Long-term Follow-Up of a Patient with FLNC Gene Mutation-Related Cardiomyopathy: A Case Report

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Introduction

Heart Failure (HF) is estimated to affect approximately 26 million people worldwide.[1,2] In Brazil, prevalence is high, with about 2 million diagnosed patients and an incidence of roughly 240,000 new cases every year. Between 2011 and 2021, more than 2.5 million HF-related hospitalizations were recorded in the Brazilian Unified Health System (SUS), underscoring the relevance of the disease in the national context.[3] These figures highlight the need for early diagnostic strategies and etiological definition for the appropriate management of these patients. Establishing an etiological diagnosis is often challenging but essential to provide disease-specific treatments and improve prognosis. Diagnosis encompasses multimodality cardiac imaging, with Cardiac Magnetic Resonance imaging (CMR) being a useful tool for evaluating non-ischemic cardiomyopathy phenotypes and establishing an etiological diagnosis.[4]

Clinical Case

A 52-year-old male patient presented in 2017 with exertional dyspnea and chest pain and was initially investigated by echocardiography, which revealed new left ventricular dysfunction. The patient had no known previous comorbidities or family history of cardiomyopathy. Additional investigations included CMR, which showed left ventricular enlargement and systolic dysfunction with a Left Ventricular Ejection Fraction (LVEF) of 38%, along with multiple non-ischemic Late Gadolinium Enhancement (LGE) foci without myocardial edema, initially interpreted as previous inflammatory cardiomyopathy (Figure 1). The patient was then diagnosed with Heart Failure with Reduced Ejection Fraction (HFrEF), and treatment with beta-blockers and angiotensin-converting enzyme inhibitors was initiated.

Keywords

Cardiomyopathies; Genetics; Cardiac Magnetic Resonance Imaging; Arrhythmias, Cardiac; Sudden Cardiac Death

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Manuscript received September 9, 2025; revised September 10, 2025 accepted September 10, 2025
Editor responsible for the review: Marcelo Tavares

DOI: https://doi.org/10.36660/abcimg.20250071i

In 2024, the patient was referred to our service due to persistent HFrEF, now associated with frequent palpitations. Repeat CMR was performed. The exam revealed biventricular systolic dysfunction (LVEF 42% and RVEF 40%), diffuse hypokinesia, absence of myocardial edema, elevated native T1 mapping (1120 ms) and extracellular volume fraction (42%), as well as extensive areas of non-ischemic LGE (> 35% of LV mass) with a ring-like pattern (Figure 2), suggesting a genetic cardiomyopathy, with possible FLNC or desmoplakin mutation. Marked progression of LGE compared with the previous exam was observed.

Due to palpitations associated with the high burden of LGE, a 24-hour Holter monitor was performed:

- Total events: 102,754
- Heart rate: 57-74-141 bpm
- Ventricular ectopy 10,130 events (10%)
  - 9,323 isolated; 44 bigeminy; 402 couplets; one non-sustained ventricular tachycardia (NSVT) with three beats.

Genetic testing (Table 1) indicated a heterozygous pathogenic variant in the FLNC gene. Clinical therapy was optimized, family screening was recommended, and an implantable cardioverter-defibrillator (ICD) was placed for sudden cardiac death prevention.

Discussion

Genetic cardiomyopathies associated with mutations in the filamin C (FLNC) gene are rare and difficult to diagnose. Filamin C is a cytoskeletal protein that plays an essential role in maintaining the structural and functional integrity of cardiomyocytes. Pathogenic mutations in this gene are associated with a wide range of clinical manifestations. Truncating filamin C mutations are prevalent in dilated cardiomyopathy and Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC). Non-truncating filamin C mutations are more common in Hypertrophic Cardiomyopathy (HCM) and Restrictive Cardiomyopathy (RCM). Two main pathogenic mechanisms in FLNC-related cardiomyopathy have been described: protein aggregation due to non-truncating mutations and haploinsufficiency caused by truncating mutations.[5]

FLNC-related cardiomyopathy, manifesting as a DCM phenotype, usually presents with LV dilation, LV systolic dysfunction, and areas of myocardial fibrosis identified as

