Case Report

Cardiac Amyloidosis: Infiltrative Cardiomyopathy with Restrictive Hemodynamic Behavior – Case Report

Amiloidose Cardíaca: Cardiomiopatia Infiltrativa com Comportamento Hemodinâmico Restritivo – Relato de Caso

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Abstract

Amyloidosis is a rare heterogeneous group of disorders that occur with the extracellular deposition of fibrillar protein aggregates in the tissues and organs. Here we report the case of a 76-year-old with a 2-month history of progressive dyspnea on minimal effort. In the investigation, a global cardiac increase was observed, and echocardiography showed infiltrative restrictive heart disease and a pericardial effusion. Cardiac magnetic resonance imaging findings were highly suggestive of cardiac amyloidosis. Thus, as reported here, cardiac involvement primarily manifests as restrictive cardiomyopathy, a chronic heart failure with a difficult-to-diagnose etiology in patients over 50 years of age and a very poor prognosis. Thus, although it remains a diagnostic challenge for clinicians, cardiac amyloidosis must always be considered in the absence of another cause of such findings.

Introduction

Amyloidosis (AL) is a heterogeneous group of disorders that involve the extracellular deposition of fibrillar protein aggregates in the tissues and organs. A rare condition, it can manifest in an isolated or systemic way. Thus, these aggregates compromise target organ function and are responsible for clinical manifestations of the disease. From this perspective, in the cardiac context, protein deposits result in a series of disorders, such as heart failure (HF), arrhythmias, and angina syndromes. In addition, infiltration of the peripheral nerves induces symptomatic neuropathy, whereas deposits in the central nervous system can trigger dementia or, in the vascular context, cerebral hemorrhage.

Here we report a clinical case of a patient with infiltrative cardiomyopathy with restrictive hemodynamic behavior and characteristic echocardiography findings for which anatomopathological evaluation findings of the fibrillar protein aggregates were suggestive of AL.

Case Report

A 76-year-old man from Fortaleza, CE, Brazil, presented with a main complaint of dyspnea on minimal effort associated with fever and a productive cough with a greenish mucus secretion that had started in March 2019. He had been admitted to a referral university hospital 2 months after the onset of symptoms with no improvement. He also complained of oscillatory postural vertigo that had started 6 months prior and recently progressed to severe ambulation and a reduced quality of life. The patient had a previous pathological history of systemic arterial hypertension, diabetic neuropathy, and tonic-clonic seizure episodes. On physical examination, he appeared in good general condition and was acyanotic, anicteric, afebrile, hydrated, and pale (++/4+) with a systemic blood pressure of 110/60 mmHg, heart rate of 90 bpm, respiratory rate of 18/min, axillary temperature of 34.6°C, and macroglossia. Cardiac auscultation showed a regular double heart rhythm with normal sounds and no murmurs as well as the presence of a mild pericardial friction rub. Electrocardiography (ECG) showed low diffuse voltage with a first-degree atrioventricular block. Echocardiography (ECHO) showed significant ventricular concentric hypertrophy, biatrial enlargement, preserved systolic function (ejection fraction, 64%), grade II diastolic dysfunction (increased left atrial volume, 39 mL/m^2; mitral flow E/A ratio, 0.64; mitral flow E-wave velocity, 79 cm/s; and mean mitral and tissue Doppler E/E', 29.39), a moderate pericardial effusion (PE), (Figure 1) and a reduced left ventricular global longitudinal strain of -8.2 (Figure 2). Chest magnetic resonance imaging (MRI) showed mediastinal lymphadenopathy and left ventricular myocardial thickening with circumferential subendocardial delayed enhancement and a pattern suggestive of cardiac AL. A cranial MRI showed areas of demyelination and left cerebellar hemisphere infarcts. In addition, his Mini-Mental State Examination score was 25 and gamma globulin, alpha-1, and alpha-2 peaks were found on protein electrophoresis. The patient underwent electroneuromyography, the findings of which were positive and showed nerve involvement, and transthyretin testing, a specific test for AL that evaluates peripheral neuromuscular involvement, findings of which were negative. The patient clinically progressed with stable vital signs, was oriented, was conscious, and was waiting for a medical opinion to better understand the cause.

