Biventricular, endocardial, and epicardial substrate characterization for ventricular tachycardia and correlation with whole-heart macropathology and histopathology in a patient with lamin A/C cardiomyopathy

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Introduction

Lamin cardiomyopathies are part of a larger spectrum of disorders involving mutations in the lamin (A/C) gene (*LMNA*).[1] The *LMNA* gene codes for A-type lamins, a group of ubiquitous nuclear membrane filament proteins, which provide nuclear stability. Defects in lamin function result in nuclear fragility, altered nuclear protein interaction, mechanotransduction, signaling, and gene expression with significant phenotypic heterogeneity.[1–3] *LMNA* mutations underpin neuromuscular and adipose tissue phenotypes such as Emery-Dreifuss muscular dystrophy, familial lipodystrophy, and Charcot-Marie-Tooth disease. Cardiac involvement can result in a characteristic phenotype with familial dilated cardiomyopathy, atrioventricular (AV) block, arrhythmias, and an aggressive clinical course.

We present a classic case of a patient that captures the archetypal natural history of LMNA cardiomyopathy, combined with comprehensive electroanatomic biventricular endocardial and epicardial substrate characterization for ventricular tachycardia (VT), complemented with whole-heart macropathology, histopathology, and genetic evaluation.

Case report

A 53-year-old woman presented with sustained monomorphic VT (Figure 1). Eight years prior, she had unexplained complete AV block in the presence of normal biventricular function, necessitating insertion of a dual-chamber pacemaker. Two years thereafter, her left ventricular (LV) function declined (ejection fraction [EF] 45%), thought to be due to pacing-induced cardiomyopathy, necessitating upgrade to a pacemaker with cardiac resynchronization therapy (CRT) capability. Atrial standstill was also noted at this time. An unprovoked deep vein thrombosis occurred a year later, requiring 6 months of anticoagulation (negative thrombophilia screen). Family history was notable for unexplained sudden cardiac death of her mother at age 80 and of a paternal uncle at age 50.

On presentation with VT, LVEF had declined to 30%, right ventricular (RV) function was normal, and there was no coronary disease on angiography. VT storm ensued despite amiodarone, maximal ß-blockade, and lignocaine. Transesophageal echocardiogram (performed owing to atrial standstill with no anticoagulation) showed a mobile left atrial appendage (LAA) thrombus (Supplemental Video 1). Aggressive antiarrhythmic drug therapy was initiated with hope for delaying ablation to allow thrombus resolution; however, recurrent VT storm necessitated urgent ablation.

A substrate-guided approach was taken to avoid multiple VT inductions and cardioversions, which may have resulted in embolization of the LAA thrombus. On endocardial biventricular mapping, extensive intramural scar was noted in the septum and LV inferior wall on unipolar mapping (Figure 2, first 3 rows). Endocardial RV unipolar mapping

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KEY TEACHING POINTS

- LMNA cardiomyopathy is characterized by atrioventricular block, atrial arrhythmias, prothrombotic tendency, ventricular arrhythmias refractory to antiarrhythmic and catheter ablation therapy, progression to end-stage heart failure, and need for emergent cardiac transplantation.

- Basal septal intramural substrate, capable of supporting multiple reentrant ventricular tachycardias, are typical, making ablation challenging.

- Fibrofatty replacement of the myocardium and characteristic nuclear changes on histopathology, such as elongation and thinning of the nucleus, irregular chromatin distribution (chromatin clumping), and altered alignment, are hallmarks of the disease.

Figure 1   The 12-lead electrogram morphologies of the clinical (VT1) and inducible ventricular tachycardias.

showed low-voltage scar in the free wall of the RV outflow tract (RVOT) extending from the pulmonary to the tricuspid valve (Figure 2, fourth row). Multiple intramural septal VTs (Figure 1) were inducible and targeted for ablation (Supplemental Figure 1) in the basal/mid-apical LV inferoseptum, basal anteroseptum, basal septal RV/RVOT, and posteromedial papillary muscle. Recurrent basal inferoseptal VT after endocardial ablation prompted epicardial access, mapping, and ablation of the basal inferoseptal region (Figures 2 and 3). A large area of electrical silence was noted over the entire RV free wall with failure to capture with high output pacing (10 mA and 9 ms), suggestive of dense scar or fat (Figure 2, last row).

