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CASE REPORT

Genotype–phenotype correlation of LMNA variants involving the Arg541 residue: a case report with multimodality imaging and literature review

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Abstract

We present a case of atypical *LMNA* cardiomyopathy associated with the pathogenic variant p.Arg541Ser. The patient had early-onset severe ventricular arrhythmias but atrioventricular conduction was normal. Segmental motion abnormalities and a large transmural scar, mainly apical and lateral, were found at cardiac magnetic resonance, corresponding to areas of severe wall thinning at computed tomography and of low voltages at electroanatomic mapping. Ventricular tachycardia ablation was successful in controlling ventricular arrhythmias. Few other cases described patients with pathogenic variants in the Arg541 residue, and they displayed similar atypical features, suggesting a genotype–phenotype correlation which may have specific prognostic and therapeutic implications.

Keywords Familiar dilated cardiomyopathy; Lamin A/C variants; Ventricular Tachycardia; Ventricular tachycardia ablation; Late gadolinium enhancement

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Introduction

Pathogenic variants in the lamin A/C gene (*LMNA*) are associated with a wide range of clinical phenotypes, with predominant neuromuscular and cardiac involvement.[1] Lamin A/C cardiomyopathy usually presents as a dilated cardiomyopathy with a high prevalence of atrioventricular (AV) conduction disturbances and significant risk of ventricular arrhythmias (VA). In two large series of patients with *LMNA* cardiomyopathy with a median follow-up of 7 years, abnormalities of the AV conduction were found in more than 70% of patients, sustained VA occurred in up to 43% of patients, heart transplantation or ventricular assist devices were needed in up to 20% of patients and mortality was between 8% and 13%.[2,3]

Myocardial fibrosis, as detected by cardiac magnetic resonance (CMR) with late gadolinium enhancement (LGE), is frequently found in *LMNA* cardiomyopathy, and it is generally distributed in the midwall of the ventricular septum.[4–6]

We present a case of *LMNA* cardiomyopathy with an atypical scar distribution and an extremely aggressive clinical course with early-onset VA refractory to antiarrhythmic therapy. After reviewing the literature, we also suggest a potential genotype–phenotype correlation for missense mutations involving the Arg541 residue.

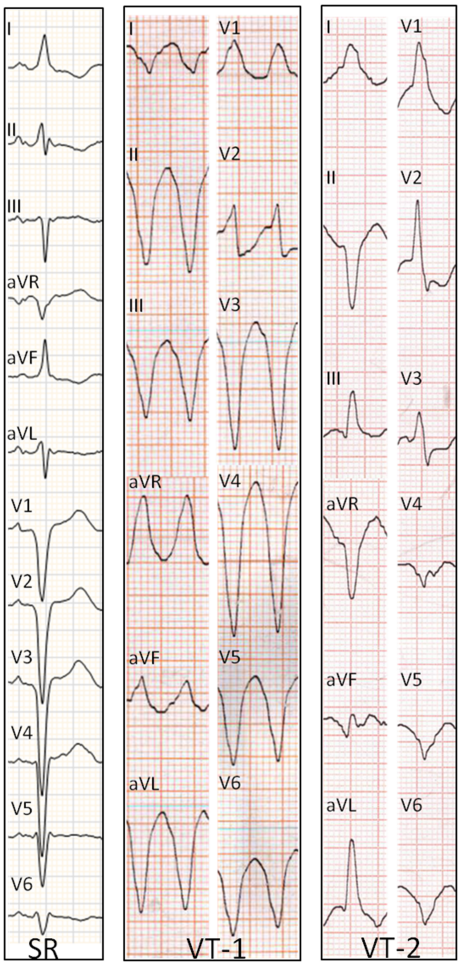
Case report

A female patient without relevant family history was diagnosed with muscular dystrophy with axial predominance at the age of 9. She underwent genetic testing showing a variant in the *LMNA* gene (Arg541Ser, c.1621C > A, NM_170707.3). This variant is considered as pathogenic, according to the criteria of the American College of Medical Genetics and Genomics.[7]

At the age of 20 (year 2011) the first echocardiogram was performed, showing a mildly dilated left ventricle and left ventricular ejection fraction (LVEF) of 40%. Beta-blocker therapy and angiotensin converting enzyme inhibitor were started and titrated to maximum tolerated doses (bisoprolol 5 mg b.i.d and enalapril 2.5 mg b.i.d, limited by hypotension).

