Journal of Community Hospital Internal Medicine Perspectives

Volume 12 | Issue 6 Article 18

2022

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Recommended Citation
Poudel, Binod; Shah, Shreeja; Khanal, Shristi; Cheema, Muhammad Arslan Asghar; and Basyal, Bikash (2022) "LMNA gene mutation presenting with ventricular tachycardia in the absence of dilated cardiomyopathy," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 12: Iss. 6, Article 18.
DOI: 10.55729/2000-9666.1116
Available at: https://scholarlycommons.gbmc.org/jchimp/vol12/iss6/18

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Cover Page Footnote

The authors have no conflicts of interest to declare.

CASE REPORT

LMNA Gene Mutation Presenting with Ventricular Tachycardia in the Absence of Dilated Cardiomyopathy

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Abstract

Genetic mutations can present with cardiomyopathies and ventricular arrhythmias in young population in the absence of other cardiac risk factors. LMNA genetic mutation is one of the causes of dilated cardiomyopathy (DCM) which can present with conduction abnormalities and arrhythmias. We present a case of LMNA genetic mutation in an African American male who presented with ventricular tachycardia in the absence of dilated cardiomyopathy initially mimicking cardiac sarcoidosis. Diagnostic challenges included initial impression of cardiac sarcoidosis as suggested by cardiac MRI, but negative tissue pathology on endomyocardial biopsy and negative activity on FDG PET scan. Treatment involved initiation of beta blocker and an implantable cardiac defibrillator placement for secondary prevention.

Keywords: LMNA gene, Ventricular tachycardia, Dilated cardiomyopathy, Cardiac sarcoidosis, Nuclear lamins, Genetic testing

1. Introduction

Ventricular tachycardia (VT) is a serious and potentially fatal cause of sudden cardiac death. It can result from structural defects in the myocardium from various ischemic or non-ischemic causes. In younger population with no overt cardiac history, VT can be an initial presentation of cardiomyopathy.[1] In addition to cardiomyopathies, VTs can occur in the setting of infiltrative diseases, channelopathies or other inherited genetic conditions. Evaluation of VT begins with workup for coronary artery disease followed by search for other less common etiologies.

Sarcoidosis is an inflammatory multisystemic disease of unknown etiology that is characterized by presence of non-caseating granulomas in various organ systems.[2] It can have various clinical manifestations in different organ systems but itmost commonly involves the lungs. However, the disease can have varied presentation with involvement of any organ including liver, skin, or eyes.[3] The cardiac manifestations of sarcoidosis result from granulomatous infiltration of cardiac muscles which can manifest with cardiomyopathy, congestive heart failure or ventricular arrhythmia. Conduction disorders leading to heart block can also occur with AV nodal involvement.[4] Cardiac sarcoidosis can remain undiagnosed in cases where other systemic manifestations of sarcoidosis are absent.

In addition to infiltrative diseases, genetic mutations can also lead to cardiomyopathy and cardiac arrhythmias. Mutation in LMNA gene, that codes for type A nuclear lamins (Lamin A and C) are one of the most commonly discovered genetic mutations in work up of dilated cardiomyopathies.[5,6] Screening for genetic mutations is important in cases where workup is unrevealing since presence of such mutations can help in recommending genetic screening for family members.[7]

We present a case of a young African American male who presented with ventricular tachycardia which was initially thought to be from cardiac

Received 3 May 2022; revised 12 July 2022; accepted 3 August 2022.
Available online 7 November 2022

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https://doi.org/10.55729/2000-9666.1116

sarcoidosis. Further workup including endomyocardial biopsy and PET scan were not suggestive of cardiac sarcoidosis and genetic testing revealed mutation in LMNA gene. We present the diagnostic challenges and the dilemma in finding the cause of ventricular arrhythmia.

2. Case description

A 33-year-old African American man presented to the emergency department (ED) with the complaint of chest pain along with shortness of breath while taking a shower at home. He didn't have any past medical or surgical history and worked as a schoolteacher. He had no known family history of any heart disease. He had played basketball and football during high school with no issues.

In the ED, he was noted to be tachycardic with heart rate 119/min. The rest of his vital signs were blood pressure 123/87 mmHg and respiratory rate 18/min. Laboratory investigations were within normal limits with a normal renal and liver function tests and a complete blood count was within normal limits. A urine drug screen was positive for opiates, benzodiazepines and cannabinoids.

