Journal of Community Hospital Internal Medicine Perspectives

Volume 13 | Issue 4 Article 5

2023

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Recommended Citation

Khan, Wahab J; Asif, Muhammad; Chaudhry, Hammad S; Aslam, Sadia; Nadeem, Ifrah; and Chowdhury, Mohammed A. (2023) "Arrhythmogenic Left Ventricular Cardiomyopathy Associated with a Phospholamban Gene Mutation in a Young Female: A Case Report and Literature Review," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 13: Iss. 4, Article 5.
DOI: 10.55729/2000-9666.1174
Available at: https://scholarlycommons.gbmc.org/jchimp/vol13/iss4/5

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CASE REPORT

Arrhythmogenic Left Ventricular Cardiomyopathy Associated With a Phospholamban Gene Mutation in a Young Female: A Case Report and Literature Review

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Abstract

Arrhythmogenic cardiomyopathy (ACM) is a myocardium disease characterized by phenotypic features of myocardial scarring due to fibrofatty myocardial replacement often associated with global or regional ventricular dysfunction. For years after arrhythmogenic right ventricular cardiomyopathy (ARVC) was first described, the left ventricle (LV) was generally considered normal or minimally involved. In recent years, however, LV involvement has been recognized. It usually presents with early-on arrhythmias more than heart failure symptoms compared to dilated cardiomyopathy. It can be right ventricular, biventricular, or left ventricular. The underlying pathophysiology involves either desmosomal or non-desmosomal mutations. Phospholamban (PLN) mutation is one of those and is associated with more severe arrhythmias and SCD.

Primary prevention with ICD implantation should be considered in these patients, even the ones with an ejection fraction greater than 35%. In addition, if such patients progress to Stage D heart failure, they need to be evaluated for advanced heart failure therapies.

Keywords: Arrhythmia, Cardiomyopathy, Phospholamban, Genetic mutations, Heart failure

1. Introduction

Arrhythmogenic cardiomyopathy (ACM) is a myocardium disease characterized by phenotypic features of myocardial scarring due to fibrofatty myocardial replacement often associated with global or regional ventricular dysfunction. It leads to potentially lethal scar-related ventricular arrhythmias. In addition, ischemic, hypertensive, or valvular heart disease must be excluded to establish this diagnosis. ACM comprises a broad spectrum of genetic, systemic, infectious, and inflammatory disorders. It includes, but is not limited to, arrhythmogenic right and left ventricular cardiomyopathy, cardiac amyloidosis, sarcoidosis, Chagas disease, and non-compaction cardiomyopathy.[1] For years after arrhythmogenic right ventricular cardiomyopathy (ARVC) was first described clinically and pathologically in the 1980s, attention was understandably focused on the RV. The left ventricle (LV) was generally considered normal or minimally involved. In recent years, however, LV involvement has been recognized, and more cases are reported in the literature. This report describes a case of arrhythmogenic left ventricular cardiomyopathy (ALVC) in a young female with a PLN mutation.

Abbreviations: ACM, Arrhythmogenic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; PLN, phospholamban; ALVC, arrhythmogenic left ventricular cardiomyopathy; GDMT, goal-directed medical therapy; ICD, implantable cardiac defibrillator; SCD, sudden cardiac death

Received 7 January 2023; revised 27 January 2023; accepted 8 February 2023.
Available online 29 June 2023

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https://doi.org/10.55729/2000-9666.1174

