Cardiac Amyloidosis: Restrictive Cardiomyopathy Prototype and Diastolic Dysfunction — Case Report

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Introduction

Amyloidosis is a rare condition that appears in isolation or systemically and in different ways, according to the etiology and biochemical nature of the amyloid fiber.

The most pronounced clinical manifestations result in the development of restrictive cardiomyopathy and progressive diastolic dysfunction.[1] Definitive diagnosis and the reference standard are given by endomyocardial biopsy, revealing amyloid deposits using a specific staining technique.[2]

Other non-invasive diagnostic modalities are important in presumptive diagnosis, including echocardiography, which evaluates the structural and hemodynamic changes caused by infiltrative disease.[3] Treatment and prognosis of disease depend on the etiology and extent of amyloid deposition.

We report the case of a patient with refractory heart failure. Echocardiographic analysis showed a classic pattern of restrictive cardiomyopathy and pathologic evaluation confirmed pronounced systemic amyloid deposit.

Case Report

Female patient, 65, admitted to the cardiology service of Hospital de Base do Distrito Federal, in August 2015, with dyspnea on exertion and at rest, abdominal distension, progressive lower extremity edema, asthenia, weight loss and fatigue. Her past history did not present hypertension, diabetes mellitus and coronary artery disease, but recurrent admissions due to a similar condition. The patient was discharged after clinical compensation.

Physical examination revealed dyspnea, tachypnea (RR 28 irpm), hypotensive (BP: 80/60 mmHg), crackles in the lower thirds of both hemithorax, regular heart rhythm with presence of B3, hypophonetic sounds and abdomen ascites with painful hepatomegaly up to 6 cm from the right costal margin.

Transthoracic echocardiography showed severe concentric left ventricular hypertrophy with myocardium of granular appearance (Figure 1); severe biatrial enlargement; moderate pericardial effusion with no signs of restriction to ventricular filling (Figure 2). Diastolic function by transmitral flow presented high early diastolic velocity — E wave, low end diastolic velocity — A wave, markedly increased E/A ratio and shortened deceleration time (Figure 3), accompanied by markedly reduced mitral annulus E' wave tissue Doppler consistent with restrictive diastolic dysfunction.

Optimized treatments were established, but continued to present recurrent polyserositis requiring a number of relieving paracentesis. The patient required hemodialysis to control blood volume and renal dysfunction. The patient developed progressive increase of pericardial fluid accompanied by signs of diastolic restriction on serial echocardiograms for control.

Pericardiocentesis with 1,300 mL serosanguineous liquid drainage did not result in hemodynamic improvement. The patient then progressed to cardiac arrest not responsive to cardiopulmonary resuscitation maneuvers.

After the family's consent, the patient was sent to autopsy. Pathological evaluation showed severe amyloid protein accumulation in the myocardium, heart valves and coronary arteries in addition to the kidneys, pancreas, liver and nervous tissue.

Discussion

Amyloidosis is characterized by extracellular deposition of proteinaceous material originating from inadequate metabolism of serum proteins called amyloids, which term derives from the observation of Rudolf Virchow in 1854 of sebaceous and eosinophilic tissue deposits stained with iodine and sulfuric acid similar to starch.[4]

It can be classified according to the extent of involvement: localized or systemic; and associated etiology: primary (AL) characterized by the deposition of monoclonal proteins of light chain secondary to plasma cell dyscrasia, especially multiple myeloma (MM); or secondary (AA) when associated with chronic conditions such as inflammatory diseases, cancer and hemodialysis. All of them have a higher prevalence in the elderly and can affect the heart tissue, being more common in amyloidosis associated with MM.[1,5]

Its pathophysiology is divided into two phases: 1) proliferation of cells in the reticuloendothelial system from an immune disorder leading to increased synthesis of serum gammaglobulin; 2) disorder of protein synthesis with consequent tissue deposition of autologous proteinaceous material in the extracellular medium. The final route is the organic dysfunction of the affected sites, responsible for clinical manifestations, morbidity and mortality.[6]

Keywords

Amyloidosis; Cardiomyopathy, Restrictive; Ventricular Dysfunction, Left; Echocardiography, Doppler; Drug Therapy.

