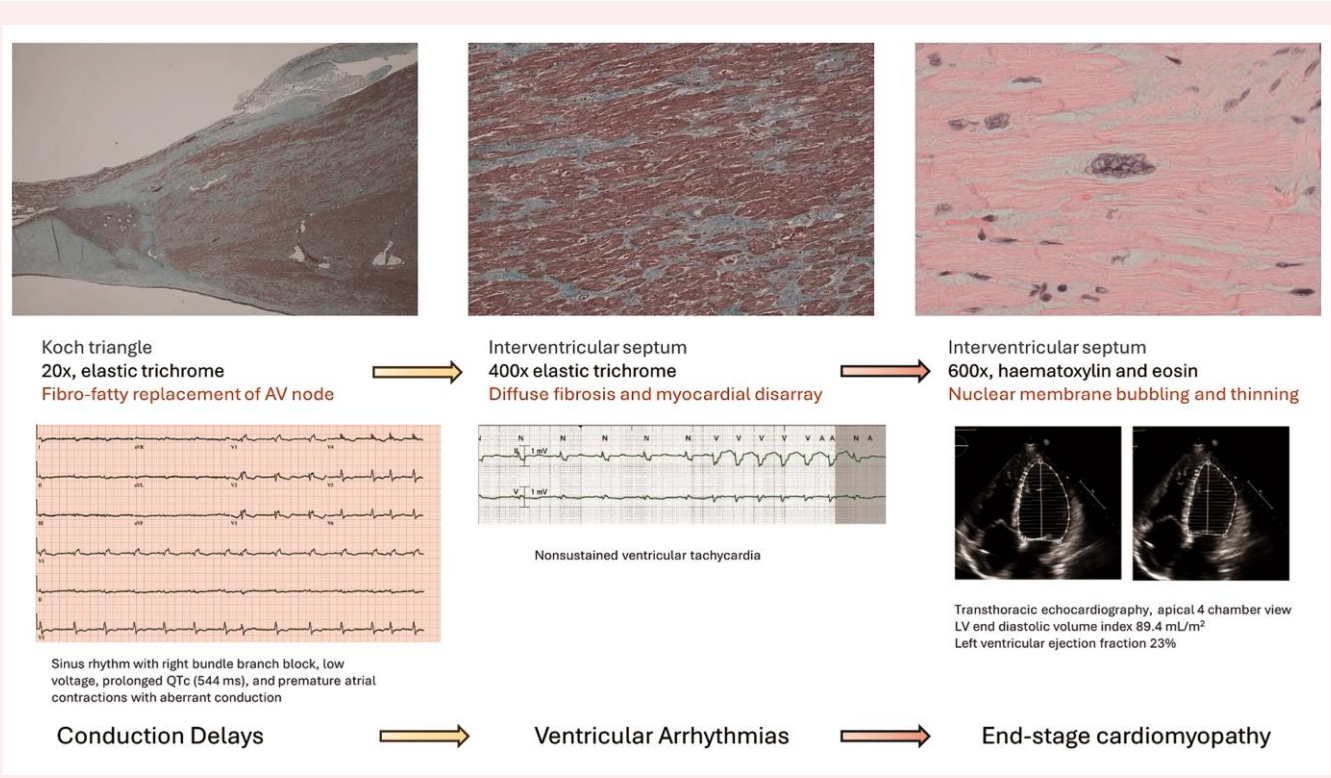
Introduction

Gene-related dilated cardiomyopathies (DCMs) result from mutations of proteins in cardiomyocyte cell membrane and cytoskeletal structural and contractile elements. Pathologies involving the nuclear envelope, including laminopathies, continue to be further elucidated.[1] Lamins A and C, the A-type lamins encoded by the *LMNA* gene, are highly expressed in differentiated tissues, namely, skeletal muscle, and provide structural support to the nucleus and maintenance of the nuclear shape.[2] Research into Emery–Dreifus muscular dystrophy, caused by mutations in emerin, suggests that A-type lamins also play a role in DNA replication, cell cycle regulation, namely, exit from the cell cycle, and apoptosis.[2]

Various pathologies result from *LMNA* mutations, including muscular dystrophies and cardiomyopathies. *LMNA*-associated cardiomyopathies frequently involve early conduction system dysfunction, and autopsy studies have correlated atrioventricular (AV) nodal block and tachyarrhythmia origin with fibrosis of the interventricular septum.[3,4] Histologic analysis of endomyocardial biopsies has also revealed fibrosis and fibro-fatty degeneration of conduction tissue, and electron microscopy or immune-electron microscopy has revealed rupture and bullae of the nuclear membrane.[5]

We present the clinicopathological findings from two patients with laminopathy who underwent heart transplantation for end-stage cardiomyopathy and provide detailed light microscopic findings focusing on cardiomyocyte nuclear changes not previously detailed with light microscopy.

