Case Report

Dilated Cardiomyopathy Associated With A Novel Truncated Filamin C Variant Mimicking Cardiac Amyloidosis: A Diagnostic Challenge

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Introduction

Filamins interconnect actin filaments and form a broad network in cardiac and skeletal muscle cells by anchoring membrane proteins to the cytoskeleton. Filamin C, encoded by the FLNC gene, is one of three filamin-related proteins and binds to several proteins in the Z-disc of the sarcomere. Mutations in FLNC were initially associated with skeletal myofibrillar myopathy but are now recognized as associated with dilated and arrhythmogenic cardiomyopathy phenotypes, with autosomal dominant inheritance and an estimated penetrance of 92–97%,[1] and are included in the genetic screening of patients with arrhythmogenic heart disease and sudden cardiac death. The prevalence of pathogenic FLNC variants is 1–4.5% among patients with dilated cardiomyopathy (DCM) and up to 6% in patients with arrhythmogenic cardiomyopathy.[1,2]

We describe the case of a patient with a novel truncated variant in the filamin C gene with a DCM phenotype who, during clinical follow-up and etiological investigation, presented imaging exams mimicking cardiac amyloidosis.

Case presentation

A 41-year-old man with no relevant cardiovascular history was diagnosed with heart failure after being hospitalized for pneumonia. A transthoracic echocardiogram showed significant left ventricular enlargement with moderate systolic dysfunction. A 24-hour Holter monitor showed frequent ventricular extrasystoles and some episodes of nonsustained ventricular tachycardia. A first-degree cousin had idiopathic DCM and died suddenly at the age of 48.

Myocardial scintigraphy and serology ruled out ischemic or chagasic involvement, respectively. Initial cardiac magnetic resonance imaging (CMRI) showed fibrosis of a midcardiac/non-ischemic pattern and significant systolic dysfunction (LVEF 23%), compatible with a DCM phenotype. During clinical follow-up, a new transthoracic echocardiogram showed septal hyperrefringence, and a second CMRI (Figure 1) demonstrated discrete diffuse subendocardial enhancement, suggesting cardiac amyloidosis (CA). Despite the lack of clinical history or phenotype compatible with CA, the patient underwent ^{99m}Tc pyrophosphate scintigraphy (Figure 2), which demonstrated, to our surprise, uptake of the radiopharmaceutical Perugini 3 and, in the quantitative analysis, a myocardial ROI/contralateral ROI ratio of 1.63. There was a limitation in the investigation of CA associated with light chains (AL), although the natural evolution of the disease over the years was against the possibility of cardiac involvement by CA in its AL form. Further investigation showed normal electroneuromyography and negative salivary gland biopsy. Given this enigmatic case, the next step was to perform a genetic evaluation. The patient underwent a genetic panel to investigate cardiomyopathies in 2021, revealing a new variant in the filamin C gene: c.3937C>T (p.Arg1313*).

Discussion

Since 2021, only two other reports have been included in Clinvar[3] of the c.3937 C>T variant (pp. Arg.1313*) as associated with DCM or cardiovascular-related disease. However, it is not included in the Exoma Sequencing Project (ExAC) or The Genome Aggregation Database (GnomAD)[4] databases. This variant has not been reported in the literature in individuals affected by conditions related to FLNC. Furthermore, this is also the first case of a variant in the FLNC gene in which imaging tests suggest transthyretin CA.

The patient presented a DCM phenotype with arrhythmic episodes, but the CMRI findings revealed a diffuse subendocardial late enhancement pattern, suggesting the hypothesis of CA. Although the DCM phenotype is unusual among patients with CA, present only in late and advanced stages of the disease, and the patient's age at diagnosis and clinical course were also poorly compatible with the diagnosis of CA, whether associated with the AL form or TTR, the pattern observed in the CMR is unequivocal. Furthermore, myocardial scintigraphy with pyrophosphate - ^{99m}Tc showed myocardial uptake higher than the costal arches. Only with the genetic test was it possible to define the etiology of DCM associated with FLNC.

