Restrictive cardiomyopathy: an unusual phenotype of a lamin A variant

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Abstract

Most individuals with cardiomyopathy associated with variants of the LMNA (lamin A) gene present with cardiac conduction abnormalities followed by dilated cardiomyopathy and cardiac failure; some also have skeletal muscle weakness. In this report, an individual with restrictive cardiomyopathy presenting with conduction defects followed by cardiac dysfunction of a restrictive nature eventually requiring cardiac transplantation is described. Subsequently, progressive skeletal muscle weakness became evident. The finding of a new LMNA pathologic gene variant in this patient increases the options for genetic testing of individuals with restrictive cardiomyopathy.

Keywords Familial cardiomyopathy; Lamin A; Limb-girdle muscular dystrophy; LNMA-related dilated cardiomyopathy; Restrictive cardiomyopathy

Introduction

Restrictive cardiomyopathy (RCM) has been linked to variants in several genes,1,2 whereas dilated cardiomyopathy (DCM) has been linked to an even larger number of gene variants.1 A few gene variants have been linked to both DCM and RCM, even within the same family.3 Familial and sporadic cases of DCM have been associated with variants of lamin A (LMNA).4 Most affected individuals present with conduction abnormalities, and some cases have skeletal muscle manifestations.5,6 LMNA variants also cause limb-girdle and Emery–Dreifuss muscular dystrophies.7,8 However, alterations in the LMNA gene have not previously been linked to RCM. This report describes an individual with RCM, conduction defects, and skeletal muscle weakness associated with an LMNA gene variant.

Case report

A previously healthy man had an incidental finding of atrial fibrillation and atrioventricular block at age 45 years. Electrocardiogram revealed a junctional rhythm that responded appropriately to exercise. As a precaution, the patient received a dual chamber pacemaker and continued to be physically active.

At age 53 years, he presented with several months of progressive dyspnoea on exertion. Echocardiogram demonstrated normal left ventricular size and wall thickness, left ventricular ejection fraction 45–50%, normal right ventricular size and function, significant biatrial enlargement, mitral inflow deceleration time of 106 ms, and increased average ratio of early diastolic mitral inflow (E) to early diastolic mitral annular tissue velocity (E') of 17. Right heart catheterization revealed right atrial pressure 26/20, mean 22 mmHg; right ventricular pressure 72/22 mmHg; pulmonary artery pressure 70/34, mean 49; pulmonary capillary wedge pressure 52/29, mean 34 mmHg; cardiac output 2.9 L/min with index of 1.7 L/min/m². Left heart catheterization confirmed no significant coronary artery disease. N terminal pro brain natriuretic peptide ranged from 1900 to 3570 pg/mL (normal range 0–125 pg/mL). Based on his echocardiographic and haemodynamic findings, he was diagnosed with RCM. Endomyocardial biopsy revealed cardiac myocyte hypertrophy, focal interstitial fibrosis with no significant inflammation or evidence of infiltrative process.

Family history revealed that the patient’s mother had died at age 80 years of heart failure believed to be of valvular
aetiology. She had sinus node dysfunction requiring a pacemaker for symptomatic bradycardia at age 60 years, subsequent atrial fibrillation, and mitral valve replacement and tricuspid valvuloplasty at age 73 years.

Within 2 years of symptom onset, at age 55 years, the patient required a cardiac transplant. Pathology of the excised heart confirmed extensive hypertrophic changes, patchy interstitial fibrosis, and non-obstructive coronary artery disease consistent with his RCM diagnosis (Figure 1A and B). The patient had a rapid, uneventful recovery and resumed biking and hiking.

At age 58 years, he reported decreased endurance during biking. Neurologic evaluation was nonspecific. He continued to have decreasing exercise tolerance with muscle weakness, muscle fatigue, and myalgia, and at age 61 years, he was unable to bicycle more than a few miles. Exam showed mild proximal weakness and areflexia. Creatine kinase was normal. Electromyography showed a generalized myopathy with the biceps and thoracic paraspinal muscles most severely involved. Biopsy of the biceps brachii demonstrated very rare necrotic and regenerating fibres with abnormal variation in fibre size and increased focal endomysial connective tissue compatible with a mild myopathy.

Muscle weakness continued to worsen. At age 63 years, he underwent genomic screening for 38 genes associated with DCM or RCM. He was found to be heterozygous for LMNA gene variant c.835 delG:p.Glu279ArgfsX201 in exon 5 (Figure 2). This variant causes a shift in the reading frame starting at the codon for glutamic acid 279, changing it to an arginine and creating a premature stop codon at position 201 of the new reading frame in the coil 2 domain. Such a frameshift variant is highly likely to lead to protein truncation or loss of protein through nonsense-mediated mRNA decay. Other such frameshift variants have been reported in the LMNA gene associated with cardiomyopathy and many are located downstream from this variant, suggesting that this variant could be more damaging than others reported with cardiomyopathy. This variant has not previously been reported in the LMNA gene, and at the present time, little is known about the variability of expression of this gene variant in family members.

Subsequently, a younger sister was found to also be heterozygous for the same LMNA variant. She was asymptomatic and had a normal echocardiogram. An electrocardiogram showed a prolonged PR interval, intermittent second-degree heart block, and a widened QRS complex.

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**Figure 1** Photomicrograph of explanted heart demonstrating fibrosis and myocyte hypertrophy with nuclear enlargement: (A) ×10 magnification; (B) ×40 magnification.

**Figure 2** Chromatogram data from Sanger sequencing showing c.835delG LMNA mutation [HG19: chr1:g.156105002del]: top panel, in silico forward reference sequence; second panel, patient data showing c.835delG mutation on forward strand; third panel, patient data showing c.835delG mutation in reverse strand; and bottom panel, in silico reverse reference sequence.
Discussion

Mutations in the lamin A gene (LMNA) are now known to be associated with a large number of human diseases including DCM and conduction defects, neuromuscular disorders, premature ageing, and some metabolic phenotypes. These disorders are now termed laminopathies. Lamin A is an important component of the nuclear lamina that provides support to the nuclear membrane. Over time, it has become apparent that there is a wide variety of phenotypic presentations of LMNA-related cardiomyopathy associated with or without conduction disease or muscle weakness. Van Tintelen et al. emphasized the occurrence of severe myocardial fibrosis and variable dilatation in a large family with DCM.

Dilated cardiomyopathy due to variants in lamin A is not rare. Individuals with familial LMNA-associated DCM often present with conduction defects prior to recognition of heart failure. Many affected patients also have skeletal myopathy, usually one of two forms of muscular dystrophy, Emery–Dreifuss or limb-girdle.

There are many striking similarities to LMNA-associated DCM in our patient. He developed atrioventricular block and atrial fibrillation 8 years prior to any symptoms referable to heart failure. Brodt et al. reported that electrocardiogram abnormalities preceded DCM in LMNA cardiomyopathy by a median of 7 years. Our patient also demonstrated a slowly progressive proximal skeletal myopathy in a limb-girdle pattern.

This report demonstrates another cardiomyopathy phenotype, RCM, associated with an LMNA variant. An alternative, more precise description of this patient’s phenotype is mildly depressed left ventricular ejection fraction and prominent restrictive features. This leads to our recommendation that individuals with RCM, as with DCM, should have testing of the LMNA gene. We recommend that the LMNA gene be added to the list of variants that can present as either DCM or RCM.

Conflict of interest

None declared.

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