Summary figure



Patient 1

A 34-year-old Caucasian male with a medical history of obesity (body mass index = 30 kg/m^2) presented with dyspnoea on exertion. Physical examination at the initial presentation revealed a regular heart rate and rhythm with a split S1 heart sound, non-laboured respiration with fine bibasilar crackles, and the absence of peripheral oedema. A three-generation family pedigree revealed DCM in his mother, who died at age 48 after the implantation of a durable left ventricular assist device while listed for heart transplantation, and sudden cardiac death

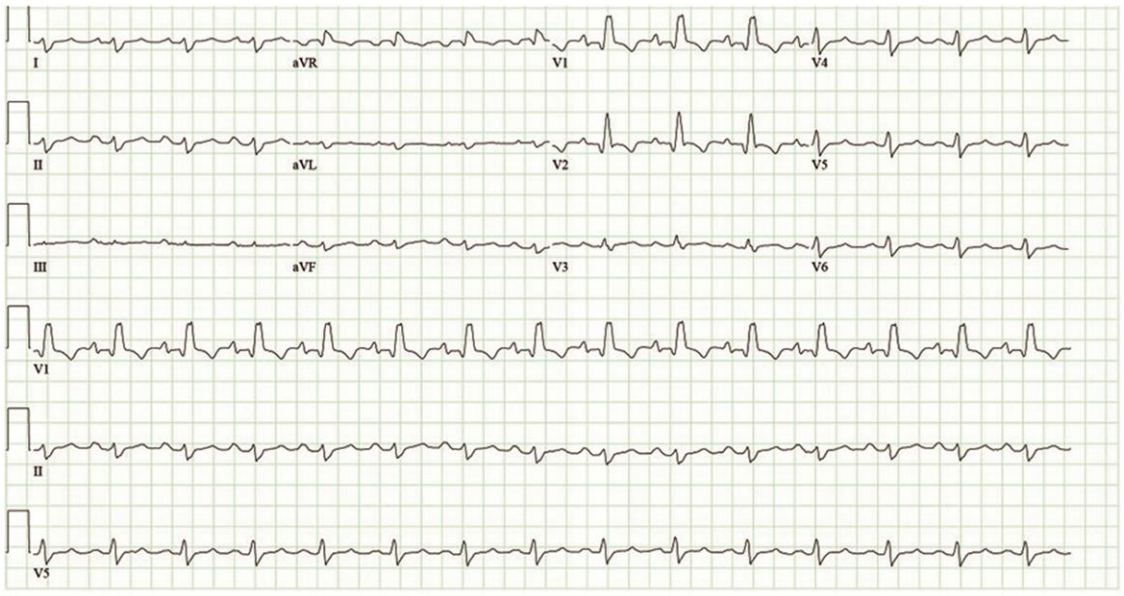


Figure 1 Patient 1: resting electrocardiogram. Sinus rhythm with right bundle branch block, normal PR interval, and prolonged QT interval ($QT_c = 493$ ms).