He developed palpitations in the ED, during which an electrocardiogram (ECG) showed a wide complex tachycardia with heart rate of 240/minute (Fig. 1). He was administered 6mg adenosine which was followed by second dose of 12mg adenosine which did not terminate the arrhythmia. He received 150mg of Amiodarone with no response. This was followed by another 150mg after which his ECG revealed a normal sinus rhythm. He was maintained on an Amiodarone drip and admitted to the cardiac critical care unit (CCU) for closer monitoring.

On hospital day 1, he developed bradycardia with ECG revealing sinus bradycardia with heart rate 44/minute (Fig. 2). Amiodarone drip was discontinued. An echocardiogram showed normal left ventricular (LV) function with normal ejection fraction. He underwent cardiac catheterization which did not reveal any coronary abnormalities or obstruction. A cardiac magnetic resonance imaging (MRI) was done which showed multiple patchy areas of mid-wall late gadolinium enhancement particularly prominent as transmural enhancement in the inferolateral mid myocardium (Fig. 3). He was started on pindolol and was evaluated by electrophysiological cardiologist for implantable cardiac defibrillator (ICD). A high-resolutioncomputerized tomography (CT) of chest done with contrast did not show any reticular opacities in lung parenchyma or hilar adenopathy. An endomyocardial biopsy was done which was negative for myocarditis or any granulomatous disease, and Congo Red stain was negative for amyloidosis. Serum angiotensinogen converting enzyme (ACE) level was 35 U/L (within normal limits). He underwent an ICD placement for secondary prevention of ventricular arrhythmias and was discharged from the hospital with a plan to pursue a positron emission tomography (PET) scan

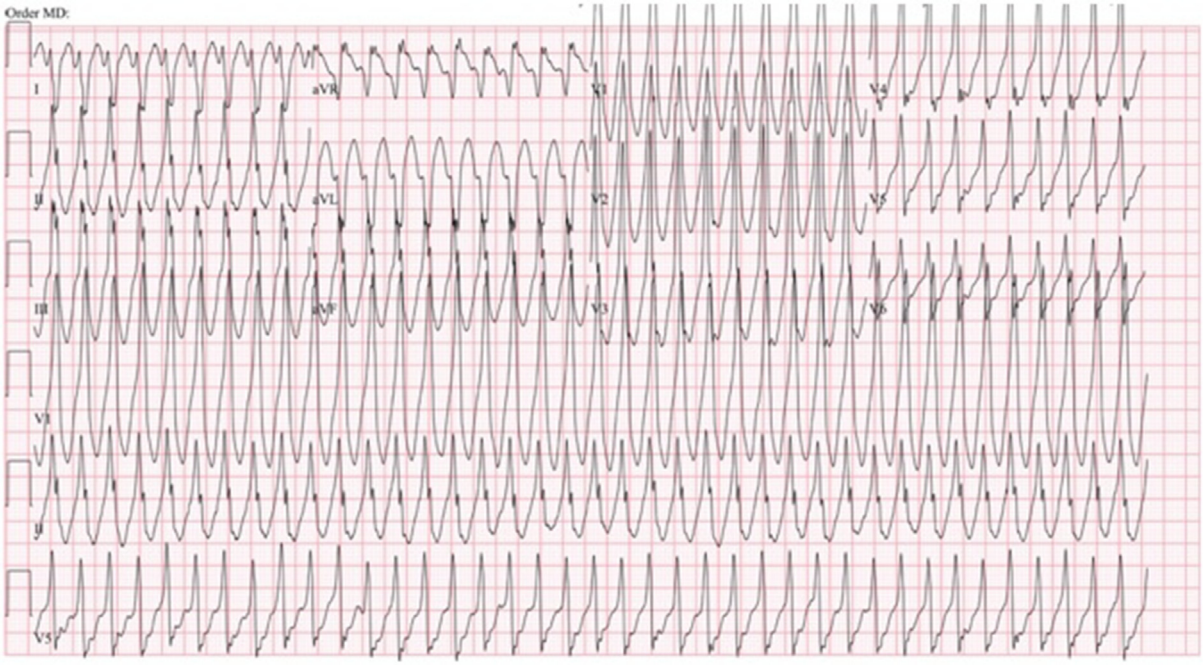

Fig. 1. Initial ECG in the ED showing ventricular tachycardia.