Recurrent basal septal VT prompted a third ablation on the basal LV and RV septum, including transcoronary ethanol ablation of the first septal perforator (Supplemental Videos 2 and 3). VT induction after the final attempt induced ventricular fibrillation with 3 extrastimuli. Amiodarone and lignocaine were stopped, and ß-blockade continued. To further investigate the cause of her cardiomyopathy, RV septal biopsy and computed tomography / positron emission tomography were negative for sarcoidosis and infiltrative disease. Cardiac magnetic resonance imaging was not feasible owing to lack of compatible leads. Her device was upgraded to a CRT-defibrillator.

Over the next 3 months she remained VT free; however, she developed progressive left and right heart failure requiring 3 hospital admissions, necessitating levosimendan, dobutamine, and furosemide infusions. Repeat echocardiography demonstrated worsening LV function (EF 25%) and severe RV dysfunction. Recurrent slow VT occurred at 4 months postpresentation, with a more apical inferoseptal exit, controlled with antitachycardia pacing and reinitiation of amiodarone (Figure 1, VT6).
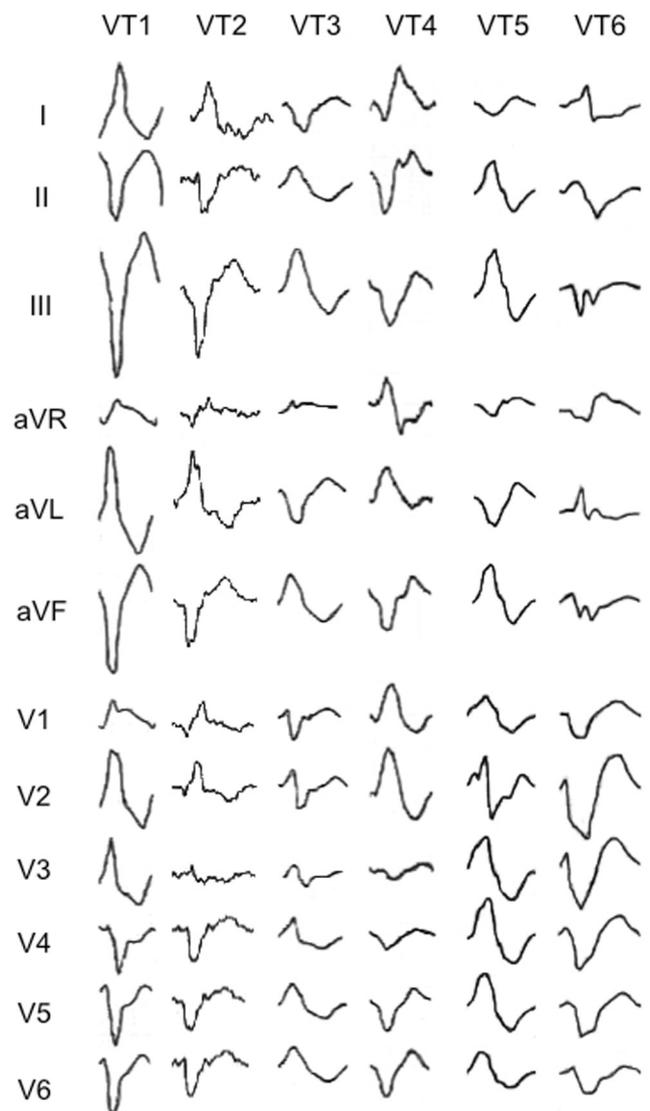
Genetic testing showed a pathogenic frameshift mutation (deletion) in the lamin A gene (*LMNA* c.1579delC, p.(Arg527Valfs*21). Given her refractory heart failure and VT and recognition of LMNA cardiomyopathy, she was referred for advanced mechanical circulatory support and cardiac transplantation. She underwent transplantation 9 months after her initial VT presentation. In follow-up, she remains well 4 months post cardiac transplant. Familial clinical and phenotyping genetic screening of her 2 daughters and her sister is under way.