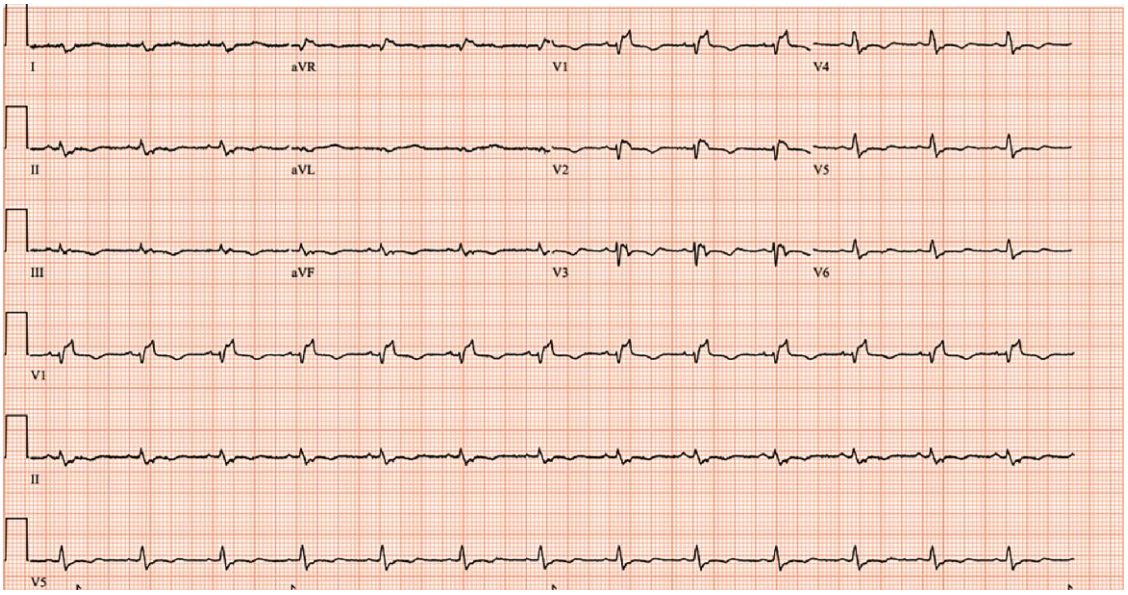


Figure 2 Patient 2: resting electrocardiogram. Sinus rhythm with right bundle branch block, short PR interval, and prolonged QT interval ($QT_c = 493$ ms).

in his maternal grandmother at age 49. The diagnostic workup included an echocardiogram revealing a left ventricular ejection fraction (LVEF) of 20–25% and an electrocardiogram (EKG), demonstrating right bundle branch block (RBBB) and a short PR interval with delta waves, consistent with the Wolff–Parkinson–White syndrome; however, this was not observed on subsequent EKGs. An EKG is presented in *Figure 1*. Subsequent stress cardiac magnetic resonance imaging (MRI) revealed normal perfusion and findings of non-compaction cardiomyopathy. Specifically, there was biventricular dilation with global left ventricular hypokinesis, prominent biventricular trabeculations with a 2:1 ratio of trabeculated to compacted myocardium, an absence of late gadolinium enhancement, and intact perfusion in all myocardial segments. Genetic testing revealed deleterious *LMNA* gene mutation. With guideline-directed medical therapies including sacubitril–valsartan 24–26 mg twice daily and spironolactone 25 mg once daily, LVEF improved to 30–35% and exertional dyspnoea improved to New York