In 2015, she experienced for the first time an episode of sustained monomorphic ventricular tachycardia (SMVT) at 200 bpm, with QRS axis at −105°, right bundle branch block (RBBB) morphology and transition in V3 (*Figure* 1), suggesting an exit site located in the apical portion of the LV infero-lateral wall. The tachycardia was accompanied by angina and dizziness, and the patient was referred to our hospital. At that point CMR showed LVEF of 31%, apical akinesia and extensive transmural fibrosis in the left ventricular (LV) apex, LV lateral wall from base to apex, LV inferior and anterior walls in their mid-apical segments (*Figure* 2). Baseline electrocardiogram (ECG) in sinus rhythm showed PR segment of 150 ms and QRS of 130 ms with left bundle branch block (LBBB) (*Figure* 1). The patient was in New York Heart Association (NYHA) class I and medical therapy at admission was unchanged since 2011. According to European guidelines[8] an implantable cardioverter defibrillator (ICD) was implanted: we choose a single-lead device with atrial sensing function (Ilesto 5 VR-T DX from Biotronik) in order to minimize the number of leads in such a young patient while maintaining the option for AV synchronous pacing in case of subsequent appearance of conduction disturbances. Spironolactone 25 mg q.d. was also added to her treatment.

Figure 1 Baseline ECG in sinus rhythm (SR) and ECGs during the two predominant VT morphologies (VT-1 and VT-2).



During the first 18 months after ICD implant, the device recorded 15 episodes of fast VT treated with anti-tachycardia pacing (ATP) and one episode of fast VT treated with shock. After the shock, in November 2016, Amiodarone was started with a loading dose of 200 mg t.i.d. during 1 week, 200 mg b.i.d. in the next week, and a maintenance dose of 200 mg q.d. thereafter.

The first VT recurrence, treated with ATP, occurred 15 days after the initiation of amiodarone and in the following 6 months, the patient experienced 13 appropriate ATPs and two appropriate shocks. Finally, in June 2017, she was admitted with VT storm. During hospital admission, despite treatment with amiodarone and procainamide, multiple episodes of SMVT were recorded, with two predominant morphologies, one identical to the first VT experienced in 2015 and the second with RBBB, transition in V4, and QRS axis at 135°, suggestive of mid-lateral origin in the LV (*Figure* 1). Cardiac computed tomography, performed to localize coronary arteries in view of epicardial mapping, was segmented with the ADAS 3D software (Galgo Medical, Barcelona, Spain) that allows 3D reconstruction with automatic measurement of LV wall thickness: severe wall thinning (<5 mm and even <3 mm) was observed in the apex, lateral wall, antero-apical, and infero-apical segments (*Figure* 2).

VT ablation with an endo-epicardial approach was performed with the support of the Ensite Precision mapping system (Abbot, Chicago USA). At endocardial electroanatomic mapping (EAM), a dense scar was found in the apex, lateral wall, infero-lateral wall (mid-apical), and antero-lateral wall (mid-apical); an area of border zone was found in the lateral wall (basal and mid) (*Figure* 3). At epicardial EAM, a large dense scar occupied the lateral wall, the apex, and the antero-lateral wall (mid-apical), with late potentials in the mid-basal segment of the lateral wall (*Figure* 3). Since clinical VTs were not inducible and only fast non-tolerated VTs were induced, a substrate endo-epicardial ablation was performed, targeting the area of border zone in the lateral wall where fragmented and late potentials were present.

