International Journal of Cardiovascular Sciences. 2018;31(4)457-460

CASE REPORT

Cardiac Amyloidosis with Heart Failure and Middle Range Ejection Fraction

Antonio Jose Lagoeiro Jorge, Diane Xavier de Ávila, Enoï Guedes Vilar, Mario Luiz Ribeiro, Karima Elias Hallack Bruno, Ana Carolina Pires

Universidade Federal Fluminense, Niterói, RJ - Brazil

Introduction

Cardiac amyloidosis (CA) is a disease with a difficult diagnosis, limited management and a reserved prognosis.[1,2] A high level of suspicion is necessary for its identification. There are some clinical clues, such as elderly individuals with unexplained left ventricular hypertrophy (LVH), heart failure with preserved ejection fraction (HFpEF) and restrictive pattern, dissociation between LVH on echocardiography and low voltage on the electrocardiogram, among others.[1,2]

CA can occur with several hemodynamic forms and patterns of remodeling, according to the disease evolution stage. It may occur as the restrictive form, with left ventricular ejection fraction > 50%; and dilated form, with reduced ejection fraction.[1,2] Recently, the European Society of Cardiology has established a new classification with the creation of "Heart Failure with Mid-Range Ejection Fraction" (HFmrEF).[3] We report a case of CA with HFmrEF.

Case report

A female patient, aged 80 years old, was treated at the emergency unit at the first evaluation showing fatigue with medium exertion, orthopnea, nocturnal paroxysmal dyspnea and lower limb edema. She also had frequent complaints of muscle weakness and asthenia. She was admitted with a diagnosis of acute heart failure (HF). She reported macrocytic anemia 3 years before, with no defined etiological diagnosis. She was submitted to an echocardiogram, which showed LVH and ejection fraction of 64%. She was discharged without an etiological definition of HF.

Fifteen days after discharge, she came to the outpatient clinic with pallor (2+/4+) and jugular swelling at 45°; *ictus cordis* in the sixth intercostal space in the anterior axillary line; presence of third heart sound; pulmonary component of the second heart sound greater than the aortic component, without murmurs. Pulmonary auscultation showed vesicular murmur abolished at both bases; crepitant rales up to the middle third of both hemithoraces. The liver was palpable at 2 cm from the right costal border. She had symmetrical lower-limb swelling, with pitting edema up to the thigh root, cold and painless. The patient was hospitalized for HF compensation and etiological investigation.

Laboratory tests showed macrocytic and hypochromic anemia; vitamin B12 deficiency; erythrocyte sedimentation rate of 134 mm; electrophoresis; and proteins with monoclonal lambda chain peak.

The electrocardiogram showed junctional rhythm, with low voltage. Chest x-ray showed signs of pulmonary congestion and moderate bilateral pleural effusion. The transthoracic echocardiogram showed dilation of the left and right atria, left ventricular ejection fraction (LVEF) of 42% and alterations suggestive of infiltrative heart disease. Global strain with apical sparing pattern (Figure 1A to 1D) was observed. Myocardial resonance (MRI) was suggestive of the presence of subendocardial amyloid deposits and late enhancement of 35%. LVEF was 45% (Figures 1E to 1H).

The bone marrow aspirate showed a predominance of plasma cells in > 90% of the slide. Immunohistochemistry confirmed the diagnosis of multiple myeloma. Biopsy of facial lesion and abdominal fat with histopathological analysis showed amyloid deposits (Figure 2).

Keywords

Heart Failure / physiopathology; Amyloidosis; Stroke Volume; Hypertrophy, Left Ventricular; Aged.

Mailing Address: Antonio Jose Lagoeiro Jorge
Avenida Marques do Paraná, 303. Postal Code: 24033-900, Centro, Niterói, RJ - Brazil.
E-mail: lagoeiro@globo.com

DOI: 10.5935/2359-4802.20180039

Manuscript received October 30, 2017; revised manuscript February 23, 2018; accepted March 3, 2018.