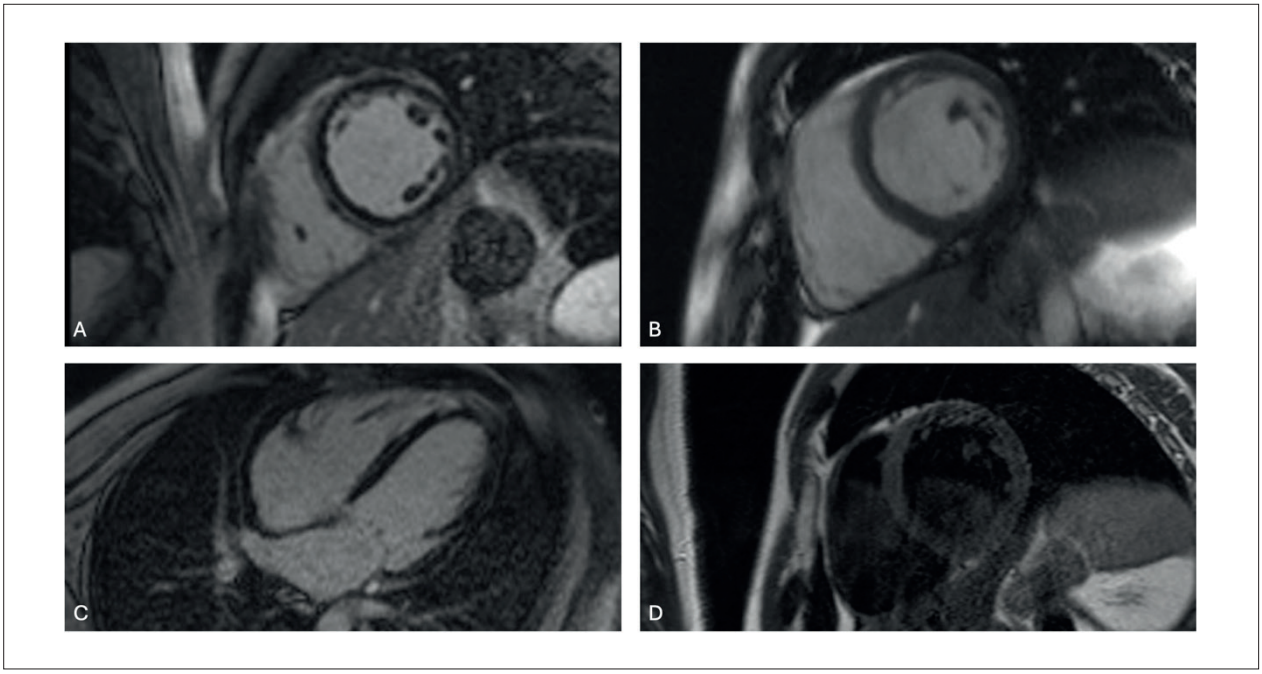

Figure 1 – *Cardiac magnetic resonance imaging performed in 2017. A and C: LGE images in short-axis and 4-chamber views. B: short-axis cine MRI image. D: dark-blood triple inversion recovery sequence image.*

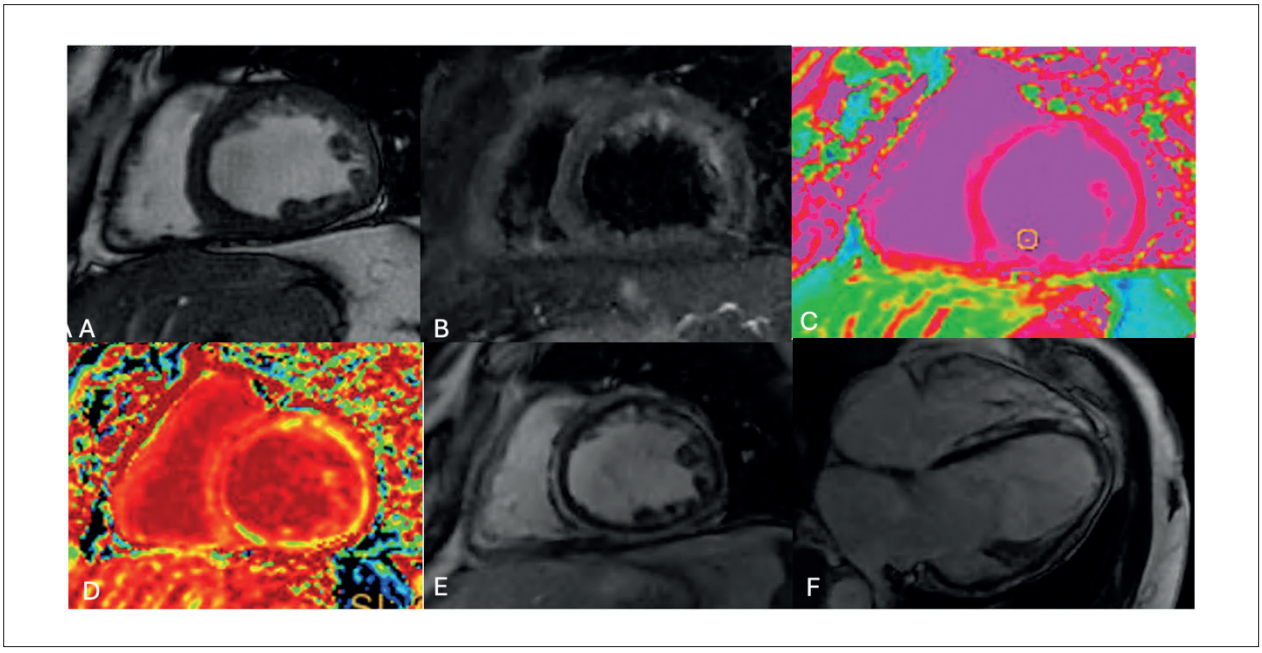

Figure 2 – *Cardiac magnetic resonance imaging performed in 2024. A: cine MRI image; B: dark-blood triple inversion recovery sequence image; C: native T1 map; D: extracellular volume map; E and F: LGE images in short-axis and 4-chamber views, respectively, showing extensive areas of non-ischemic LGE.*