Discussion

Cardiac AL is characterized by the extracellular deposition of insoluble fibrillar amyloid β-protein in the heart. It can be part of a systemic disease, which is more common, or a localized phenomenon.[1] Its clinical presentation varies according to the affected organs and the importance of their involvement. Less than 5% of patients with light-chain

Keywords

Amyloidosis; Restrictive cardiomyopathy; Echocardiography.

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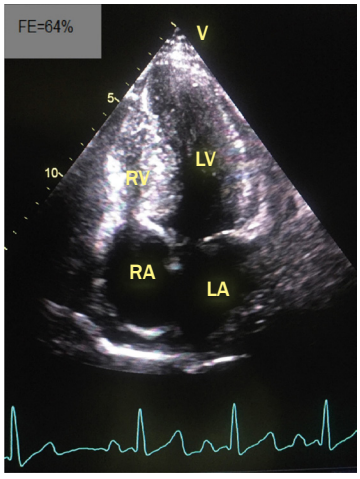

LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Figure 1 – *Echocardiogram showing significant ventricular concentric hypertrophy, biatrial enlargement, preserved systolic function, and a moderate pericardial effusion.*

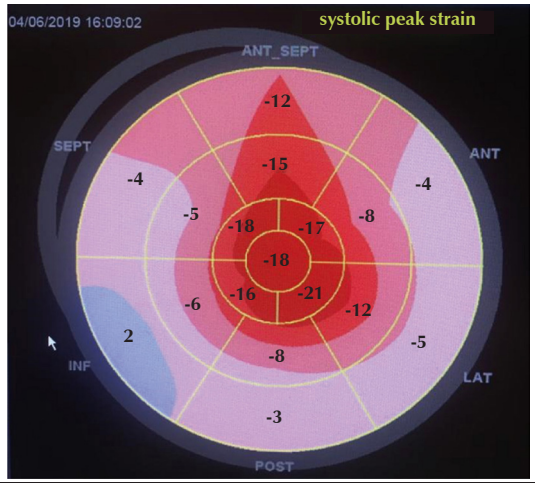

Figure 2 – *Reduced left ventricular global longitudinal strain of -8.2 with involvement of the basal and median regions of the heart and apical sparing.*

AL involving the heart have clinically isolated heart disease. Non-cardiac symptom complaints should be investigated because their presence is a clue to the systemic nature of the disease. Each patient should be carefully questioned about dizziness and syncope with emphasis placed on the positional nature of any of these symptoms since there are several potential syncope mechanisms in AL. As in the reported case, macroglossia, which is characterized by tongue stiffness and enlargement and often associated with dental indentation, is seen in about 10–20% of patients and can result in dysphonia or dysgeusia. Neurological symptoms include carpal tunnel syndrome and peripheral and autonomic neuropathy.[2]

The cardiac form is heterogeneous, with amyloid deposition in the myocardium, interatrial septum, cardiac valves, papillary muscles, and coronary arteries. Cardiac involvement can lead to diastolic dysfunction or, in the later course of the disease, systolic dysfunction and HF symptoms with conduction disorders, low cardiac output, autonomic dysfunction, PE, and arrhythmias such as atrial fibrillation, ventricular tachycardia, or ventricular fibrillation.[3] Its main cardiac presentation is restrictive cardiomyopathy, an intractable chronic HF of unknown etiology in patients over 50 years of age.

At least 30 different proteins have been identified to date,[4] with the most common being AL, serum amyloid A protein, and transthyretin AL (ATTR). Cardiac AL is more commonly caused by the ATTR and AL forms. Thus, despite their heterogeneous structure and function, these proteins deposit in the amyloid form in several organs in a localized or systemic manner, which may cause multiorgan dysfunction.