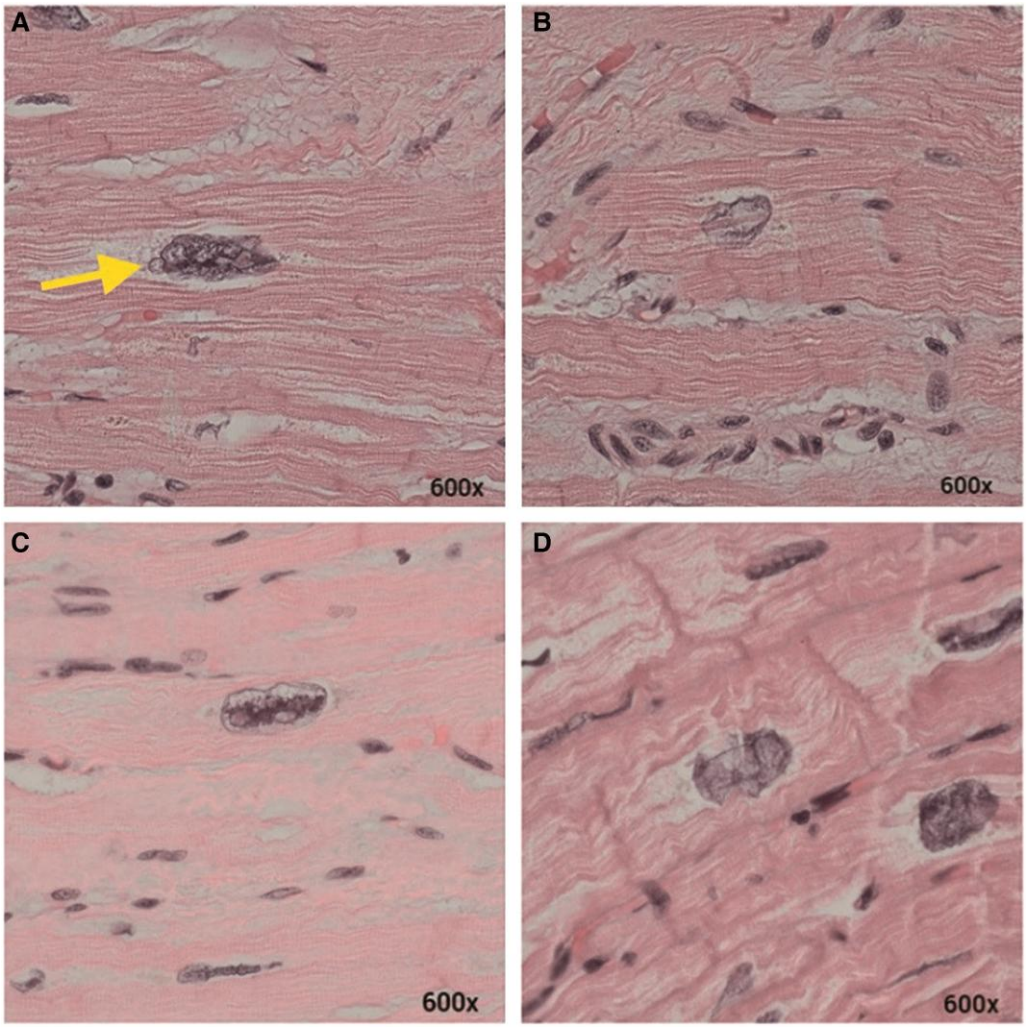


Figure 3 Characteristic nuclear changes: (*A* and *B*) Patient 1 and (*C* and *D*) Patient 2 (600×, high power). Cardiomyocyte changes demonstrating nuclear membrane bubbling and thinning (arrow).

Heart Association (NYHA) Class II symptoms. Notably, he was intolerant of any beta blockade due to sinus node dysfunction and symptomatic bradycardia. An implantable cardioverter defibrillator (ICD) was implanted for primary prevention due to reduced LVEF, conduction delay, and *LMNA* mutation.

The patient's clinical status declined over the following 2 years. Due to NYHA Class IV, American Heart Association (AHA) Stage D heart failure, he required continuous, outpatient milrinone infusion through a peripherally inserted central catheter (PICC) to complete activities of daily living. Treatment became complicated by asymptomatic, self-terminating episodes of sustained, monomorphic ventricular tachycardia, with three morphologies manifesting separately. He was listed for heart transplantation as an outpatient and underwent orthotopic heart transplantation at age 36.

Surgical pathology examination of the explanted native heart showed chronic dilated cardiomyopathy with cardiomegaly and pathologic changes throughout the atrial and ventricular myocardium with secondary endocardial fibrosis. Microscopically diffuse, chronic cardiomyopathic changes with interstitial fibrosis included loss of AV bundle branch. Cardiomyocyte cytoplasmic perinuclear inclusions staining as glycoprotein occupied many cells and indented the nuclei. Prominent nuclear membrane thinning and bubbling with nuclear infolding was observed throughout the myocardium (*Figures 3A, B* and *4A, B*).

The post-transplant clinical course was complicated by systemic cytomegalovirus infection and leukopenia, necessitating discontinuation of mycophenolate mofetil and symptomatic grade 2R rejection 2 weeks after transplantation, which was successfully treated with intravenous steroids and diuretics. Subsequently, routine echocardiography, right heart catheterization, screening for coronary allograft vasculopathy, and screening for rejection with both serum antibodies and endomyocardial biopsy were performed. At the 6-year follow-up, he had preserved graft function and there was no significant rejection, complication, or evidence of skeletal myopathy. The patient and his family elected not to screen their children for *LMNA* mutation until they reached adulthood.