LGE on CMR.[4] Clinical suspicion may arise in patients with recurrent or familial myocarditis, in patients with arrhythmias, or when CMR demonstrates progression of fibrosis. FLNC mutation-related cardiomyopathy is notable for its association with inflammatory pathways overlapping with classical myocarditis, representing a rare but increasingly recognized cause of arrhythmogenic cardiomyopathy.[6]

The risk of sudden cardiac death in these patients is high, mainly due to a predisposition to malignant ventricular arrhythmias such as sustained ventricular tachycardia or

Table 1 – Genetic testing

Gene/Transcript	Exon	Variant	Population frequency	Zygosity	Classification
FLNC (NM_001458.5)	4	C850+1G>A p.?	0%	Heterozygous	Likely Pathogenic

ventricular fibrillation. This risk justifies the early consideration of preventive strategies, such as implantable cardioverter-defibrillators (ICDs), particularly in individuals with a history of complex arrhythmias or significant ventricular dysfunction.[7] In the present case, ventricular dysfunction (LVEF < 45%), associated with extensive fibrosis, survival greater than one year, supported ICD implantation with a class IIa recommendation.[4,8]

CMR plays a fundamental role in the diagnosis of non-ischemic cardiomyopathies, including those related to FLNC mutations. This exam allows both morphofunctional evaluation and tissue characterization with identification of myocardial fibrosis. The location and pattern of myocardial fibrosis, such as ring-like or diffuse, may provide valuable information for differentiating ischemic and non-ischemic etiologies, as well as correlate with prognosis and arrhythmic risk. Moreover, CMR with T1 mapping and extracellular volume quantification may be useful for the early detection of tissue changes, even in the absence of overt morphological abnormalities.[4,6,9]

The integration of genetic, clinical, and imaging findings is essential for effective diagnostic and therapeutic approaches in genetic cardiomyopathies, particularly in patients such as the one described, in whom disease progression was significant. Identification of FLNC mutations should raise concern for the potential risk of refractory HF and SCD, making regular follow-up crucial for these patients.

Author Contributions

Conception and design of the research: Costa IBSS, Rangel BSS. Writing of the manuscript: Costa IBSS, Rangel BSS, Paladino Filho AT,Colombo BN, Morais TC. Critical revision of the manuscript for intellectual content: Hajjar LA.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Hospital São Luiz, Rede D'Or, under the protocol number CAAE 91628425.0.0000.0087. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

Use of Artificial Intelligence

The authors did not use any artificial intelligence tools in the development of this work.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

References

1. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of Heart Failure: The Prevalence of Heart Failure and Ventricular Dysfunction in Older Adults Over Time. A systematic review. Eur J Heart Fail. 2016;18(3):242-52. doi: 10.1002/ejhf.483.
2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2021;42(36):3599-726. doi: 10.1093/eurheartj/ehab368.
3. Brasil. Ministério da Saúde. Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde (CONITEC) [Internet]. Brasília: Ministério da Saúde; 2024 [cited 2025 Nov 4]. Available from: https://www.gov.br/conitec.
4. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, et al. 2023 ESC Guidelines for the Management of Cardiomyopathies. Eur Heart J. 2023;44(37):3503-626. doi: 10.1093/eurheartj/ehad194.
5. Song S, Shi A, Lian H, Hu S, Nie Y. Filamin C in Cardiomyopathy: From Physiological Roles to DNA Variants. Heart Fail Rev. 2022;27(4):1373-85. doi: 10.1007/s10741-021-10172-z.
6. Del Franco A, Ruggieri R, Pieroni M, Ciabatti M, Zocchi C, Biagioni G, et al. Atlas of Regional Left Ventricular Scar in Nonischemic Cardiomyopathies: Substrates and Etiologies. JACC Adv. 2024;3(10):101214. doi: 10.1016/j.jacadv.2024.101214.
7. Ortiz-Genga MF, Cuenca S, Dal Ferro M, Zorio E, Salgado-Aranda R, Climent V, et al. Truncating FLNC Mutations are Associated with High-Risk Dilated and Arrhythmogenic Cardiomyopathies. J Am Coll Cardiol. 2016;68(22):2440-51. doi: 10.1016/j.jacc.2016.09.927.

8. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, et al. 2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy: Executive Summary. Heart Rhythm. 2019;16(11):e373-e407. doi: 10.1016/j.hrthm.2019.09.019.

9. Schoonvelde SAC, Ruijmbeek CWB, Hirsch A, van Slegtenhorst MA, Wessels MW, von der Thüsen JH, et al. Phenotypic Variability of Filamin C-Related Cardiomyopathy: Insights from a Novel Dutch Founder Variant. Heart Rhythm. 2023;20(11):1512-21. doi: 10.1016/j.hrthm.2023.08.003.