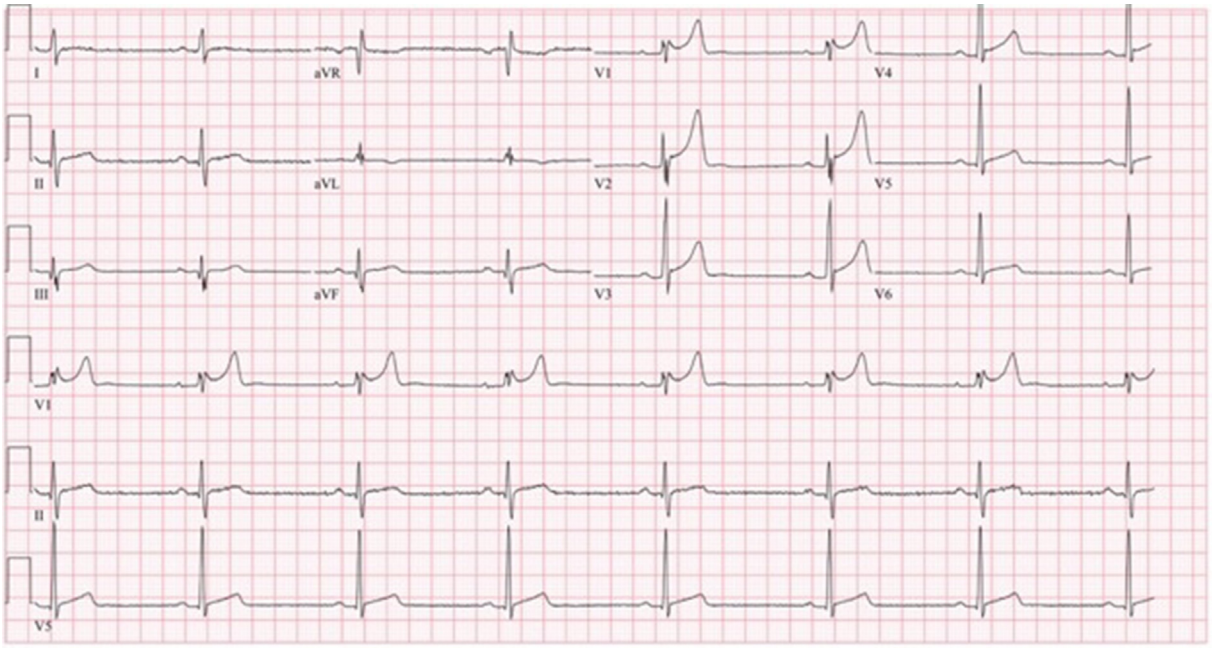

Fig. 2. EKG on day 1 showing bradycardia.

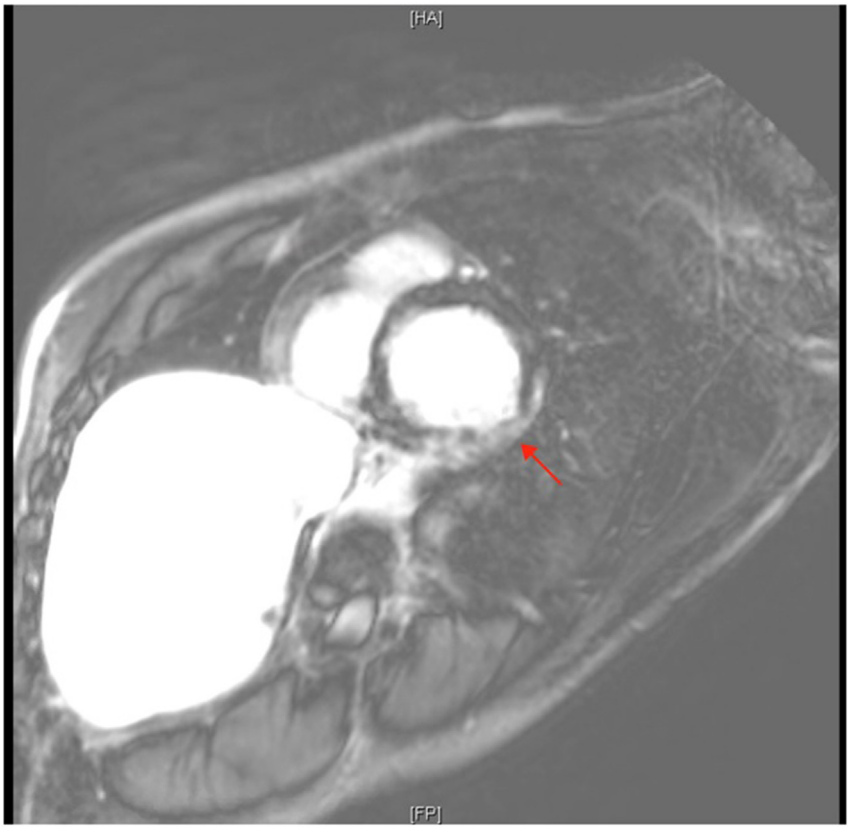

Fig. 3. Patchy areas of mid wall late gadolinium enhancement particularly prominent as transmural enhancement in the inferolateral mid myocardium (red arrow).

as an outpatient and discuss further treatment options.

