Isolated ventricular noncompaction in a patient with a sarcomeric gene mutation: A case report

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Introduction

Noncompaction cardiomyopathy (NCCM) is characterized by heavy trabeculations, deep intertrabecular recesses, and a thickened myocardium consisting of a thin compacted and a thick noncompacted layer.[1] Previously an "unclassified cardiomyopathy," NCCM is now recognized as a congenital cardiomyopathy that can occur with other congenital heart diseases or as isolated cases. Although a rare condition, isolated NCCM shares a genetic profile with hypertrophic cardiomyopathy and dilated cardiomyopathy, leading to a strong familial association of heart failure, embolic events, and arrhythmias.[1,2] Here we present a case of a 42-year-old man without known medical conditions diagnosed with isolated NCCM with findings of a sarcomere protein mutation and a family history significant for sudden cardiac death (SCD).

KEY TEACHING POINTS

- Noncompaction cardiomyopathy is a congenital cardiomyopathy that can lead to heart failure, embolic events, and arrhythmias.
- A detailed family history should be elucidated in otherwise healthy patients presenting with cardiac symptoms.
- Sudden death in multiple family members should influence cardiac and genetic testing to identify and treat patients and at-risk family members.

Case report

A 42-year-old man with no past medical history presented to our hospital with 2 days of intermittent stabbing midsternal chest pain not associated with any dyspnea, palpitations, or syncope. His family history was significant for the sudden death of his mother at the age of 62, and sudden death of 2 maternal aunts and a maternal grandfather in their 40s and 50s (Figure 1). None of his family members underwent an autopsy. His heart rate was 81 and blood pressure was 147/98. Physical examination was significant for a regular heart rate and rhythm with normal heart sounds without murmurs, rubs, or gallops. His labs and cardiac enzymes were normal. His electrocardiogram displayed a normal sinus rhythm and normal intervals without evidence of premature contractions or arrhythmias (Figure 2). He underwent a computed tomography coronary angiography without significant findings and an observed calcium score of 0 (Figure 3A). Owing to his family history of multiple sudden deaths, the patient underwent a transthoracic echocardiogram, which revealed prominent trabeculations within the left and right ventricles (Figure 3B). The left ventricle also demonstrated global systolic dysfunction with an ejection fraction of 46% along with mild-to-moderate mitral regurgitation. Further investigations included a cardiac magnetic resonance imaging (cMRI), revealing hypertrabeculations with a noncompacted-to-compacted end-diastolic ratio of 2.75 without myocardial scarring on delayed enhancement (Figure 3C). He was discharged without event monitoring devices with cardiology and electrophysiology follow-up. Targeted genetic testing was done with a combined cardiac panel offered through GeneDx, consisting of 138 genes associated with cardiomyopathies analyzed for deletions and duplications. The results revealed a likely pathogenic (LP) heterozygous variant in the *TTN* gene (p.Leu11862Ter (L11862X) (TTA>TGA): c.35585 T>G in exon 169), which is likely consistent with a genetic form of cardiomyopathy. Since variants in the *TTN* gene may cause skeletal myopathy, creatine kinase (CK) levels were also ordered. Although our patient did not have muscle weakness on physical examination, his CK levels were found to be elevated at 420 U/L (reference range: 30–200 U/L). Targeted genetic testing of family members revealed the same LP variant in