Analysis of the explanted heart showed prominent macroscopic fatty infiltration of the RV epicardial surface (Figure 3A). Near transmural scar was seen in the basal and mid LV anteroseptum and inferoseptum and in the RV septum (from intrinsic disease and subsequent ablation), as well as punctate subendocardial scar over the posteromedial papillary muscle, likely from ablation (Figure 3B). Histologic analysis showed prominent lipomatous replacement of myocardial tissue (Figure 3C). Cardiomyocytes contained

RAO
LV Endo

PA
LV Endo

PA
RV Endo

RAO
RV Endo

RAO Epi   Inf Epi
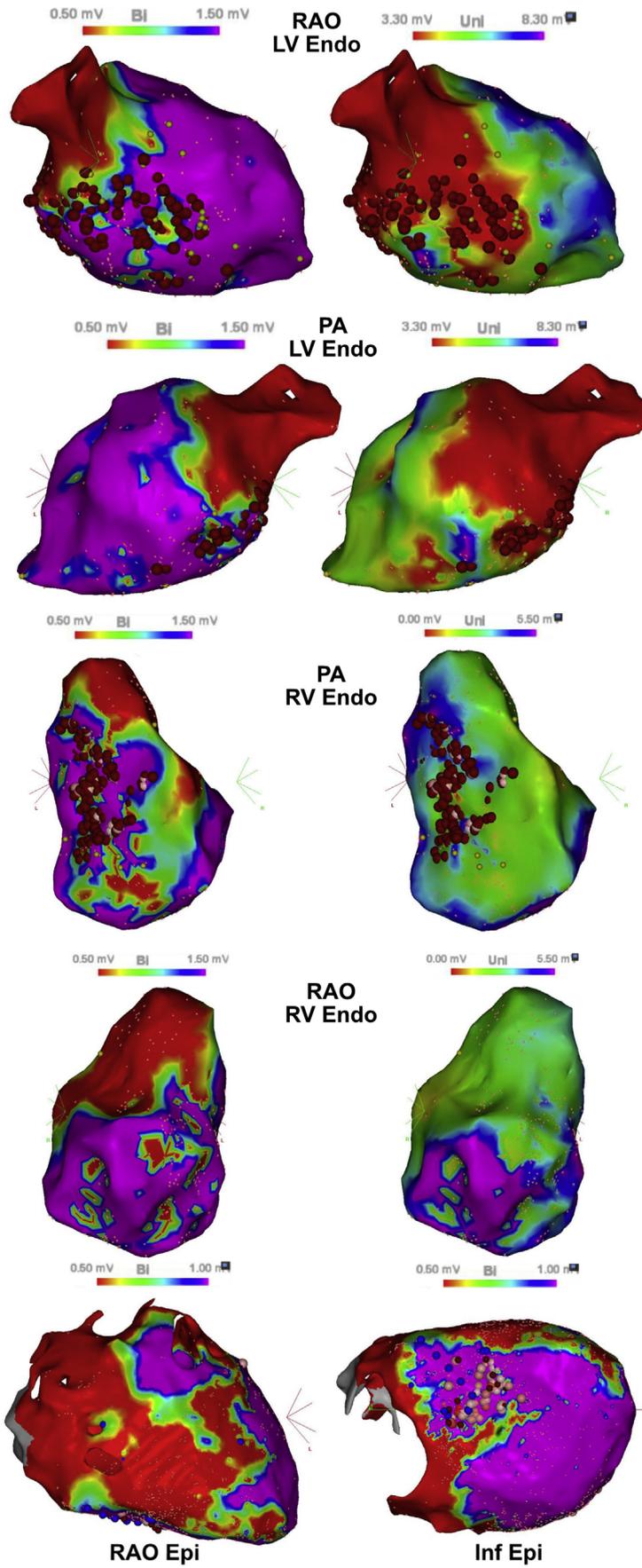
nuclei that were elongated and lobulated with irregular, central chromatin clumps and a barely visible nucleolus (Figure 3D).