Patient 2

A 25-year-old Caucasian male with no known medical history presented with recurrent palpitations and associated pre-syncope. Physical examination at initial presentation revealed a thin man with

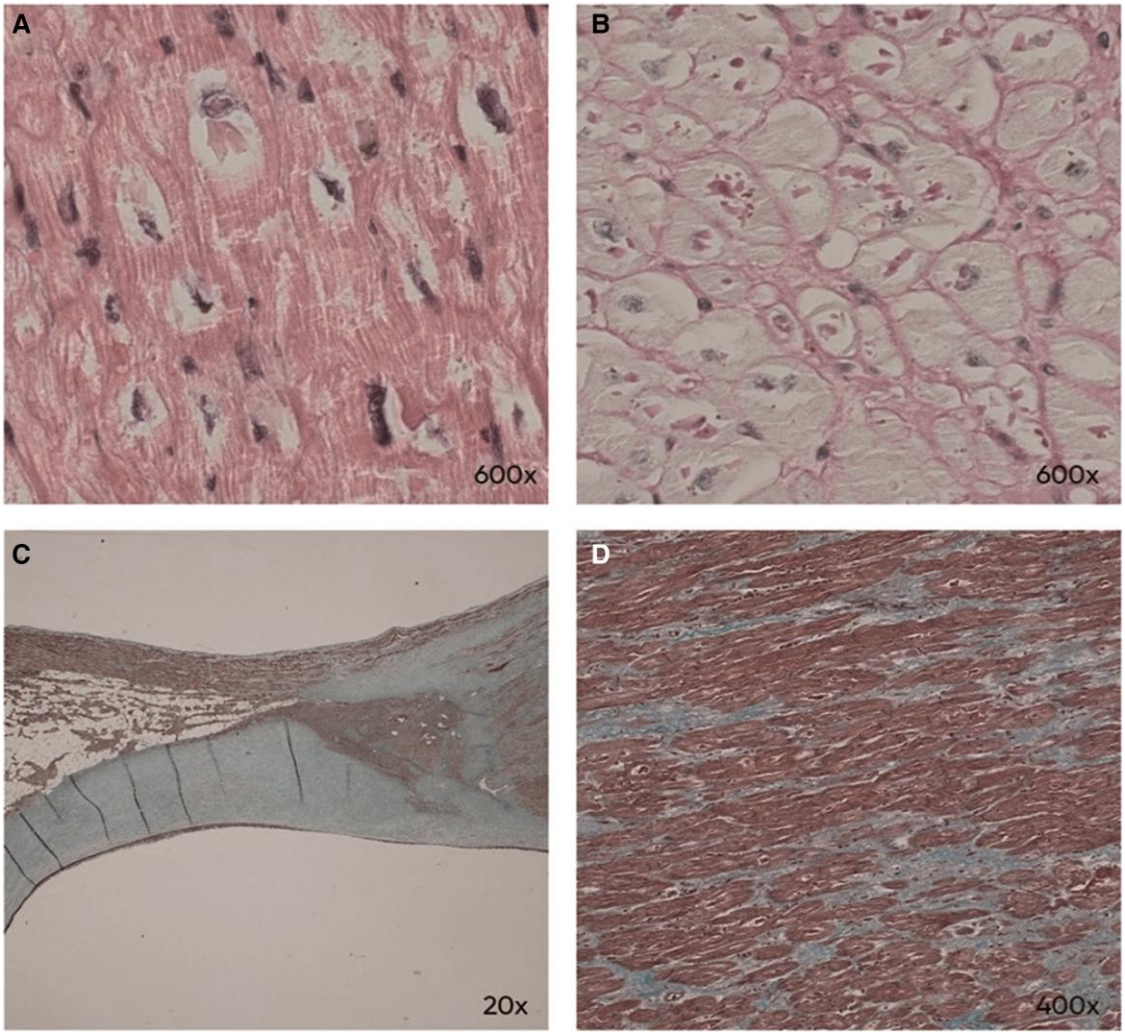


Figure 4 Patient 1: cytoplasmic inclusions haematoxylin and eosin and periodic acid-Schiff at (*A* and *B*) 600×. Patient 2: Low power elastic trichrome combination. Section through region of atrioventricular bundle of His (*C*, 20×, centre) with right atrial wall and subaortic left ventricular outflow tract to the left and scarred basal interventricular septum (*D*, 400×) to the right. Loss of atrial muscle with adipose replacement with the absence of atrioventricular nodal is in white.