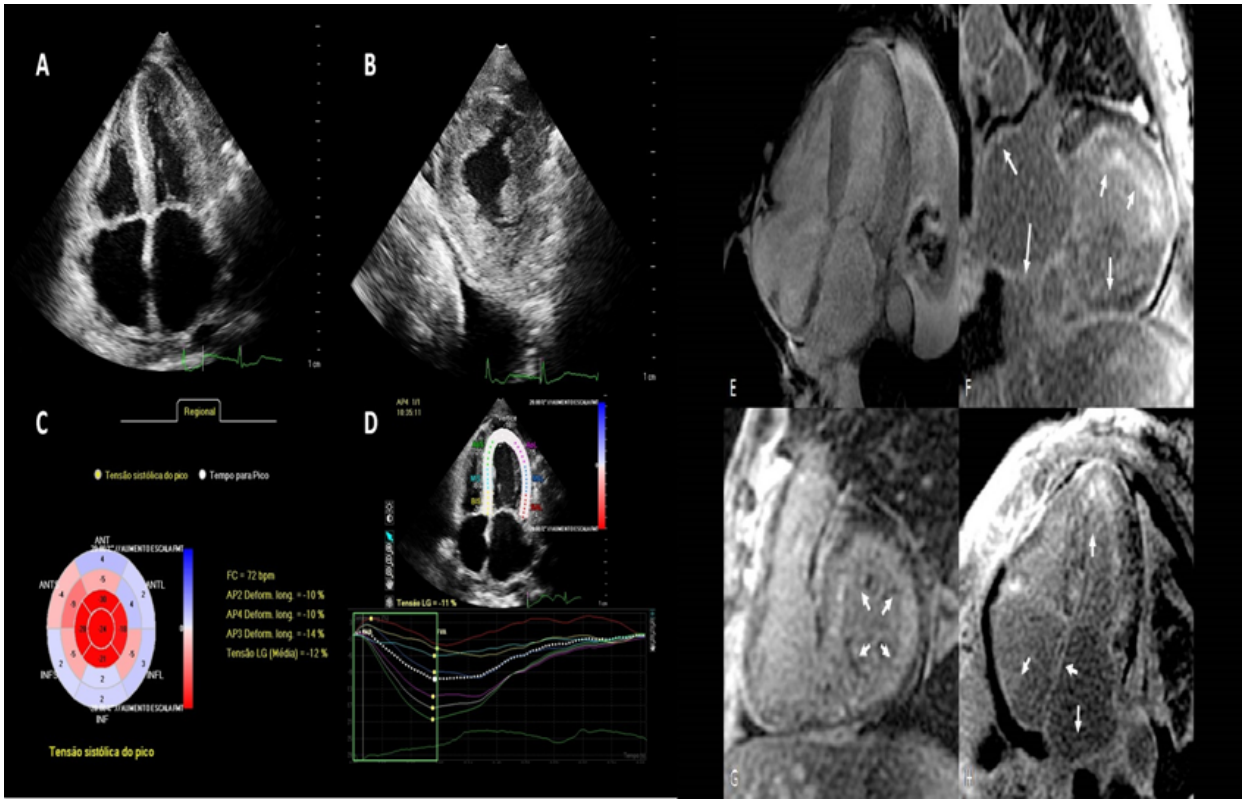

Figure 1 - (A) Apical four-chamber view showing biatrial enlargement, thickened interatrial septum, left ventricular wall hypertrophy, with hyperechoic texture of the myocardium. (B) Parasternal short axis view. Concentric left ventricular hypertrophy. (C) Bullseyes. Global longitudinal systolic strain (mean value of (-)12%), with prominent basal and medium impairment, and preserved apical mechanical function. (D) Apical four-chamber strain showing that the ratio between the apical inferior septal strain and the lower basal septal strain is greater than 3. (E) Cine-mode of the stationary state free precession showing diffuse left ventricular myocardial thickening. (F) Long axis post-gadolinium image showing diffuse late improvements (arrows) in the left atrium, as well as subendocardial enlargement of the left ventricle, more prominent in the anterior wall. (G) Short axis post-gadolinium image showing diffuse subendocardial enhancement (arrows) in the left ventricle. (H) Four-chamber post-gadolinium image showing late enhancement (arrows) not only in the left chambers, but also of the right atrium.

The diagnosis was systemic amyloidosis and multiple myeloma associated with cardiac involvement. Pulse therapy with prednisone was initiated. The HF became refractory to treatment, and the patient died 3 months after the disease onset.