VTs recurred soon after ablation and a second endocardial procedure was performed; the two clinical VTs were induced and ablated in the mid portion of the lateral wall and in the apical portion of the infero-lateral wall. At the end of the procedure, a fast non-tolerated VT was induced but clinical VTs were not inducible. The patient was discharged on

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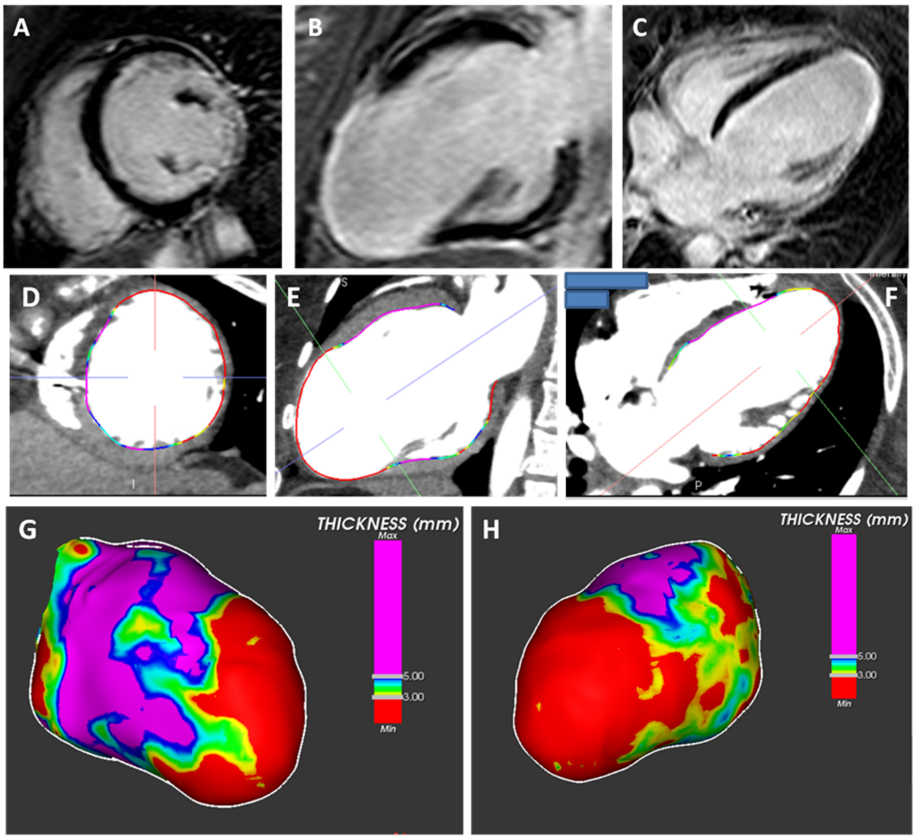
Figure 2 Myocardial abnormalities are analysed by different techniques. Panels A–C from CMR show transmural LGE in the lateral and apical walls, with extension to the apical segments of the anterior and inferior wall. Panels D–F from computed tomography show severe wall thinning in the same segments where LGE is present at cMR; the coloured line is the endocardial border drawn with the ADAS 3D software. Panels G and H show the 3D reconstruction of the cardiac computed tomography, with severe wall thinning (<3 mm, coloured in red) in the apex, lateral wall, and antero-apical segment; only the basal and mid portion of the septum and the anterior wall have a wall thickness >5 mm.



amiodarone 200 mg o.d. and mexiletine 100 mg t.i.d.; the dosage of amiodarone was reduced to 200 mg five times a week in 2018. During a follow-up of 33 months, she had no appropriate ICD therapies. She has always continued being in NYHA class I and never had a heart failure hospitalization. Last echocardiogram in June 2019 showed mild LV dilation (end-diastolic LV volume of 72 mL/m2) and LVEF of 39%.