tachycardic heart rate, regular cardiac rhythm, Grade 2/6 systolic murmur best heard at the left lower sternal border, normal pulmonary examination, and the absence of peripheral oedema. A three-generation family pedigree revealed heart failure and sudden cardiac death in his mother at age 30 and in multiple extended family members. The EKG showed a short PR interval, RBBB pattern, and prolonged QT_c. The EKG is presented in *Figure 2*. Ambulatory EKG monitoring revealed frequent episodes of non-sustained ventricular tachycardia (NSVT) and ventricular ectopy of various morphologies. Transthoracic echocardiography revealed LVEF of 25–30% with severe global hypokinesis. Coronary computed tomography angiography did not reveal any significant coronary artery abnormalities. Cardiac MRI ruled out infiltrative aetiologies. Specifically, the left ventricle was dilated and globally hypokinetic, there was hypertrabeculation of the left ventricle at less than a 2:1 ratio of trabeculated to compacted myocardium, there was an increased T1 mapping signal (1350 ms), and no evidence of late gadolinium enhancement. Genetic testing revealed the presence of a Lamin A/C mutation. Guideline-directed medical therapy, including beta-blockers, was started and a dual-chamber ICD (right atrial and right ventricular leads) was implanted for primary prevention due to reduced LVEF, *LMNA* mutation, frequent NSVT, conduction delay, and sudden cardiac death in a first-degree relative.

Despite aggressive titration of guideline-directed medical therapies, including metoprolol succinate 25 mg once daily, sacubitril–valsartan 49–51 mg twice daily, and spironolactone 25 mg once daily, he had no reduction in symptoms or improvement in cardiac function. Within 2 years, the patient was dependent on continuous outpatient milrinone infusion through a PICC due to NYHA Class IV, AHA Stage D heart failure, complicated by frequent NSVT. He was listed for heart transplantation as an inpatient, which he underwent 2 years after symptom onset at the age of 27.

The surgical pathology of the native explanted heart confirmed features of chronic dilated cardiomyopathy with cardiomegaly and pathologic changes throughout the myocardium of the atria and ventricles with secondary endocardial fibrosis. Microscopically, there was an absence of AV nodal tissue with fibro-fatty replacement, while the AV bundle of His remained. Chronic cardiomyopathic changes were observed in the myocardium of all chambers, with diffuse transmural

interstitial fibrosis being particularly prominent in the LV myocardium of the basal interventricular septum. Ventricular cardiomyocytes exhibited nuclear abnormalities, including envelope thinning, bubbling, and marked convolutions (*Figures 3C, D* and *4C, D*).

During the follow-up period, in addition to regular post-transplant care and immune suppression, the patient underwent monitoring with echocardiography, right heart catheterization, screening for coronary allograft vasculopathy, and screening for rejection with both serum antibodies and endomyocardial biopsy. At the 16-month follow-up, graft function was preserved and there was no significant rejection, transplant complication, or skeletal myopathy. The patient's children were screened for cardiomyopathy and *LMNA* mutation. His son was genotype positive and phenotype negative at 5 years old, and his daughter was genotype and phenotype negative when screened at 19 months of age.

Discussion

Mutations in the *LMNA* gene (Chromosome 1q21.2-q21.3), responsible for encoding Lamin A/C proteins, have been linked to skeletal muscle and cardiac pathologies and account for 5–8% of genetic DCM cases.[6] Inheritance is autosomal dominant and phenotypic penetrance exceeds 90%.[7] These nuclear membrane myocyte proteins polymerize and construct the cardiomyocyte and skeletal muscle cell nuclear lamina, providing structural support to the inner nuclear membrane.[8] Lamin A/C proteins also possess regulatory functions impacting gene expression and signalling.[9]