2. Case

A 40-year-old female with a history of psoriatic arthritis on Adalimumab was evaluated for two syncopal events. She was initially worked up by neurology, and the workup for seizure was unremarkable. As part of her syncope workup, she also underwent Holter monitoring which reported 8% premature ventricular beat burden. She had 33 episodes of symptomatic non-sustained ventricular tachycardia, with a maximum heart rate of 222 bpm. She was admitted for further evaluation of her ventricular arrhythmias. On presentation, the patient complained of exertional dyspnea and generalized fatigue. Her vital signs were BP 108/74, HR 63, RR 18, O2 Sat 99% on room air, and temperature of 97.8F. Initial lab work reported normal CBC and BMP profiles. High sensitivity troponin was 92 pg/ml (n < 12 pg/ml), which peaked at 98 pg/ml. BNP was elevated at 438 pg/ml (5–100 pg/ml). Furthermore, her D-dimers were negative. ESR/CRP was in the normal range, and the Chest x-ray demonstrated no evidence of consolidation or pleural effusion. EKG showed sinus rhythm with multiple PVCs and low voltage QRS complex (Fig. 1). Her QTC was measured at 550 msec. Her echocardiogram reported an ejection fraction of 40% with mild concentric left ventricular hypertrophy and global hypokinesis of the left ventricle (Fig. 2). Right ventricular systolic function was normal. Her coronary angiogram reported normal coronary arteries with an LVEDP of 28 mmHg. Cardiac MRI showed an ejection fraction of 40% with a thick area of delayed gadolinium uptake in the anteroinferior, apical and lateral segments suggestive of myocarditis with a 25% scar burden (Fig. 3a and b). There was no evidence of prior infarction, infiltrative disease, or iron overload. She was then diagnosed with nonischemic cardiomyopathy and started on goal-directed medical therapy (GDMT). Her Adalimumab treatment was discontinued due to her left ventricular dysfunction. While in the hospital, the patient continued to have recurrent runs of non-sustained ventricular tachycardia and was started on amiodarone and underwent dual-chamber implantable cardiac defibrillator (ICD) implantation. Biopsy was initially considered to rule out giant cell myocarditis, however, during her inpatient stay, she was

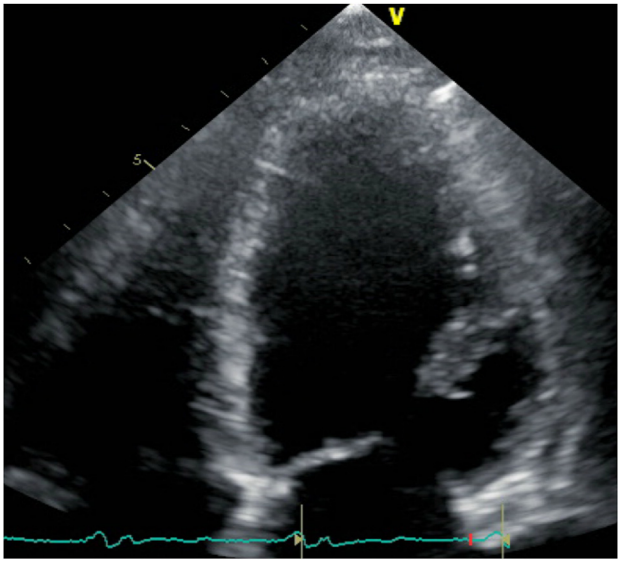

Fig. 2. Echocardiogram demonstrating mildly dilated left ventricle with an ejection fraction of 45%.

