Cardiac Amyloidosis with Heart Failure and Middle Range Ejection Fraction

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Introduction

Cardiac amyloidosis (CA) is a disease with a difficult diagnosis, limited management and a reserved prognosis. 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.

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. Recently, the European Society of Cardiology has established a new classification with the creation of “Heart Failure with Mid-Range Ejection Fraction” (HFmrEF). 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).
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
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. 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.

HF in amyloidosis is classically described as either HFrEF or HFrEF (heart failure with reduced ejection fraction) in their more advanced forms. HF guidelines have recognized that there is a gray area between HFrEF and HFrEF, which shows mild systolic dysfunction and has some characteristics of diastolic dysfunction, defined as HF with mid-range ejection fraction (HFmrEF). 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. The definitive diagnosis of amyloid
cardiomyopathy is obtained from an endomyocardial biopsy using Congo red or thioflavin staining\textsuperscript{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.\textsuperscript{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.

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