

All That Light Up Are Not Sarcoidosis – The Great Masquerader: A Case of LMNA Cardiomyopathy

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ABSTRACT

Lamin A/C (LMNA) cardiomyopathy is a rare cause of non-ischemic dilated cardiomyopathy (DCM), caused by a gene mutation in Lamin A/C. It manifests with electrical abnormalities before the onset of heart failure, much like cardiac sarcoidosis (CS). Both have similar imaging findings. Detailed family history and genetic testing are crucial in making the correct diagnosis.

Keywords: infiltrative cardiomyopathy, dilated cardiomyopathy, Lamin A/C gene, cardiac sarcoidosis, FDG PET

INTRODUCTION

Dilated cardiomyopathies (DCM) are a common cause of heart failure, with up to 40-50% of familial cardiomyopathies attributed to genetic mutations [1]. Among the genetic cardiomyopathies, LMNA gene mutation is the second most common cause of familial DCM after titin truncating mutations [1,2]. This gene encodes proteins in the nuclear membrane involved in gene transcription and regulation [1,2]. LMNA mutation is attributed to 5-8% of genetic DCM cases, usually presents in the 3rd-4th decade of life, with almost 100% age-dependent penetrance [1].

The LMNA cardiomyopathy initially manifests with electrical abnormalities, such as heart block, brady-tachy syndrome, and atrial/supraventricular/ventricular arrhythmias before the onset of heart failure due to pump dysfunction [2]. LMNA mutation carriers often have a poor prognosis due to progression of heart failure and risk of sudden cardiac death due to malignant arrhythmias [1]. Interestingly, the LMNA DCM variant can have similar inflammatory findings

on cardiac imaging to sarcoidosis, which can confound and delay the correct diagnosis of LMNA DCM [5]. As such, it is important for early detection and appropriate treatment for patients affected by LMNA DCM.

CLINICAL CASE

A 57-year-old woman with hypertension, Grave's disease status post radiofrequency ablation, tobacco use disorder, and obstructive sleep apnea on continuous positive airway pressure (CPAP) therapy was referred to cardiology by her primary care doctor for evaluation of an abnormal electrocardiogram (ECG). During an outpatient colonoscopy, she was noted to have 1st degree AV block and premature ventricular contractions (Figure 1) on a routine pre-operative ECG. Upon presentation, she noted exertional shortness of breath and easy fatigability. At this visit, blood pressure was 126/73 mmHg, heart rate 55 beats per minute, oxygen saturation of 98% on room air, and BMI of 37.6 kg/m². Physical exam findings were notable for jugular venous pressure of 5 cm of water, physiologic split of S2, clear breath sounds, and no peripheral edema. She had no rashes, red eyes, or lymphadenopathy. She denied any significant family history of sudden cardiac death or heart failure at this time.