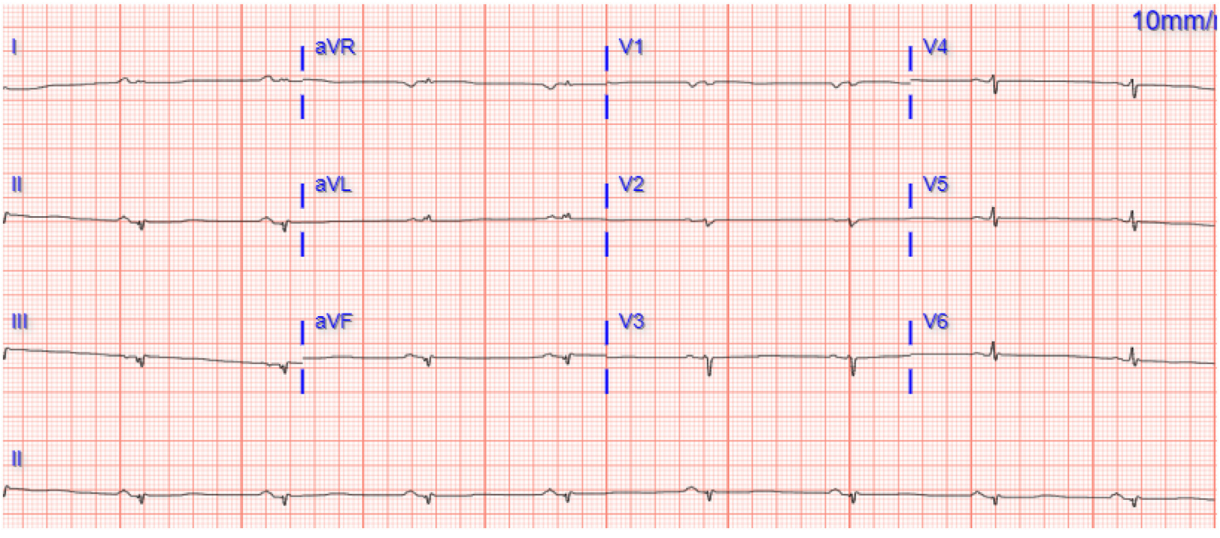

Fig. 1. EKG showing low voltage QRS complex.

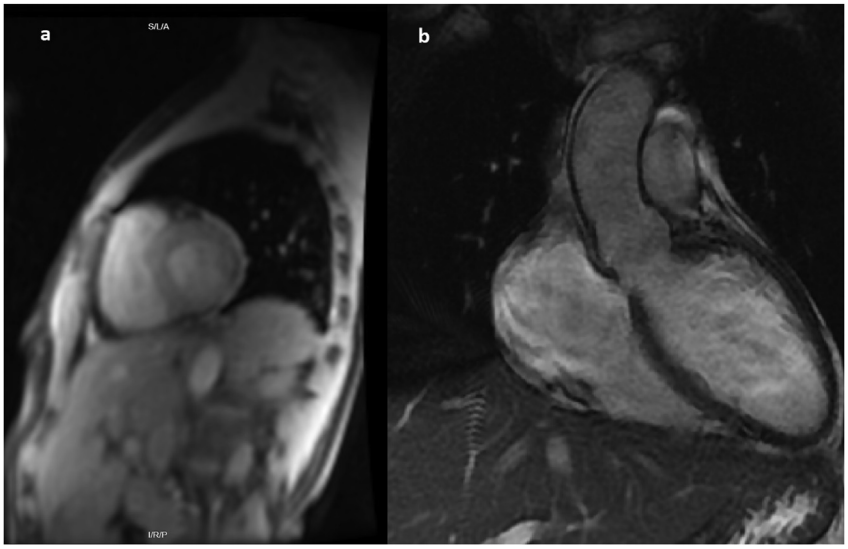

Fig. 3. a and b. Cardiac MRI images demonstrating extensive delayed gadolinium enhancement.

hemodynamically stable, and her ventricular arrhythmias improved with amiodarone. Thus, at that point, it was felt that an invasive procedure would not change our management and was deferred. She underwent genetic testing, which reported a pathologic variant in the phospholamban (PLN) gene (C 40_42 DEL (p.Arg14del heterozygous). The patient has been doing well with GDMT and amiodarone with no syncope recurrence. Her three-month follow-up echocardiogram reported an EF of 45%.