LMNA mutations can manifest various phenotypes, including dilated cardiomyopathy and arrhythmogenic cardiomyopathy.[9] Unlike other gene-associated cardiomyopathies, *LMNA*-related DCM frequently presents with conduction system disease or arrhythmias before the onset of heart failure.[7] Likewise, in *LMNA* carriers experiencing arrhythmias, myocardial fibrosis is observed histologically prior to left ventricular dysfunction.[10] In the early stages of the disease, conduction system disorders, such as first-degree AV block or inter/intraventricular conduction delays, are commonly observed.[11] Supraventricular arrhythmias, specifically atrial flutter and atrial fibrillation, and sinus node dysfunction or intolerance of beta blockade are also common.[5,12–14]

Importantly, *LMNA*-related DCM exhibits a four-fold higher incidence of sudden cardiac death than other DCM aetiologies.[5,12,14] Therefore, the European Society of Cardiology has assigned a Class IIa recommendation for ICD implantation for patients with *LMNA* cardiomyopathies experiencing NSVT, atrioventricular conduction delay, or those with a reduced LVEF and higher risk of ventricular arrhythmias.[15–17]

The pathophysiology of *LMNA*-associated DCM is attributed to myocardial fibrosis, causing both conduction and contractile impairment.[10] *LMNA* fibrosis is dominant in the interventricular septum especially at the base without myocyte disarray. The mechanism may involve increased autophagy in the setting of progressive stress-related mechanical activation through the cytoplasm to the defective nucleus with altered remodelling. Unlike secondary fibrosis seen in other cardiomyopathies, *LMNA*-associated fibrosis is independent of activation in the renin–angiotensin–aldosterone axis.[18]

Our microscopic examinations disclosed striking findings affecting cardiomyocyte nuclear envelopes throughout the myocardium, reflecting diffuse somatic cell mutational derangements of the inner membrane. Other shared myocardial findings include advanced chronic cytoplasmic size variation together with prominent pericellular and zonal replacement fibrosis. Furthermore, adipose tissue replacement of lost AV nodal and bundle branch elements was observed, underlying electrophysiological abnormalities. The heart explant specimen from Patient 2 revealed complete fibro-fatty replacement of the AV node, while in Patient 1, fatty replacement was limited to the bundle branch. These findings perhaps explain the earlier occurrence of conduction delays before left ventricular dysfunction, which is a characteristic feature of *LMNA*-related cardiomyopathy.[17]

In a large study of patients with dilated or arrhythmogenic cardiomyopathy followed for a median of 118 months, Paldino *et al.*[19] found the *LMNA*-associated cardiomyopathy had variable phenotypes at diagnosis, a high rate of phenotype change from dilated to arrhythmogenic cardiomyopathy over follow-up (21%), and the highest rates of death or heart transplant (41%). While myocardial fibrosis and fibro-fatty degeneration of conduction tissue have been documented early in the disease course via endomyocardial biopsy,[3,4] our findings of nuclear alterations in late-stage disease may explain the common endpoints. These alterations, due to ongoing damage to the nuclear membrane, whose components require Lamins A and C for integrity, underscore the pathophysiology of *LMNA*-related cardiomyopathy. Our findings support the need for genetic testing early in the disease course for prognostication, early implantation of ICD, and early referral to a heart transplant centre.

Lead author biography

William N. O'Connor, MD, an Irish-born physician, completed his medical schooling during 1966–72, and graduated with MB, BCh, BAO from the National University of Ireland at Cork in 1972. He completed Anatomic Pathology Residency at Georgetown University, Washington, DC, and his MD through Flex in 1974. He has been working as a pathology faculty at the University of Kentucky, Lexington, 1978 to present. He was a professor of pathology and paediatrics (1993), a fellow at the College of American Pathologists, and a fellow at American College of Cardiology. He also worked in Autopsy Service, General Surgical Pathology, Cardiac (Pediatric and Adult), Vascular and Heart/Lung Transplant Pathology, and worked as an invited faculty for the Hands-on Cardiac Morphology Course, Imperial College, London, UK (1995–2019). He published 87 peer-reviewed publications.

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Consent: The authors confirm that both patients have provided consent for submission and publication of this case series including diagnostic images, histology, and associated text in line with the Committee on Publication Ethics guidance.

Conflict of interest: The authors have nothing to disclose.

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Data availability

No new data were generated or analysed in support of this research.

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