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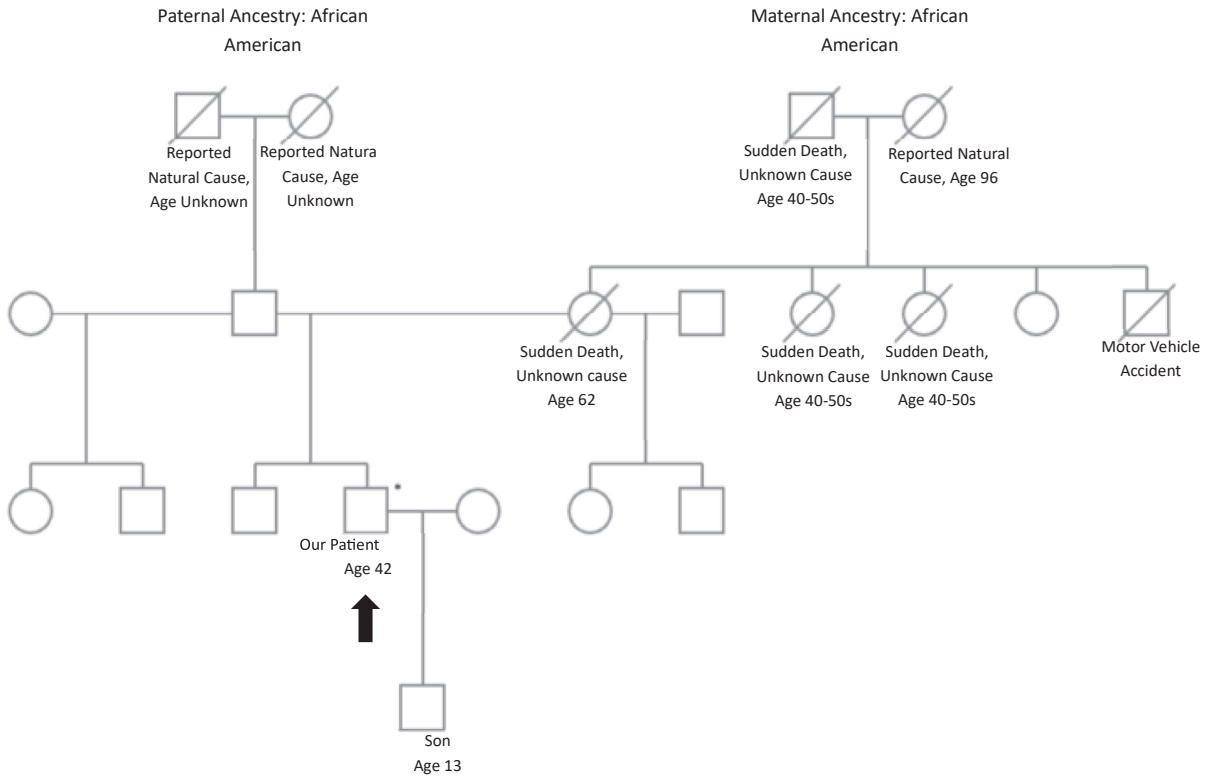

Figure 1 Family pedigree. Arrow indicating our patient. Notable for the sudden death of patient's mother, 2 aunts, and maternal grandfather.

the *TTN* gene in his 2-year-old son. Guideline-directed medical therapy for heart failure with reduced ejection fraction was initiated with lisinopril and metoprolol succinate. Given the increased risk of SCD, our patient is under evaluation for an extravascular implantable cardioverter-defibrillator (ICD).