3. Discussion

The prevalence of ACM is estimated to be between 1:1000 and 1:5000,[2] depending on geographical differences. However, the actual prevalence of ACM, especially of ALVC, is unknown and presumably higher due to many non-diagnosed and misdiagnosed cases. In one study, up to 25% of decedents with sudden cardiac death (SCD) had genetic variants and morphologic and histologic findings of ACM. It predominantly affects males. Until recently, it was generally held that the left ventricle was normal or minimally involved initially and was mainly a late complication of ARVC. In 2020, however, LV involvement was recognized, and diagnostic criteria were revised to include left-sided involvement. (Padua criteria).[3] ALVC and biventricular variants (BVACM) are more likely to be associated with SCD. Athletes with a genetic predisposition for ACM are particularly at risk for SCD.[4] Many patients with ACM remain clinically silent and asymptomatic for decades, making the disease difficult to recognize, especially in sporadic cases with no recognized familial involvement. The clinical presentations of ACM are variable, including palpitations, syncope, chest pain, dyspnea, and, rarely, SCD. The pathologic process in classic ARVC predominantly involves the RV and sometimes extends to the LV. In contrast, patients with ALVC (also known as left-dominant arrhythmogenic cardiomyopathy) have pathological changes that primarily affect LV in the early course of the disease. The underlying pathophysiology involves either desmosomal or non-desmosomal mutations. Many, including Phospholamban (PLN) mutations, have been linked with both the ACM (ARVC and biventricular ACM but not with isolated ALVC) and Idiopathic dilated cardiomyopathies (DCM).[5] Phospholamban (PLN) is a non-desmosomal gene implicated in ACM. It regulates the sarcoplasmic reticulum calcium pump (SERCA2) and plays a crucial role in Ca+2 homeostasis. The R14del mutation in PLN was first identified in patients with DCM but more recently has been spotted in patients in a Dutch cohort with a clinical and pathological phenotype of ACM.[4] About 1% of patients with ARVC in the United States and 12% of Dutch patients with ARVC have been identified to have this pathogenic p.R14del-PLN variant. Patients with this variant usually have low-voltage EKGs. They are considered to have a high risk for developing malignant ventricular arrhythmias and end-stage HF, with LVEF <45% and sustained VT or NSVT as independent risk factors.[1] Early detection of these genetic CM remains challenging, especially without a family history. One study showed early EKG changes (attenuated R waves irrespective of

echocardiographic abnormalities) in people with PLN-R14Del mutation before the disease heralded itself as cardiac dysfunction, signifying a mutation-related remodeling process could start before ventricular dysfunction is evident.[6] The diagnosis of ACM involves multiple parameters that are grouped into six categories, including structural and functional ventricular abnormalities. It also involves EKG alterations, ventricular arrhythmias, and familial/genetic components.[3] The differential diagnoses are myocarditis, DCM, and other infiltrative cardiomyopathies. It may be challenging to differentiate between ALVC and myocarditis (chest pain and enzyme rise), especially at presentation. Myocarditis can show ventricular arrhythmias with an RBBB morphology, denoting the origin from the LV, and ECG anomalies such as negative T-waves and low QRS voltages.[7] In this context, molecular genetic testing with a demonstration of AC-gene mutation is usually critical to differentiate these two from each other.[8] Another difficult-to-differentiate diagnosis can be DCM. Especially because DCM and left predominant or biventricular ACM also share a greater degree of genetic mutations.[5] "DCM with hypokinetic non-dilated cardiomyopathy," considered a less expressed DCM phenotype, can be a great mimicker of ALVC. Arrhythmogenic cardiomyopathy is distinguished from DCM by a propensity towards arrhythmia exceeding the degree of ventricular dysfunction.[5] In these instances, cardiac MR tissue characterization (late gadolinium enhancement (LGE) amount and distribution pattern correlating to fibrofatty myocardial replacement) can help differentiate these two conditions. Almost all patients with ALVC and LV systolic dysfunction show the presence of LV LGE compared to <50% of DCM cases.[9] LV LGE distribution predominately affects the subepicardial inferolateral segments in ALVC and septal segments in DCM.[9] In addition, the LGE appears as a stria pattern than a patchy pattern observed in DCM. Another differential could be sarcoidosis, which can be separated based on multi-system involvement and earlier involvement of basal septum and, consequently, heart blocks.[10]

4. Conclusion

ALVC is not uncommon, as was previously believed. It is also not rare in the female population. PLN mutations and consequent structural dysfunction are frequently associated with DCM, which predominantly presents as CHF and is managed with recommended GDMT. This mutation is also common in ACM, especially the ones involving the left ventricle, usually in a biventricular pattern. Our case shows that it may occur in predominant left ventricular ACM conditions. Moreover, PLN mutation in ACM is associated with more severe arrhythmias and SCD.[5] Primary prevention with ICD implantation should be considered in these patients, even the ones with an ejection fraction greater than 35%.[11,12] In addition, if such patients progress to Stage D heart failure, they need to be evaluated for advanced heart failure therapies. More studies are needed to devise strategies for early detection of the population at risk before adverse events occur that are usually fatal like SCD.

Conflict of interest

The authors have nothing to disclose.

Funding

There was no funding involved.

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