As a pathology with a nonspecific clinical presentation, cardiac AL is usually diagnosed late after being frequently ignored or confused with other pathologies. From this perspective, AL complementary exams play an important role in the characterization of the case and the patient's respective prognosis. Some noninvasive tests may provide

supportive but not definitive findings. Some examples include speckle-tracking ECHO for standard strain evaluation, cardiac scintigraphy with technetium uptake, and delayed subendothelial gadolinium enhancement on cardiac MRI.

Our patient's ECG and ECHO exams showed several changes related to cardiac AL, such as concentric ventricular hypertrophy (Figure 3) associated with an absence of ECG high voltage. This pattern corroborates the findings of Selvanayagam et al.,[5] showing high sensitivity (72–79%) and specificity (91–100%) for AL.

In addition, 70–74% of patients presenting concentric left ventricular hypertrophy are likely to have low-voltage ECG findings.[9] In the present case, the preserved systolic function was associated with diastolic dysfunction (in this case, grade 2) (Figure 4). This is the most common clinical presentation in patients with heart disease resulting from AL. The dysfunction often begins with relaxation changes and progresses with advanced restrictive conditions and more severe clinical repercussions.[6] Severely ill patients present a high ventricular filling pressure and shortened deceleration time < 150 ms. In addition, the relationship between ventricular wall thickening and PE has already been mentioned, and 43% of patients with systemic AL and left ventricular wall thickening had PE.[7] Our patient had left ventricular hypertrophy and a PE.

Echocardiographic changes suggestive of advanced forms of cardiac AL include increased ventricular wall thickness, small ventricular chambers, PE, atrial dilation, and interatrial septum thickening. The increased wall thickness is peculiar on two-dimensional ECHO, presenting a grainy texture. In many cases, ECHO is the first test to show the suspected diagnosis due to the identification of diastolic dysfunction and absence of ventricular dilation.

Cardiac MRI is a useful noninvasive diagnostic tool with 80% sensitivity and 94% specificity. The cardiac involvement of AL is translated by the presence of delayed enhancement that is more often subendocardial and diffuse throughout

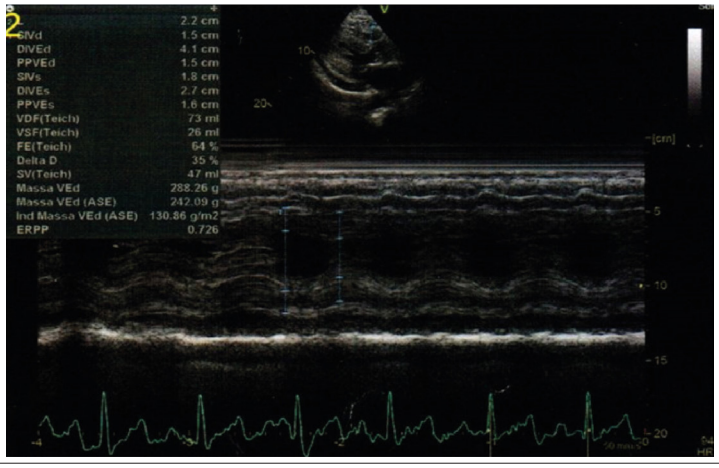

Figure 3 – *Evidence of concentric left ventricular hypertrophy through a 15-mm interventricular septum, 15-mm posterior wall, 130 g/m2 left ventricular mass index, and 0.726- relative posterior wall thickness.*