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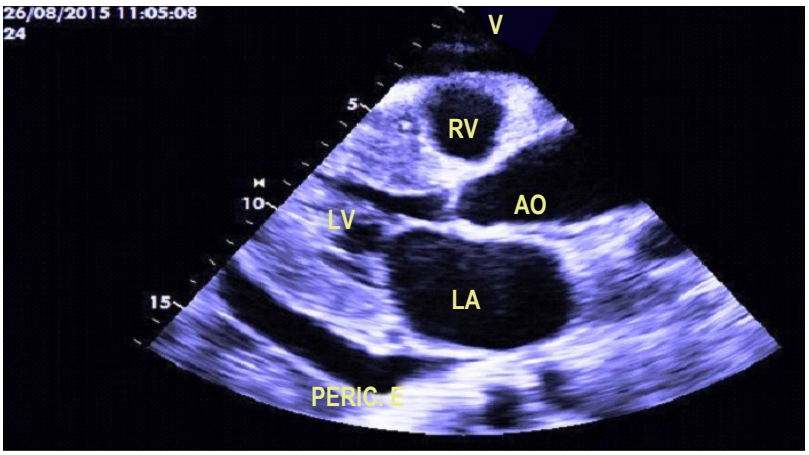

Figure 1 – *Two-dimensional echocardiography. LV: left ventricle; RV: right ventricle; AO: aorta; LA: left atrium; PERIC. E: pericardial effusion.*

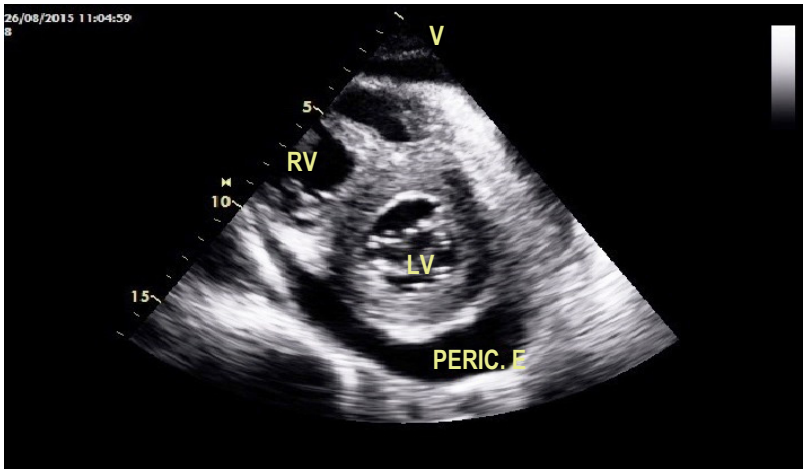

Figure 2 – *Two-dimensional echocardiography. LV: left ventricle; RV: right ventricle; PERIC. E: pericardial effusion.*