Discussion

Amyloidosis is a rare and multisystemic disease. Patients with amyloidosis usually have few specific symptoms, which makes the diagnosis difficult in the initial phase, as the case presented herein. Cardiac impairment due to amyloidosis can lead to HF, as well as conduction system involvement, with low voltage at the ECG, which increases clinical suspicion.[4] In addition to myocardial infiltration, amyloid infiltrates can be found in the conduction system, valve tissues, coronary arteries, large vessels and autonomic or peripheral nerves, leading to many clinical manifestations.[2]

More than 25 proteins have been described as possible amyloid-forming agents; however, two of them predominate in cardiovascular impairment: transthyretin (TTR) and immunoglobulin light chains – amyloid light chains or AL.[2] The TTR protein is synthesized and secreted by the liver and choroid plexus, and functions as a carrier of thyroxine and retinol binding protein. This protein is typically found in soluble tetramers in their native form. TTR has become the most prevalent form of CA found in clinical practice, with greater identification being made by noninvasive imaging tools.[5] Cardiac involvement by TTR occurs most commonly in the sixth and seventh decades of life as HFpEF,[6] with the wild-type or senile

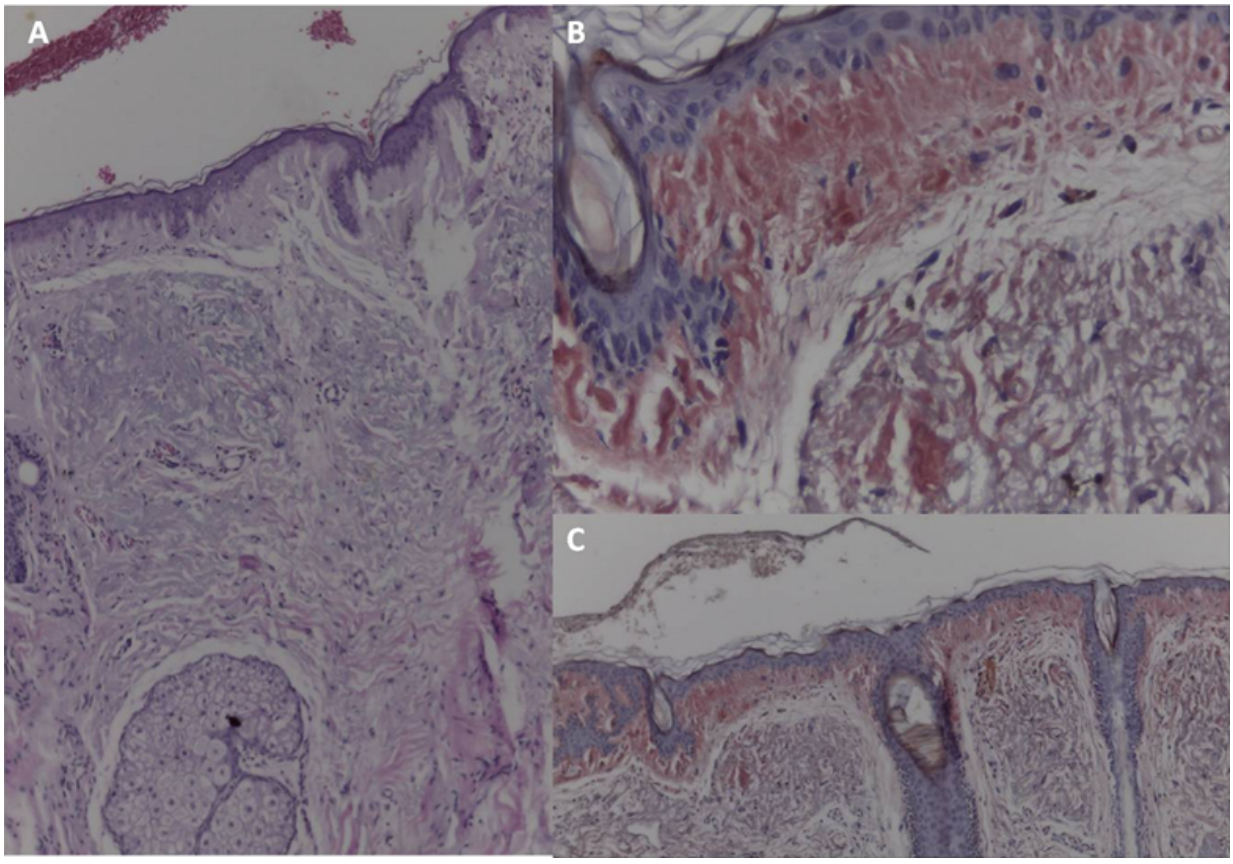

Figure 2 - (A) Skin biopsy showing deposits of amorphous and eosinophilic material on the papillary dermis (hematoxylin-eosin - original 40x magnification). (B) Congo red staining showing amyloid material in the dermal papillae (original magnification 100x and 400x). (C) Amyloid deposit around the sebaceous gland (Congo red - original magnification 400x). (D) Amyloid deposit around adipocytes (Congo red - original magnification 400x).