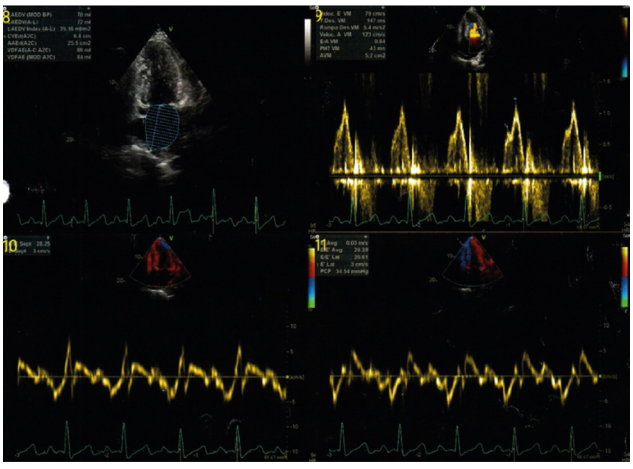

Figure 4 – *Evidence of grade II diastolic dysfunction (increased left atrial volume, 39 mL/m2; E/A ratio, 0.64; E-wave velocity, 79 cm/s, and mean E/E', 29.39).*

the ventricular circumference. Thus, MRI can identify the presence of myocardial and interatrial septum thickening, diastolic dysfunction signs, and the typical subendocardial delayed enhancement pattern in the left ventricle, which may affect all of the cardiac chambers. Amyloid tissue changes the pattern of delayed myocardial enhancement after gadolinium use.[8] Such changes were observed in this case. (Figure 5)

Scintigraphy detects cardiac transthyretin accumulation. It is an extremely useful method for distinguishing between AL and ATTR since there is selective cardiac technetium uptake in this disorder but not in AL. If scintigraphy detects transthyretin accumulation, the investigation can be complemented with genetic transthyretin testing to distinguish ATTR (mutant transthyretin) from senile amyloidosis (wild-type transthyretin).

The definitive diagnosis is made by endomyocardial biopsy, which allows the histological characterization of the amyloid substance considering specific Congo red or immunohistochemical staining under polarized light microscopy.

Systemic AL treatment includes the support of organic dysfunction and the treatment of associated clinical conditions, particularly inflammatory processes, to avoid the formation of new amyloid fibril precursors and provide a specific treatment to remove existing amyloid deposits. The main objectives are treating the underlying disease and relieving the symptoms, and the treatment must be coordinated by a multidisciplinary team.

In recent years, the first-line options for controlling amyloid deposits have been chemotherapy and immunomodulation, especially melphalan, dimethyl sulfoxide, colchicine, and corticosteroids.[3]

Cardiac involvement support includes blood volume management, a fundamental decompensation factor, with sodium restriction and the careful administration of diuretics; and ventricular arrhythmia management, usually with amiodarone and the careful use of some drugs, including digoxin, due to their specific binding to amyloid fibrils and high toxicity despite normal serum levels. Other general supportive measures include the use of gabapentin to manage neuropathic pain and the control of possible comorbidities and complications.[6]

Cardiac AL remains a clinical challenge. Patients with AL and congestive HF have a worse prognosis and a mean survival of 6–9 months. AL awareness and understanding is important for cardiologists and clinicians since an early diagnosis is associated with increased patient survival rates.

Cardiac AL results in a wide range of changes in which cardiac involvement imposes a worse prognosis and the development of an infiltrative cardiomyopathy with restrictive hemodynamic behavior. In cases of rare pathology, the diagnosis requires a high index of suspicion based on clinical and complementary noninvasive exams, especially transthoracic ECHO and cardiac MRI. The final diagnosis always requires histological confirmation. The intervention focuses on treating the underlying disease and relieving the patient's symptoms. This scenario emphasizes the importance of investigating cardiac AL among HF diagnostic possibilities with unfavorable chronic progression and an unknown etiology, especially in patients over 50 years of age.

Therefore, cardiac AL requires an early diagnosis due to the possibility of an unfavorable clinical progression with an important degree of cardiac restriction and congestive HF. At this point, patient prognosis is poor with a low chance of recovery.[1] Furthermore, it is important to note that AL usually involves other organs and systems, and its diagnosis is also important to treating other areas early, such as the nervous system as in the case reported here, which involve neurological clinical signs and changes on exams such as electroneuromyography.