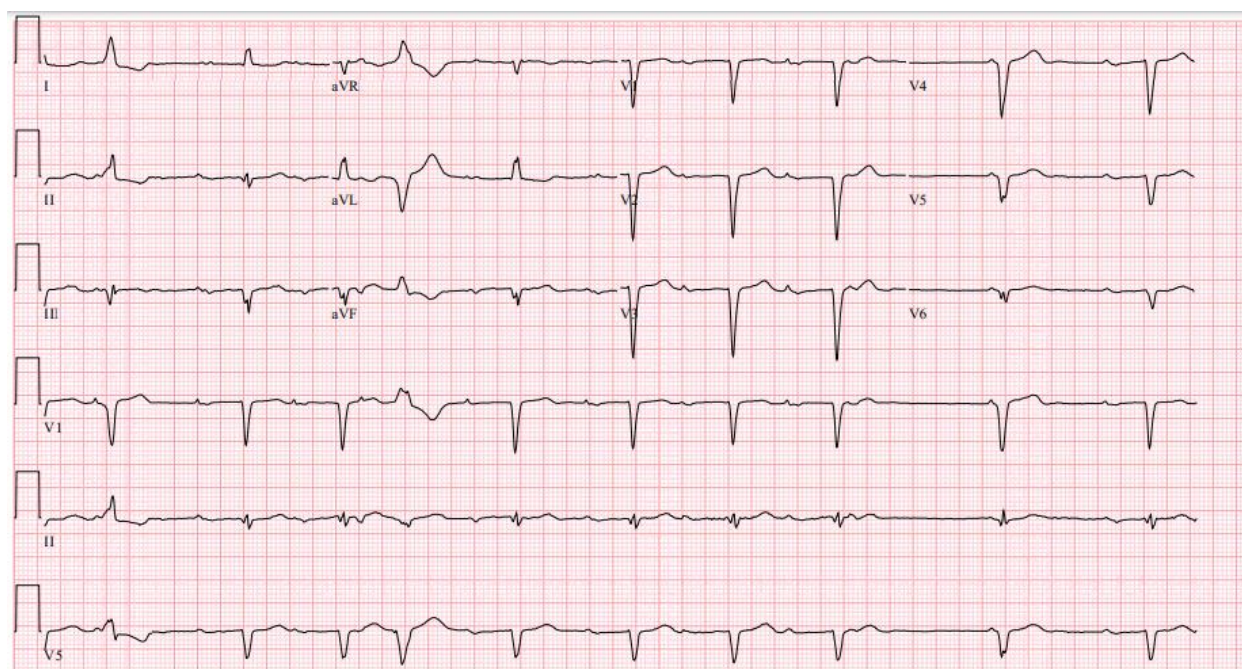


Figure 1: ECG. Pre-operative 12 lead EKG with 1st degree grade AV block and premature ventricular contractions.

A cardiac work-up included a transthoracic echocardiogram (TTE) which noted a moderately depressed left ventricle ejection fraction (LVEF) of 35-40% with global hypokinesia of the left ventricle. The left ventricle was mildly dilated with an internal diameter of 5.8cm. Right and left heart catheterization noted non-obstructive coronary artery disease and elevated intracardiac filling pressures, with preserved cardiac output. Cardiac magnetic resonance imaging (cMRI) showed patchy late gadolinium enhancement (LGE) in the basal anteroseptum and inferolateral left ventricular segments (Figures 2A and B).

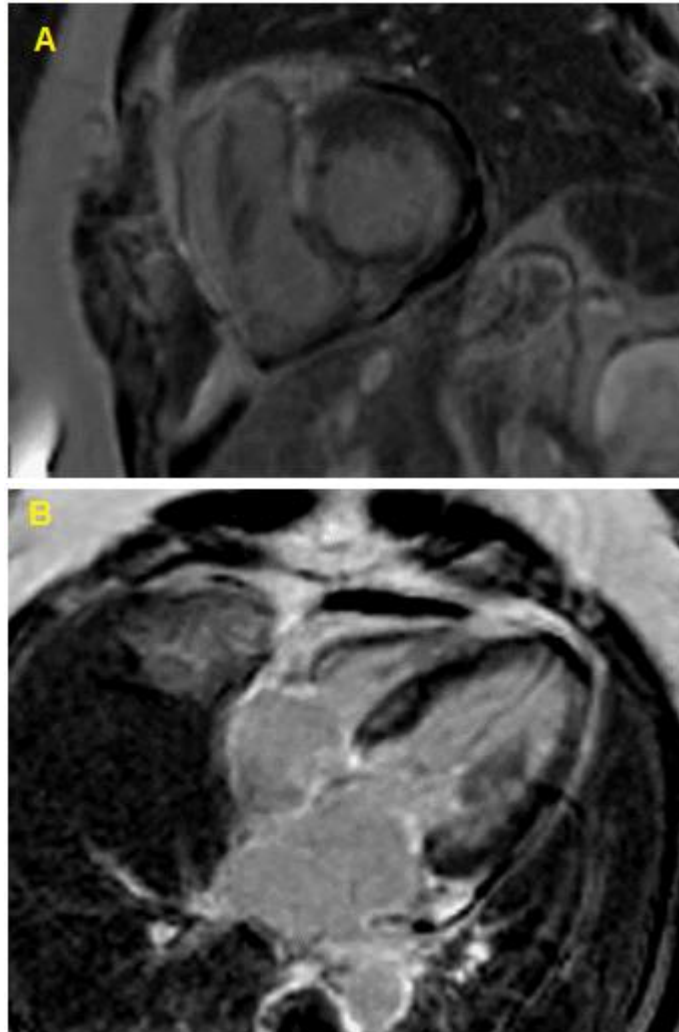


Figure 2: Cardiac MRI Images. (A) Cardiac MRI late gadolinium (phase sensitive inversion recovery sequence) short axis basal slice showing transmural late gadolinium enhancement of the basal anteroseptum and inferolateral left ventricular segments. (B) Corresponding apical 4 chamber showing enhancement of the basal to mid lateral segments.