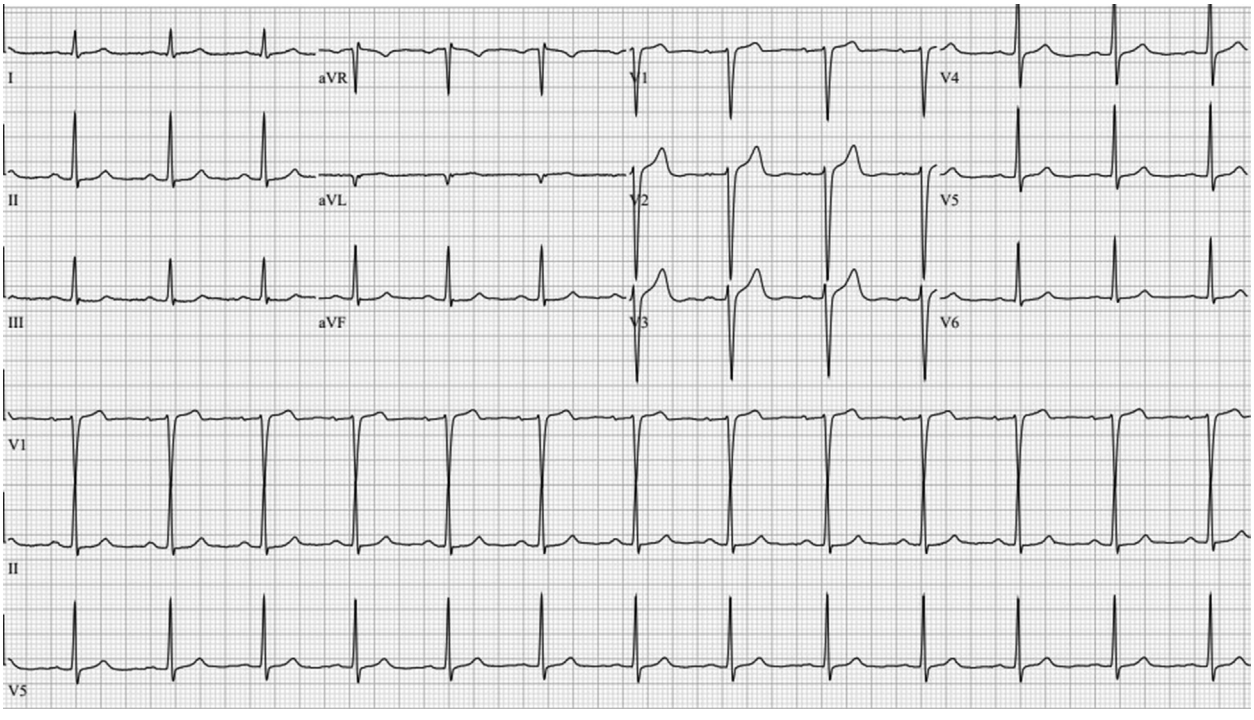

Figure 2 Electrocardiogram on admission. Normal sinus rhythm and rate with appropriate intervals. Narrow QRS complexes without ST changes.