As an outpatient, he underwent a PET scan which did not show any tracer activity in the myocardium or any evidence of cardiac sarcoidosis. He was also evaluated by Ophthalmologist and was not found to have any manifestations of ocular sarcoidosis. He was referred for genetic testing which revealed heterozygous mutation in LMNA gene. Interrogation of his ICD did not show any further VT in subsequent office visit and his family members including children were recommended to get genetic testing for screening.

In the absence of other identifiable etiology and a known association of LMNA gene mutation with ventricular arrhythmia, we think the VT in this young patient is due to LMNA gene mutation.

3. Discussion

LMNA gene encodes Lamin A and Lamin C which are structural proteins of nuclear lamina. Mutation in this gene can manifest either as isolated muscular dystrophy, isolated cardiomyopathy or a combination of both.[8] LMNA gene mutations have been linked to Emery-Dreifuss muscular dystrophy and other rare forms of muscular dystrophies like limb girdle muscular dystrophy.[9] LMNA related cardiomyopathy can present with symptomatic conduction system disease, arrhythmias, or with symptoms of heart failure.[8] LMNA related cardiomyopathy is an autosomal dominant disorder with age dependent penetrance with onset in the third and fourth decade and more than 90% penetrance by the 7th decade.[10] The frequency of LMNA gene mutation has been found to be as high as 8% in patients with familial dilated cardiomyopathies.[11] Ventricular arrhythmia or sudden cardiac death can sometimes be the presenting manifestation even in the absence of underlying systolic dysfunction.[12] In one longitudinal retrospective observational study including 27 families with 164 members, 94 had LMNA gene mutation and among them 60 were phenotypically affected. Out of the 60, 40 had DCM with AV Block (AVB), 12 had DCM with ventricular arrhythmias, 6 had DCM, AVB and Emery-Dreifuss muscular dystrophy type 2 (EDMD2) and 2 had AVB with EDMD2.[10]

LMNA sequence analysis identifies pathogenic variants in most individuals with LMNA-related DCM. It should be suspected in individuals with a clinical diagnosis of idiopathic DCM (etiology not attributed to coronary artery disease, structural heart disease, or other conditions that may cause DCM), almost always in the setting of conduction system disease and/or supraventricular or ventricular arrhythmias.

Management of genetic cardiomyopathies including LMNA related CMP involves referral to centers with special expertise in cardiovascular genetic medicine. With an established arrhythmia or known risk of arrhythmia, ICD implantation is advised before the ejection fraction falls below 35%.[12] If patients develop atrial fibrillation, cardioversion is advised. Patients unresponsive to cardioversion are treated with anticoagulants and agents for ventricular rate control.

Screening and identification of DCM before the onset of symptoms enables the initiation of medical therapy that may delay disease progression. Individuals with an LMNA pathogenic variant who are found to have any ECG abnormality should undergo a cardiovascular evaluation for disease progression at least. This should include, minimally, an ECG, 24- or 48-hour rhythm monitoring, and measurement of ventricular function.

When the LMNA pathogenic variant has been identified in a family, molecular genetic testing can be offered to relatives at risk in order to facilitate prompt diagnosis, surveillance, and treatment in those in whom the LMNA pathogenic variant has been detected.

Our patient had presented with chest discomfort and in the absence of any prior cardiac disease, his initial arrhythmia was wide complex tachycardia which was ventricular tachycardia. Extensive workup did not reveal any cause of cardiomyopathy. Genetic testing revealed LMNA related cardiomyopathy. Surprisingly, his echocardiogram showed normal left ventricular dimensions. Most of the LMNA related cardiomyopathy cases show increased left ventricular dimension. Our case was unique in the sense that LV dimensions were within the normal limits.

4. Conclusion

Despite the advancement in imaging techniques, establishing a definite etiology for VT is challenging. LMNA-related cardiomyopathy should be in differential diagnosis of idiopathic cardiomyopathy. Sometimes this cardiomyopathy can present without LV dilation. Screening and identification of LMNA related cardiomyopathy before the onset of symptoms enables the initiation of medical therapy that may delay disease progression.

Conflict of interest

There are no conflicts of interest for the authors to disclose.

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