The initial positron emission tomography (PET) scan noted fluorodeoxyglucose (FGD) uptake in the corresponding areas, suggestive of cardiac sarcoidosis (CS) (Figure 3A). She had no extracardiac uptake to suggest systemic sarcoidosis. Ambulatory heart monitor showed salvos of non-sustained ventricular tachycardia and episodes of atrial fibrillation. She refused to undergo invasive endomyocardial biopsy. Given the clinical and imaging findings she was presumed to have isolated CS. She was empirically started on prednisone daily for treatment of CS. An implantable cardiac resynchronization therapy defibrillator was placed for primary prevention. She had no improvement on a 12 week follow up PET scan. She was then started on methotrexate. Again, she had no improvement in symptoms or improvement on follow up PET scan (Figure 3B). Unfortunately, during the course of patient's treatment, her 48-year-old sister passed away due to a heart attack. Upon further probing, the patient revealed her grandmother may have had congestive heart failure and her father had a defibrillator. This prompted additional work up and genetic testing which revealed a pathogenic variant in the LMNA gene. She was then transitioned to guideline-directed medical therapy (GDMT), including

sacubitril/valsartan, spironolactone, and beta blocker with subsequent improvement in her symptoms. At her most recent outpatient follow up appointment, she was almost back to her baseline functional status and was able to go on a hike. Follow up TTE revealed her LVEF had improved to 55-60% and she was NYHA class 1.