systemic amyloidosis. The AL form of amyloidosis is caused by the deposition of immunoglobulin light chains segregated from monoclonal proliferation of plasma cells. Currently, the AL amyloidosis is considered less frequent than TTR. The cardiac diagnosis in patients with AL amyloidosis is often earlier, at a mean age of 65 years and more commonly associated with the female gender, with lower left ventricular mass and lower voltage at the ECG than those with TTR.[2] The AL form of amyloidosis (immunoglobulin light chain deposition disease) may coexist in patients with myeloma in 10 to 15% of cases, such as the patient in this case report. That does not mean the presence of multiple myeloma with secondary amyloidosis, but the coexistence of two separate and concomitant plasma cell diseases.[7]

HF in amyloidosis is classically described as either HFpEF or HFrEF (heart failure with reduced ejection fraction) in their more advanced forms.[8] HF guidelines have recognized that there is a gray area between HFrEF and HFpEF, which shows mild systolic dysfunction and has some characteristics of diastolic dysfunction, defined as HF with mid-range ejection fraction (HFmrEF).[3] The patient in this case had LVEF between 40 and 49% both in the second echocardiogram and the cardiac MRI and, therefore, was characterized as having HFmrEF.

The disease can be suspected noninvasively through a characteristic low-voltage ECG. Recently, cardiac imaging techniques have allowed the diagnosis to be attained through the echo-doppler-cardiogram with an apical sparing of the longitudinal strain, MRI with transmural global subendocardial late enhancement, and technetium-99m-pyrophosphate myocardial scintigraphy.[1] The definitive diagnosis of amyloid

cardiomyopathy is obtained from an endomyocardial biopsy using Congo red or thioflavin staining[2,9] technique and identifying the type of amyloid infiltrate by molecular genetic techniques.

The gold standard for the diagnosis of amyloidosis is the myocardial biopsy. The guidelines of the American Heart Association/American College of Cardiology Foundation show a II-A recommendation for endomyocardial biopsy in the presence of HF associated with unexplained restrictive cardiomyopathy.[10] The abdominal fat biopsy can confirm the diagnosis in 70% of cases and, in this reported case, amyloidosis was confirmed by the abdominal biopsy.

The prognosis of patients with amyloidosis is reserved. The mean untreated survival is 13 months and may be extended to 17 months with melphalan and prednisone, which in this case were not used due to the patient's clinical worsening. The cardiac impairment makes the prognosis even worse, with a life expectancy of approximately 6 months.

Author contributions

Conception and design of the research: Jorge AJL, Avila D, Ribeiro ML, Bruno KEH, Pires C; Acquisition of data: Jorge AJL, Avila D, Vilar EG, Ribeiro ML, Bruno KEH, Pires C; Analysis and interpretation of the data: Jorge AJL, Avila D, Bruno KEH; Writing of the manuscript: Jorge AJL, Avila D, Pires C; Critical revision of the manuscript for intellectual content: Jorge AJL.

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.

References

1. Maurer MS, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing common questions encountered in the diagnosis and management of cardiac amyloidosis. Circulation. 2017;135(14):1357-77.
2. Mesquita ET, Jorge AJ, Souza CV Junior, Andrade TR. Cardiac amyloidosis and its new clinical phenotype: heart failure with preserved ejection fraction. Arq Bras Cardiol. 2017;109(1):71-80.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18(8):891-975.
4. Murtagh B, Hammill SC, Gertz MA, Kyle RA, Tajik AJ, Grogan M. Electrocardiographic findings in primary systemic amyloidosis and biopsy-proven cardiac involvement. Am J Cardiol. 2005;95(4):535-7.
5. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation. 2016;133(24):2404-12.
6. Sperry BW, Vranian MN, Hachamovitch R, Joshi H, Ikram A, Phelan D, et al. Subtype-specific interactions and prognosis in cardiac amyloidosis. J Am Heart Assoc. 2016;24(3):e002877.
7. Dubrey SW, Hawkins PN, Falk RH. Amyloid diseases of the heart: assessment, diagnosis, and referral. Heart. 2011;97(1):75-84.
8. Liu D, Niemann M, Hu K, Herrmann S, Störk S, Knop S, et al. Echocardiographic evaluation of systolic and diastolic function in patients with cardiac amyloidosis. Am J Cardiol. 2011;108(4):591-8.
9. Phelan D, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. Heart. 2012;98(19):1442-8.
10. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, et al; American Heart Association; American College of Cardiology; European Society of Cardiology. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Circulation. 2007;116(19):2216-33.