Authors' contributions

Manuscript writing: Lopes LF; data collection: Liberato ILR; critical review of the manuscript for important intellectual content: Rocha Júnior LG; manuscript reading and reviewing: Rocha LMQ; and study supervision: Liberato CBR.

Conflict of interest

The authors have declared that they have no conflict of interest.

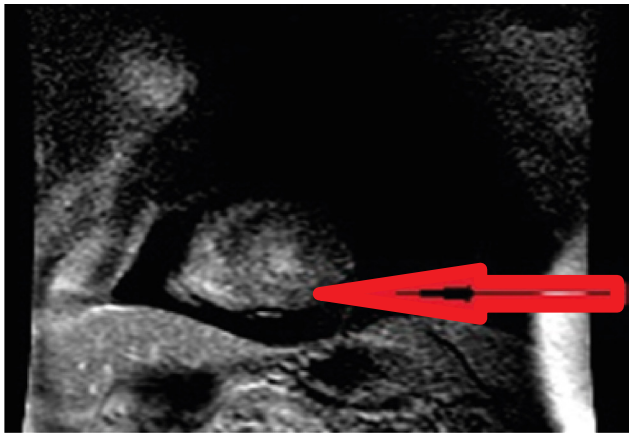

Figure 5 – *Cross-sectional chest magnetic resonance image showing circumferential subendocardial delayed enhancement.*

References

1. Mendes RG, Evora PR, Mendes JA, Haddad J, Carvalho A. Comprometimento cardíaco na amiloidose sistêmica. Diagnóstico in vivo. Arq Bras Cardiol, 1998;70(2):119-23.
2. Falk RH. Diagnosis and management of the cardiac amyloidoses. Circulation. 2005;112(13):2047-60. doi: 10.1161/CIRCULATIONAHA.104.489187
3. Di Bella G, Pizzino F, Minutoli F, Zito C, Donato R, Dattilo G, et al. The mosaic of the cardiac amyloidosis diagnosis: role of imaging in subtypes and stages of the disease. Eur Heart J Cardiovasc Imaging. 2014;15(12):1307-15. doi: 10.1093/ehjci/jeu158
4. Seldin DC, Sanchorawala V. Adapting to AL amyloidosis. Haematologica. 2006;91(12):1591-5
5. Selvanayagam JB, Hawkins PN, Paul B, Myerson SG, Neubauer S. Evaluation and management of the cardiac amyloidosis. J Am Coll Cardiol. 2007 Nov 27;50(22):2101-10. doi: 10.1016/j.jacc.2007.08.028. Epub 2007 Nov 13. Erratum in: J Am Coll Cardiol. 2011 Mar 29;57(13):1501.
6. Vieira TA, Negreiros SB, Sousa DW, Garbero RF, Capanema CO. Amiloidose cardíaca: protótipo de miocardiopatia restritiva e disfunção diastólica – relato de caso. Arq Bras Cardiol: Imagem Cardiovasc. 2017;30(1):13-7.
7. Al-Zahrani GB, Bellavia D, Pellikka PA, Dispenzieri A, Hayman SR, Oh JK, et al. Doppler myocardial imaging compared to standard two-dimensional and Doppler echocardiography for assessment of diastolic function in patients with systemic amyloidosis. J Am Soc Echocardiogr. 2009 Mar;22(3):290-8. doi: 10.1016/j.echo.2008.11.013
8. Lakdawala Neal K. Miocardiopatia e miocardite. In: Kasper D. Medicina interna de Harisson. 19. ed. Porto Alegre: Amgh; 2017. Cap. 287. p. 1566-1568.
9. Selvanayagam JB, Hawkins PN, Paul B, Myerson SG, Neubauer S. Evaluation and management of the cardiac amyloidosis. J Am Coll Cardiol. 2007;50(22):2101-10. doi: 10.1016/j.jacc.2007.08.028. Erratum in: J Am Coll Cardiol. 2011;57(13):1501.