Truncated variants in the FLNC gene are defined as alterations that introduce a stop code into the protein sequence (nonsense or frameshift) or that may alter the splicing process, resulting in a dysfunctional or disruptive protein.[5]

Keywords

Dilated Cardiomyopathy; Genetic Testing; Cardiac Arrhythmias; Amyloidosis

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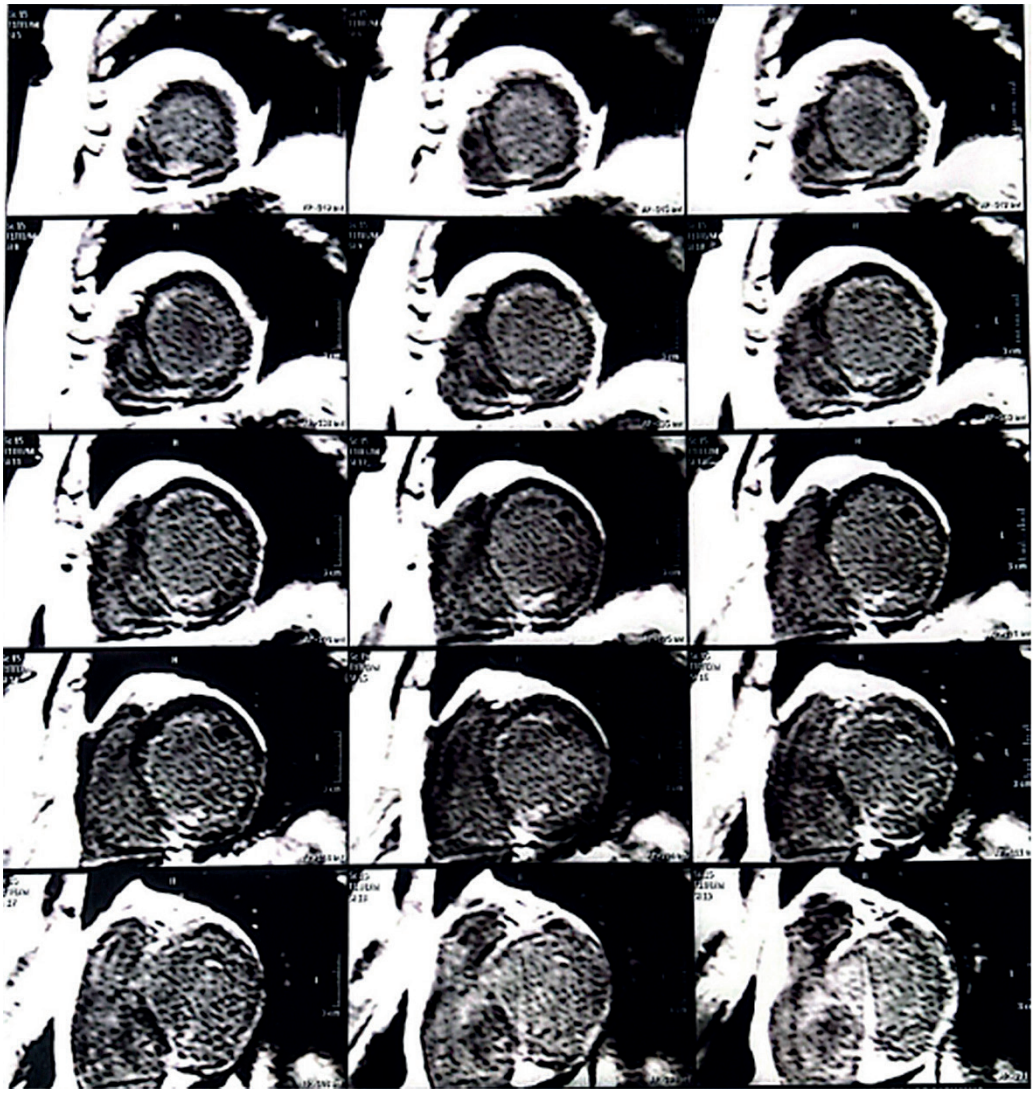