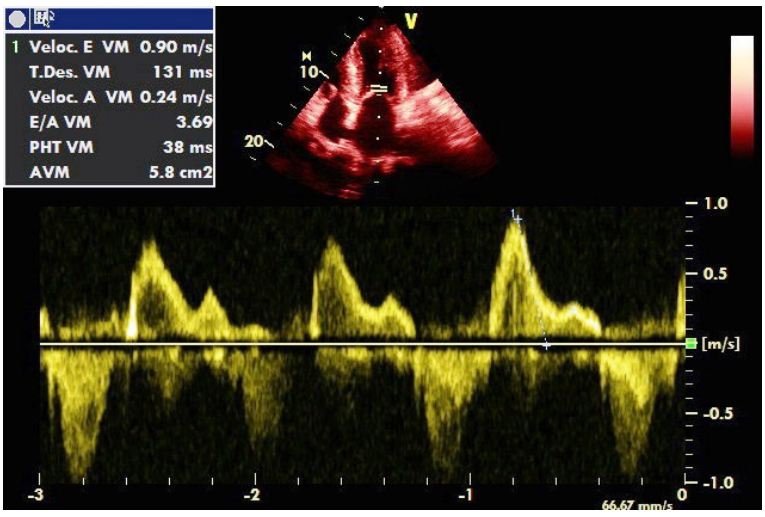

Figure 3 – *Spectral record of transmitral flow.*

The clinical presentation is variable due to the diversity installation in the organs and the importance of its impairment. The heart shape is heterogeneous, with amyloid deposition in the myocardium, atrial septum, heart valves, papillary muscles and coronary arteries. There may be conduction disorder, low cardiac output, autonomic dysfunction, systolic dysfunction, pericardial effusion and arrhythmia, such as atrial fibrillation, ventricular tachycardia or ventricular fibrillation.[7]

Its main form of cardiac manifestation is restrictive cardiomyopathy, intractable chronic heart failure of unknown etiology in patients older than 50.[8] It is characterized by the presence of the myocardium and thickened endocardium with reduced compliance and sites of interstitial fibrosis. The consequence is restriction to ventricular filling, atrial enlargement, reduced cardiac output and increased filling pressures.

Clinical manifestations include non-specific symptoms such as fatigue, weight loss, asthenia, purpura, bleeding and diarrhea or constipation due to autonomic dysfunction; and cardiovascular symptoms: angina; syncope, either due to autonomic failure or serious arrhythmia, and the spectrum of ventricular dysfunction ranging from asymptomatic until the final stage of progressive heart failure.[7]

Echocardiography with Doppler identifies the anatomical changes caused by amyloid deposit and hemodynamic repercussion. The findings of two-dimensional imaging include myocardium of refractive texture, bright granular echogenicity,[7] biventricular symmetric thickening, dilated atria, pericardial effusion and valvular thickening.

Predominant hemodynamic behavior is diastolic dysfunction with intensity proportional to the degree of infiltration. It progresses from abnormal relaxation in the early stages to pseudonormal in intermediate and restrictive conditions in the advanced stages. This final phase is responsible for greater clinical repercussion characterized by high filling pressures, shortened deceleration time (< 150 ms) and high E/A ratio (> 2.0) due to transmitral flow. Tissue Doppler of the mitral annulus shows reduced E' wave peak speed, high sensitivity finding observed even in incipient impairments.[9]

In our case, the patient had the clinical manifestations expected in the context of cardiac amyloidosis. Refractory congestive symptoms as well as structural and hemodynamic echocardiographic changes reinforced our suspicions.

The reference standard for diagnosis is endomyocardial biopsy[10] and definitive diagnosis requires histological demonstration of amyloid deposits by hematoxylin-eosin (HE) stain revealing amorphous eosinophilic substance or by Congo red stain revealing a red-orange appearance in light microscopy with birefringence when viewed under polarized light.[2] After confirming the deposit, the fibrils involved are determined by using immunofluorescence and immunohistochemistry.

Our histological evaluation was performed by HE staining revealing extensive deposition of amyloid material involving the ventricular myocardium and coronary arteries (Figure 4).

The differential diagnosis of cardiac amyloidosis is done with constrictive pericarditis, which has similar clinical manifestations and hemodynamic aspects but with different specific echocardiographic parameters; and conditions that compromise ventricular myocardial compliance. These include infiltrative diseases (sarcoidosis and Gaucher's disease), deposit diseases (glycogen storage disease, hemochromatosis and Fabry disease), non-infiltrative diseases (idiopathic, diabetic) and endomyocardial disease (endomyocardial fibrosis, hypereosinophilia and post-radiation).