Discussion

Mutations in the *LMNA* gene (OMIM 150330) on chromosome 1q21.1–21.3, which encodes the nuclear envelope protein lamin A/C, manifest in a large spectrum of disorders with neuromuscular, cardiac muscle and conduction, premature aging, and metabolic phenotypes, collectively termed the laminopathies.[1] *LMNA* mutations are responsible for 5%–6.2% of familial dilated cardiomyopathies, characterized by autosomal dominant inheritance. The disease exhibits age-dependent penetrance, such that disease manifestation approaches 100% by the seventh decade, and variable expressivity among family members. The natural history of LMNA cardiomyopathy is one characterized by progressive cardiac conduction abnormalities (ie, first-degree AV block, progressing to higher degrees of AV block), atrial arrhythmias, and ventricular arrhythmias that classically precede ventricular dilatation or dysfunction.[7] The disease aggressively progresses to heart failure, with up to 20% of patients requiring cardiac transplantation within 7 years of diagnosis.[7] LMNA mutations are also known to be associated with a prothrombotic phenotype, with an increased risk of arterial and venous thromboses, thought to be owing to altered platelet function and increased thrombin generation.[8]

This singular case captures the unique natural history of progression of LMNA cardiomyopathy and characterizes the disease in the classic sense using biventricular whole-heart electroanatomic mapping, histopathology, and genetic evaluation. The natural history of AV block with atrial arrhythmia, prothrombotic tendency, and intramural basal septal scar-mediated VT rapidly progressing to end-stage heart failure is typical of this disease.[7] Moreover, macroscopic lipomatous infiltration on pathology[1] and chromatin clumping on histopathology were consistent with noted description of the disease.[3] Timely genetic diagnosis allowed for rapid evaluation and institution of cardiac transplantation in this highly morbid condition.

Atrial arrhythmias are noted in up to 76% of patients within 7 years of diagnosis, of which atrial fibrillation is the most dominant (56%), followed by atrial flutter (21%) and atrial tachycardia (16%).[7] Atrial standstill was indeed unique in this patient, but likely represented progression from atrial fibrillation as a consequence of progressive atrial myopathy. Complete AV block is the presenting symptom in 6% of patients with LMNA cardiomyopathy, progressing to 28% by 7 years follow-up.[7] The pathogenesis is progressive septal fibrosis leading to first-degree and then higher degrees of AV block with time. The unprovoked deep vein thrombosis is consistent with the prothrombotic phenotype of this disease.[8]

Ventricular arrhythmias in LMNA cardiomyopathy are invariably related to basal septal intramural substrate.[9] Sustained monomorphic VT is seen in 35% of patients within 7 years of diagnosis.[9] A previous multicenter study noted intramural substrate in the basal septum, inferior LV wall, and subaortic mitral continuity in LMNA cardiomyopathy, capable of supporting multiple reentrant VTs, consistent with the present report.[9] Catheter ablation is challenging, requiring multiple procedures (including transcoronary ethanol ablation in one quarter of patients), with a low rate of noninducibility of all VTs (25%) and a high rate of VT recurrence (91% by 7 months) attributed to deep septal substrate.[9] The present report is thus typical for this disease. Moreover, LMNA cardiomyopathy is associated with a high rate of progression to end-stage heart failure, with 44% of patients receiving or awaiting mechanical circulatory support or cardiac transplantation,[7] consistent with the history described in this case report. The disease is associated with high mortality (13% by 7 years), underpinning the need for early genetic diagnosis, emergent transplant evaluation, and familial screening. Nonmissense mutations have been associated with more aggressive disease progression, as evidenced by this case.[7]