Figure 1 – *Cardiac magnetic resonance image with diffuse subendocardial delayed enhancement pattern of the LV, suggestive of cardiac amyloidosis.*

In terms of clinical manifestations, patients with truncated variants of FLNC present dyspnea on exertion and palpitations as the most frequent symptoms. They usually present a phenotype of ventricular dilation associated with left ventricular dysfunction and, to a lesser extent, biventricular dysfunction. On electrocardiogram, they present nonspecific findings such as T wave inversion mainly in left precordial leads.[5]

The presence of non-ischemic myocardial fibrosis on magnetic resonance imaging is another finding identified in these patients. The most frequently found pattern was a subepicardial ring-shaped delayed enhancement located in the infero-posterolateral region.[6]

Another relevant aspect of patients with FLNC is the greater probability of suffering some arrhythmic event or even sudden death, with the phenotype of left-sided arrhythmogenic cardiomyopathy being described in these patients. Patients with NCFL did not present a lower risk of sudden cardiac death or major arrhythmic events compared to patients with pathogenic variants in the laminin A/C and desmin genes, established models of arrhythmogenic cardiomyopathy, which demonstrates their arrhythmogenic potential. It is important to emphasize that the presence of left ventricular dysfunction does not correlate with a higher risk of sudden death among patients with NCFL.[6,7] Thus, since 2019, truncated variants of filamin C have been among the genes responsible for arrhythmogenic cardiomyopathy in the Heart Rhythm Society guidelines and are even considered a high-risk marker for sudden death, with a specific recommendation for ICD implantation in patients with an identified variant and LVEF <45% as primary prophylaxis for sudden death (class of recommendation IIa).[8]

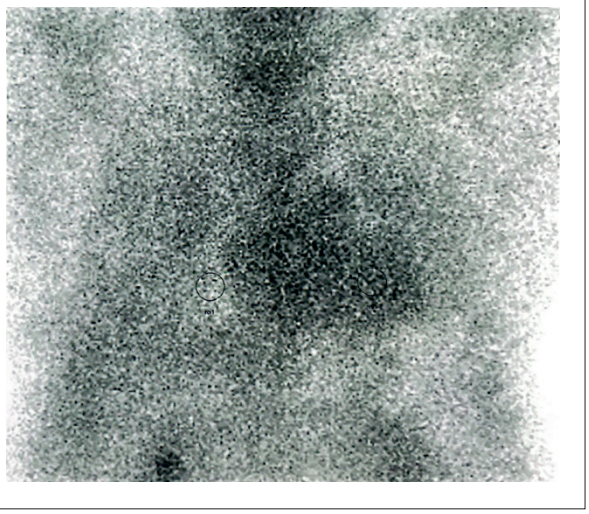

Figure 2 – *Myocardial scintigraphy image with pyrophosphate-99mTc with Perugini 3 uptake.*

Unfortunately, genetic diagnosis for hereditary cardiovascular diseases is not available in the Brazilian Unified Health System (SUS) or the supplementary health system. The private network provides the test at a high cost, which, combined with the lack of information and training in cardiogenomics, results in the underutilization of this test. In this sense, projects such as the National Cardiovascular Genomics Network (RENOMICA)[9] are essential in making cardiovascular genetic testing available in the SUS, shedding light on the investigation of hereditary cardiomyopathies that, until recently, were considered to be of idiopathic etiology.

Conclusion

We present the case of a patient with DCM associated with the c.3937C>T (p.Arg1313*) variant of the filamin C gene and false-positive findings for CA-TTR. The integration of clinical data, family history, and genetic testing is essential for the correct diagnosis and prognostic evaluation of the patient.

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Author Contributions

Conception and design of the research: Sousa KKC, Diniz RVZ, Mastrocola F; Acquisition of data: Sousa KKC, Costa CKRA, Costa BA; Analysis and interpretation of the data: Sousa KKC, Maia FGSS, Costa CKRA, Costa BA; Writing of the manuscript: Sousa KKC, Maia FGSS, Diniz RVZ; Critical revision of the manuscript for content: Sousa KKC, Maia FGSS, Mastrocola F.

Potential conflict of interest

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Study association

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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