Treatment of systemic amyloidosis includes support of organic dysfunctions, treatment of associated

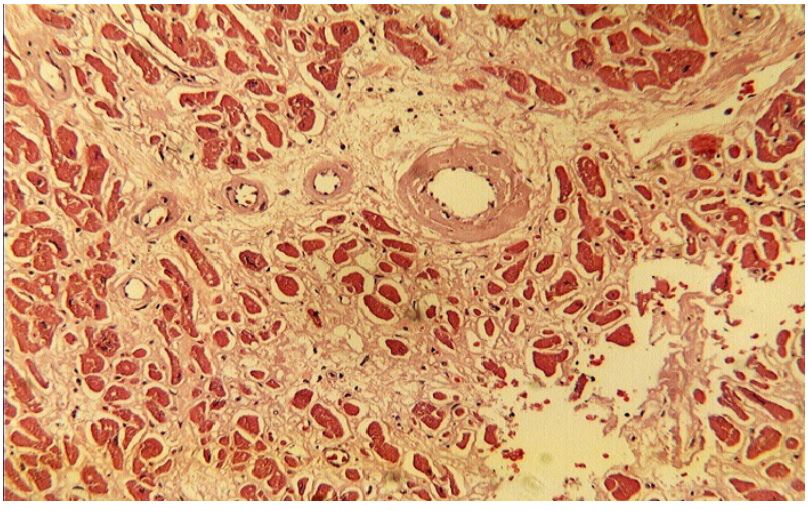

Figure 4 – *Myocardial amyloid deposition - stained with hematoxylin-eosin.*

medical conditions, especially inflammatory processes to prevent the formation of new precursors of amyloid fibril and specific treatment to remove existing amyloid deposits. In recent years, the first choice in the control of amyloid deposits is the treatment of chemotherapy and immunomodulation, including melphalan, dimethyl sulfoxide, colchicine and corticosteroids.[11]

As for cardiac involvement, the support includes: 1) management of blood volume, a key factor of decompensation, with sodium restriction, combined with careful management of diuretics; 2) management of ventricular arrhythmia usually with amiodarone; 3) careful use of some drugs, including digoxin,[9] because of its specific binding to amyloid fibrils and high incidence of toxicity, even within normal serum levels. Other general supportive measures include gabapentin to manage neuropathic pain, control of potential comorbidities and complications.

The natural history of amyloidosis is usually slowly progressive and leads to death if not diagnosed early and treated properly. The development of restrictive cardiomyopathy is an important factor of poor prognosis,[12] occurring in about 25% of patients with the AL form and responsible for most deaths.[7]

Due to the unavailability of endomyocardial biopsy, definitive diagnosis in vivo was not possible and specific treatment has not been established. However, based on clinical and echocardiographic data, it was possible to establish a reliable presumptive diagnosis of restrictive cardiomyopathy from amyloid deposition, allowing appropriate supportive treatment. Specific treatment in turn would not be likely to change the outcome of the case due to direct relationship between poor prognosis and this form of cardiac involvement.

Conclusion

Amyloidosis is a rare condition resulting from a wide range of precursor genetic, neoplastic, inflammatory or autoimmune abnormalities. Cardiac involvement imposes worse prognosis and develops infiltrative cardiomyopathy with restrictive hemodynamic behavior. In this scenario, we emphasize its importance among the diagnostic possibilities of heart failure of adverse outcome.

Early diagnosis and institution of treatment has changed the natural history of the disease, from fatal to partial or complete remission. Despite important progress, especially in diagnostic modalities, investigation of the molecular mechanisms involved in the development of the disease must be established, as they may offer new opportunities for therapeutic options.

Authors' contributions

Research creation and design: Vieira TA, Negreiros SBC; Data acquisition: Vieira TA, Negreiros SBC; Manuscript drafting: Vieira TA, Negreiros SBC; Critical revision of the manuscript as for important intellectual content: Vieira TA, Negreiros SBC, Garbero RF, Capanema CO.

Potential Conflicts of Interest

There are no relevant conflicts of interest.

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Academic Association

This study is not associated with any graduate program.

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