Fatkin and colleagues[1] described prominent fat infiltration in skeletal muscle of patients with *LMNA* mutations with dilated cardiomyopathy and conduction system disease. Increased fibrofatty infiltration of the RV epicardium and endocardial replacement fibrosis has also been noted in autopsy specimens of patients with LMNA cardiomyopathy.[4] Fibrofatty degeneration of the AV node has been noted in a large Japanese family with LMNA cardiomyopathy.[5] Extensive RV fatty infiltration, mimicking an ARVC-like phenotype, has been noted in patients with LMNA mutations.[6] In mouse models of LMNA-deficient hearts, Nikolova and colleagues[3] and Chandar and colleagues[2] have demonstrated that LMNA-deficient cardiomyocytes exhibit distinct changes in nuclear shape, size, and chromatin clumping. Whereas normal cardiomyocytes' nuclei have a well-rounded oval shape with a granular, dispersed pattern of chromatin and a distinct nucleolus, LMNA-deficient cardiomyocyte nuclei are characteristically longer and thinner, with irregular chromatin distribution and altered alignment (classically peripheral and central heterochromatin clumping).[2,3] Similar irregularities in nuclear shape were noted in autopsy specimens of patients with LMNA mutation.[4] These histologic findings were also noted in our case.

Figure 2   Right anterior oblique (RAO) views (*first row*) and posteroanterior views (*second row*) of the left ventricular (LV) endocardial (Endo) bipolar (*left*) and unipolar (*right*) voltage maps showing normal bipolar voltages and abnormal unipolar voltages consistent with intramural scar. Third row illustrates posteroanterior (PA) view of right ventricle (RV) with bipolar (*left*) and unipolar (*right*) voltage maps, and fourth row illustrates RAO views of the RV, with both rows showing extensive RV septa scar. Fifth row shows RAO and inferior (Inf) views of the extensive epicardial (Epi) low voltage of the surface of the RV (*left*), which failed to capture with high-output pacing (10 mA and 9 ms) with absence of electrical signals, suggestive of dense scar or fat. *Red and pink dots* denote ablation lesions. In all voltage maps, *purple* indicates normal tissue whereas *red* indicates scar tissue; *yellow*, *green*, and *violet* indicate border zones between scar and normal tissue.
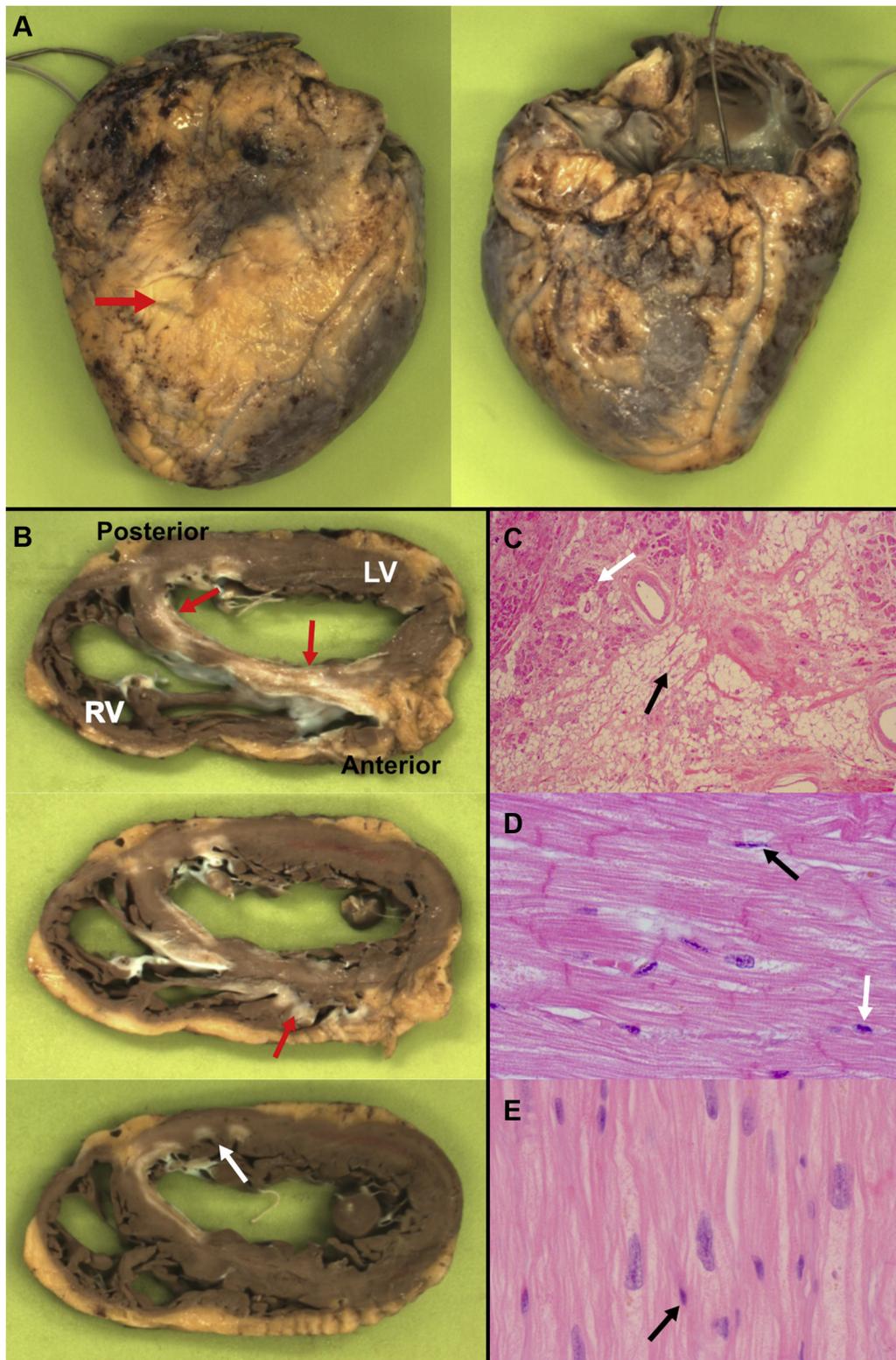