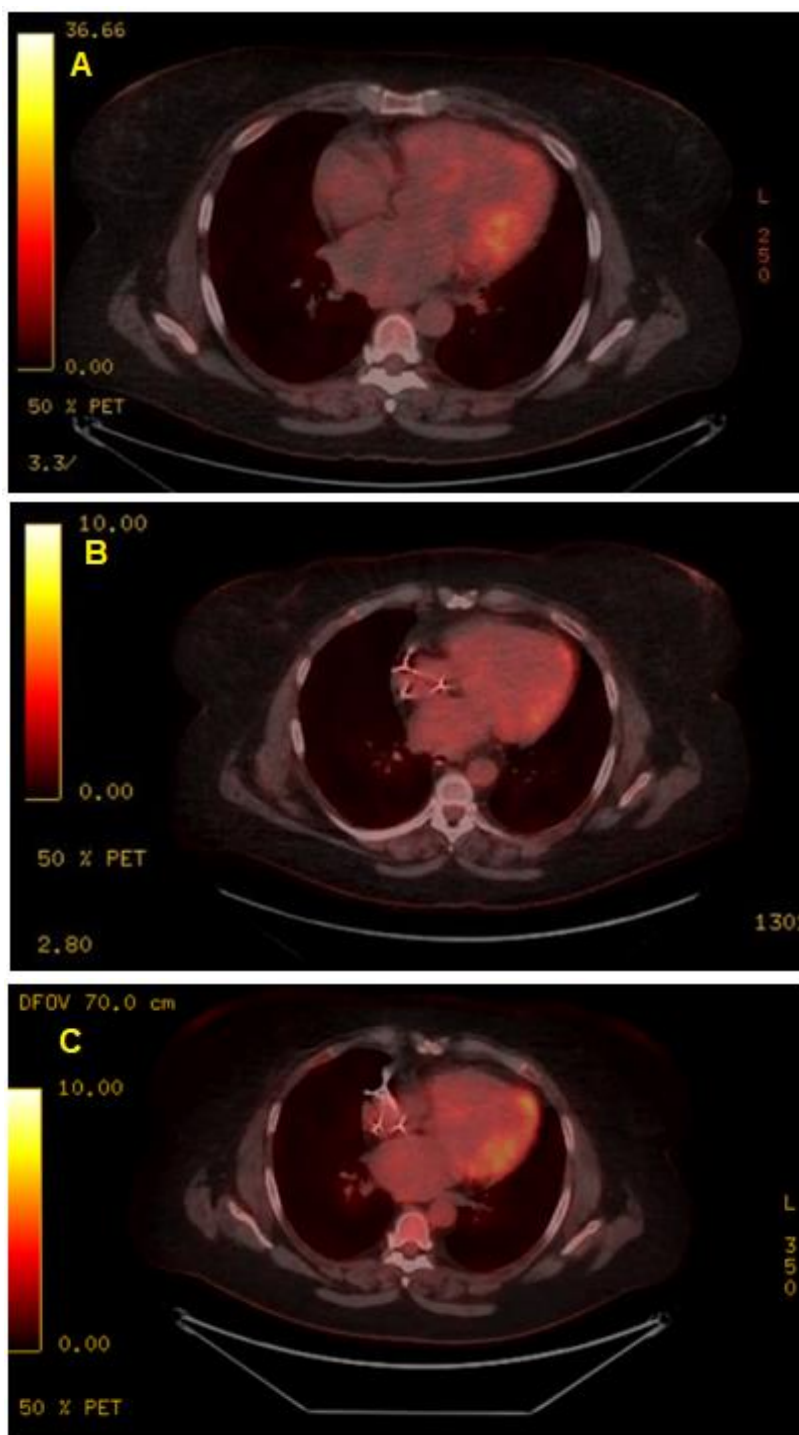


Figure 3: PET Images. (A) Fused FDG-18 PET/CT axial view shows FDG uptake in the basal to mid lateral left ventricular segments. (B) Fused FDG-18 PET/CT scan after prednisone therapy

redemonstrates FDG avidity in the lateral segments and increased uptake extending into the apex. (C) Fused FDG-18 PET/CT after 3 months of methotrexate shows persistent FDG uptake.

DISCUSSION

Isolated CS is a rare condition which almost always is a tissue diagnosis according to the HRS consensus statement [6]. The clinical presentation of CS varies from asymptomatic heart block to hemodynamically unstable arrhythmias and heart failure [7]. Multimodality imaging has revolutionized the diagnosis of CS in the right clinical setting [8], however obtaining tissue diagnosis remains the key factor. There are recent studies showing the overlap of imaging and clinical findings between CS and genetic cardiomyopathies [9,10]. In such cases, a detailed family history and genetic testing are crucial to make the correct diagnosis before subjecting the patient to disease modifying immunosuppressive therapies.

Interestingly, the LMNA DCM variant can have inflammatory findings on cMRI and PET imaging similar to sarcoidosis [4,11], which can confound and delay the correct diagnosis of LMNA DCM. CS is accompanied by mid myocardial patchy LGE in a non-coronary distribution on cMRI [7,11]. Similarly, the LMNA variant has LGE in the septal mid-wall in a non-ischemic pattern [4]. Further adding complexity to differentiating between CS and LMNA DCM are the similarities on PET scan. Both are inflammatory conditions which can have focal or diffuse FDG uptake on PET scan [11].

The LMNA variant of DCM should be considered in any patient presenting with dysrhythmias, heart failure, and a positive cardiac family history [1], especially when there is no tissue diagnosis of extra CS. Prompt genetic testing can help with timely diagnosis and referral for advanced therapies if indicated [12]. Once diagnosed with LMNA cardiomyopathy, treatment is focused on GDMT, primary prevention implantable cardioverter-defibrillator, and potential heart transplant [1]. Due to a high risk of malignant ventricular arrhythmias and conduction abnormalities, it is prudent to consider placement of permanent pacemaker and implantable cardioverter-defibrillator for primary prevention. The 2017 AHA/HRS Guidelines recommend implantable cardioverter-defibrillator placement in patients with LMNA cardiomyopathy with high risk features a Class IIa indication [1].

As presented in this case, the patient had cardiac imaging findings concerning for isolated CS however, we did not have tissue diagnosis. Evidently, she did not respond to CS treatment which prompted further investigations. After genetic testing revealed a LMNA mutation, she was appropriately started on GDMT for heart failure and had prompt improvement.

CONCLUSIONS

This case highlights the importance of tissue diagnosis in isolated CS and the need to look for genetic cardiomyopathies in patients presenting with isolated CS before starting immunosuppression. Imaging findings are only ancillary to tissue diagnosis in CS. Although the LMNA mutation DCM is rare, it can have similar imaging findings to CS and it is important to consider genetic testing at the time of initial assessment. The use of advanced cardiac imaging for detection and diagnosis of inflammatory cardiomyopathies requires further research to define the specific patterns for various types of DCM.

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