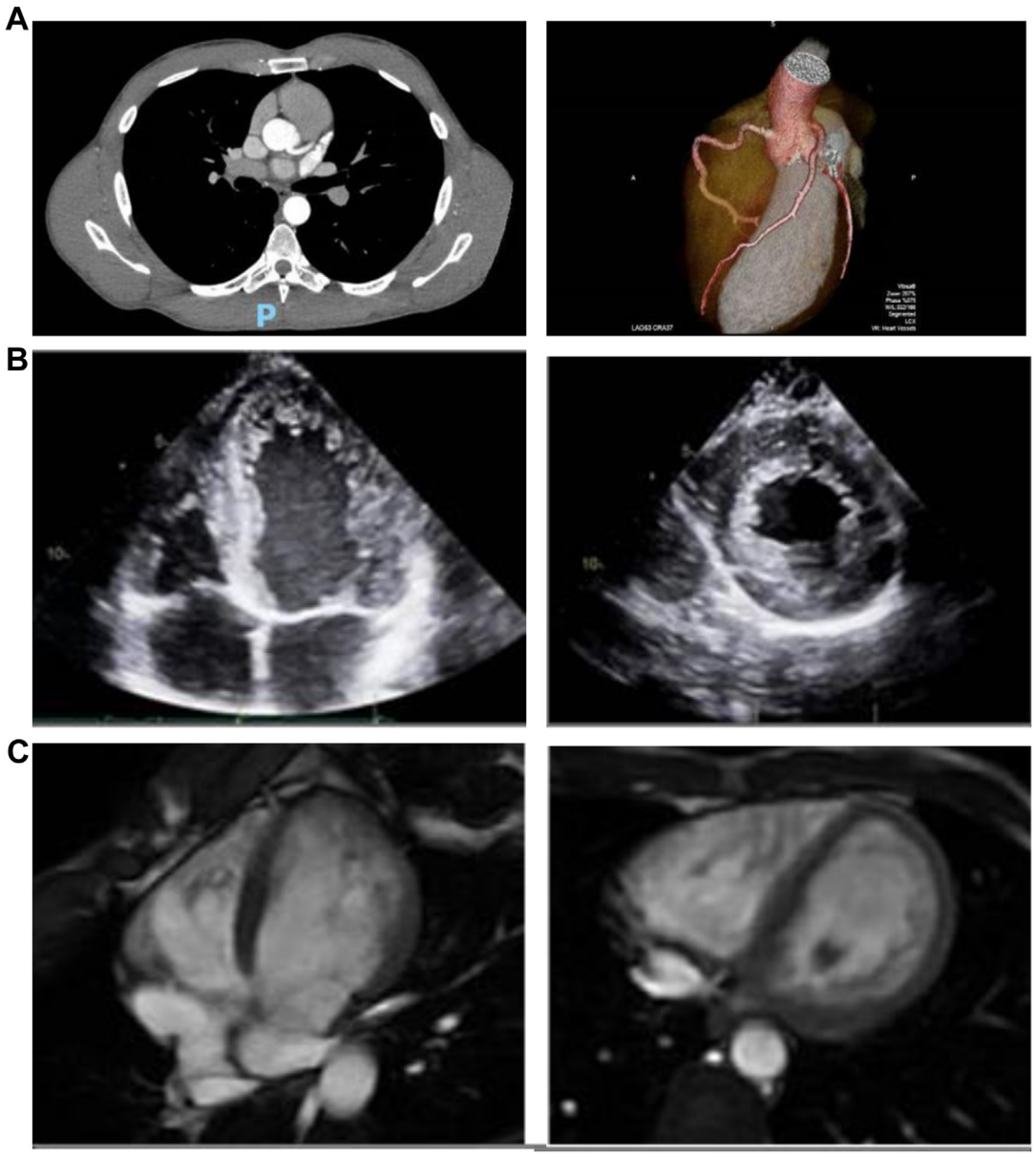

Figure 3 Imaging modalities used. **A:** Computed tomography angiography of coronary arteries. Limited view (left). Normal coronary anatomy without anomalous arteries and an observed calcium score of 0. Reconstruction in 3D showing patent vessels (right). **B:** Noncompaction on transthoracic echocardiogram. Prominent trabeculations in the mid distal inferolateral wall, anterolateral wall, distal inferior wall, and apex of the left ventricle consistent with isolated noncompaction cardiomyopathy (NCCM). **C:** Noncompaction on cardiac magnetic resonance imaging. Hypertrabeculations in the mid inferior and mid-to-apical inferolateral left ventricle along with a noncompacted-to-compacted myocardial ratio of 2.75, diagnostic of isolated NCCM.

Discussion

Trabeculations within the developing heart increase myocardial mass and contribute to coordinated contractility. Ontogenesis progresses with the trabeculations compacting into the myocardium; however, pathologic persistence of the trabecular layer results in isolated NCCM.[3] Although universally affecting the left ventricle, right ventricular involvement has also been described.[4,5]

Transthoracic echocardiography is the most common imaging modality used in diagnosis; however, the use of cMRI has been on the rise. To aid in diagnosis, the Jenni criteria for echocardiography are often used in the literature and use a noncompacted-to-compacted ratio >2 at end-systole along with color Doppler evidence of intraventricular blood contiguous with blood in the intertrabecular recesses as hallmarks to differentiate isolated NCCM from other causes of heavy trabeculations.[6] The Peterson criteria are often used with cMRI and suggest a noncompacted-to-compacted end-diastolic ratio >2.3 to identify isolated NCCM.[7]

Isolated NCCM has been associated with the clinical triad of heart failure, embolic events, and arrhythmias.[1] Chin and colleagues[8] found more than half of their study population to have reduced ejection fractions and ventricular arrhythmias, including ventricular tachycardia and fibrillation. Similarly,

Oechslin and colleagues[9] described a study population with 85% of individuals demonstrating reduced ejection fractions and 41% with ventricular tachycardias. Systemic thromboembolic events were present in both studies.[8,9] Importantly, isolated NCCM has shown strong familial associations in multiple studies, with up to half of the study participants having relatives screened and diagnosed with isolated NCCM.[8–10] Interestingly, most familial cases appear to show an autosomal dominant inheritance pattern.[11]

The genetic profile associated with isolated NCCM has also been reported in hypertrophic cardiomyopathy and dilated cardiomyopathy. A large-scale systematic review showed that the most common mutations were those involving sarcomere genes, including *MYH7*, *MYBPC3*, and *TTN*.[11] The *TTN* gene encodes titin, a structural sarcomere filament that provides elasticity to cardiac and skeletal muscle cells. Genetic testing performed in our patient revealed an LP variant (c.35585 T>G in exon 169 of the *TTN* gene) that represents a nonsense mutation located in one of the I-band regions and is predicted to result in protein truncation or a nonsense-mediated decay. TTN truncation variants have previously been described in the literature and are associated with the majority of isolated NCCM and dilated cardiomyopathies, as well as atrial and ventricular arrhythmias.[12,13]

The increased risk for fatal arrythmias and SCD in isolated NCCM from heart failure and arrhythmias warrants an ICD placement as a reasonable strategy for the primary prevention of SCD.[14] Targeted genetic testing for pathogenic variants in first-degree and other at-risk relatives is also recommended and, if positive, followed by a cardiac assessment, event monitoring, and imaging. For family members who choose not to undergo genetic testing, cardiac assessment and monitoring should still be performed. If normal cardiac function is noted, then annual event monitoring with cardiac imaging every 2–3 years is recommended.[15] Owing to the increased risk of fatal arrhythmias in our patient, he is currently under evaluation for an extravascular ICD placement for the primary prevention of SCD. He was also referred to neurology for his elevated CK levels. Genetic testing in his 2-year-old son revealed the same LP TTN variant with findings of slightly prominent trabeculations on cardiac imaging. He is now under the care of a pediatric cardiologist for continued surveillance.

Conclusions

This case demonstrates isolated NCCM in an otherwise healthy young individual with a family history significant for sudden death in multiple members. We emphasize the importance of taking a thorough family history in individuals presenting with cardiac symptoms to influence additional work-up with cardiac imaging and genetic testing as well as to identify, screen, and treat high-risk family members.

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