Discussion

A typical substrate has been described in patients with *LMNA* cardiomyopathy, characterized by midwall LGE in the basal and mid ventricular septum,[4–6] which has also been linked to the occurrence of AV conduction abnormalities.[4–6] Moreover, LV thickness is generally preserved in all myocardial segments.[5] These characteristics may contribute to the disappointing results reported for VT ablation in *LMNA* mutation carriers, with a 91% VT recurrence after a median of two procedures.[9] In fact, failed ablations were mostly related to intramural septal scar, which is often extremely complex to eliminate. Given these results, a recent consensus document considered that VT ablation has only a palliative role in lamin cardiomyopathy.[10]

By contrast, several features of the presented case depict a specific and atypical phenotype: (i) AV conduction was normal; (ii) scar distribution was not in the midwall of the septum but rather transmural, mainly apical and lateral and very extensive; (iii) severe regional LV wall thinning was present; and (iv) VT ablation was successful in controlling SMVTs.

Although it is recognized that *LMNA* pathogenic variants are associated with a higher risk of VA, even in the absence of heart failure symptoms, this patient had an extremely aggressive course with early-onset severe VTs and VT storm despite antiarrhythmic therapy. Moreover, AV block is usually present in patients with LMNA cardiomyopathy who experience sustained VA: in one series, the absence of AV block had 100% negative predictive value for the occurrence of VA.[2] By contrast, our patient had recurrent VA with normal AV conduction.

Although the cardiac phenotype was atypical for *LMNA* cardiomyopathy, the neuromuscular manifestations were

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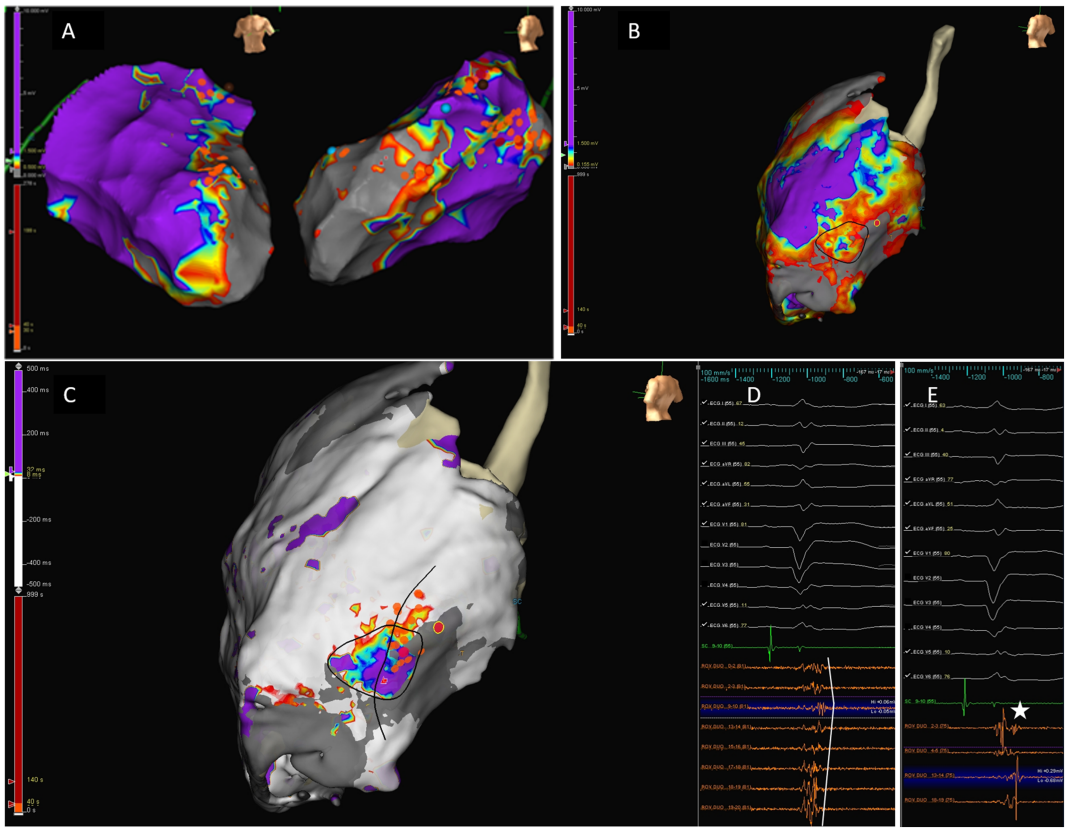
Figure 3 Images from electroanatomic mapping during the first ablation. Panel A shows the endocardial electroanatomic map with a large area of dense scar (voltage <0.5 mV, coloured in grey) in the apex, the apical portion of the antero-lateral and lateral wall, and the basal segment of the lateral wall; an area of border zone (voltage 1.5–0.5 mV, coloured from blue to red) is present in the mid portion of the lateral wall. These segments correspond to LGE at CMR and wall thinning on computed tomography. Panel B shows the epicardial electroanatomic map with a large area of dense scar in the apex and all along the lateral wall. A black circle marks an area of border zone that was of special interest due to the presence of late potentials. Panel C shows a map of late potentials: late potentials go from red to purple, with purple corresponding to the latest ones. The area of late potential is marked with a black circle. The black line shows a potential channel of slow conduction whose signals are shown in Panel D: when the duo-decapolar Liverwire catheter (Abbot, Chicago, USA) was positioned along this channel crossing the area of late potentials, we observed fragmented and double potentials all through the channel, with a progressive delay in the second potential as we enter the core of the purple area, and a progressive anticipation of the second potential as we exit this area (white lines). In Panel E, a clearly separated late potential is also showed (white star). Of note, this area of border zone and late potentials in the mid portion of the lateral wall matches with an area of intermediate wall thinning (3–5 mm) at computed tomography (*Figure* 2, Panel H). Red circles observed in all the electroanatomic maps correspond to ablation points.