Figure 3   **A:** Explanted heart in anteroposterior view (*left*) and posteroanterior view (*right*). The left panel shows extensive fatty replacement (*red arrow*). **B:** Cross-sections through the basal left ventricle (LV) / right ventricle (RV) (*top*), basal-mid LV/RV (*middle*), and mid-LV/RV (*bottom*). Transmural scar is seen in the basal-mid anterior and inferior septal LV (*top panel, red arrows*), and septal RV and RV outflow tract (*middle panel, red arrow*). These may have resulted from a combination of intrinsic disease, endocardial radiofrequency ablation, and transcoronary ethanol embolization. **C:** Histopathology slide taken at the septum showing fibrofatty (*black arrow*) replacement of myocardial tissue (*white arrow*), previously described by others.[1,4–6] **D:** Histology shows elongated nuclei (*black arrow*) with chromatin clumping (*white arrow*), previously described by Nikolova and colleagues,[3] felt to be classic for LMNA cardiomyopathic hearts. **E:** Histology of the right atrium showing similar cardiomyopathic changes seen in the ventricles, with evidence of chromatin clumping (*black arrow*) to a lesser degree.

Conclusion

This case illustrates the classic natural history of LMNA cardiomyopathy encompassing AV block, atrial arrhythmias, prothrombotic tendency, ventricular arrhythmias, progression to end-stage heart failure, and need for emergent cardiac transplantation, illustrated through electroanatomic mapping, macropathology and histopathology, and genetic evaluation. Uniquely, we described comprehensive biventricular endocardial and epicardial electroanatomic substrate involving the basal septum LV inferoseptum, capable of supporting multiple reentrant VTs. Ablation was technically challenging, requiring endocardial, epicardial, and transcoronary ethanol ablation for VT control. Early genetic testing led to the diagnosis of an aggressive form of cardiomyopathy and prompt evaluation for cardiac transplantation. Moreover, whole-heart macropathology and histopathology of the explanted heart was consistent with classic descriptions for LMNA-deficient cardiomyocytes in experimental settings and in reported individuals.

Appendix
Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2018.11.009.

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