similar to those commonly observed in patients with *LMNA* variants.[11]

Few case reports have described patients with *LMNA* cardiomyopathy and missense variants involving the Arg541 residue, and all of them displayed an atypical presentation with many similarities to our case. Kwon and colleagues reported the case of an adolescent girl with the same variant as our patient, who presented with recurrent VT and had severe wall thinning and transmural LGE in the LV apex and lateral wall.[12] Other authors have described that patients with genetic variants involving the Arg541 residue are characterized by the presence of regional wall motion abnormalities (akinesia or diskinesia) in the LV apex[13,14] or LV mid and apical infero-lateral wall[15], regional wall thinning,[14,15] almost transmural LGE[15] and early-onset aggressive VT episodes.[13,14] Moreover, in these cases, AV conduction was generally normal, and an LBBB pattern or at least Q waves in precordial leads V1-V3/V4 were described, similarly to our patient. Missense variants affecting Arg541had also been identified as highly aggressive in a previous series, but a detailed characterization of the phenotype was not provided in that manuscript.[16]

We have provided a multi-parametric characterization of the atypical substrate in a patient with the missense pathogenic variant p.Arg541Ser in the *LMNA* gene: regional wall motion abnormalities and transmural LGE in CMR, wall thinning in computed tomography, and decreased voltages at endo-epicardial EAM were all coherent and allowed to localize the VT circuit.

Although based on few cases, we consider that the available evidence suggests a specific genotype–phenotype correlation characterized by an atypical substrate and a highly

aggressive course in terms of VA, in the absence of AV block. In these patients, early ICD implantation might be life-saving. Moreover, in contrast to what has been previously described in *LMNA* patients, VT ablation may provide midterm freedom from VT recurrence in the subgroup with Arg541 variants, since their VT substrate is easier to access as compared to the midwall septal scar found in most *LMNA* cases.

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