Miocardiopatia amilóide – uma entidade de difícil diagnóstico

Amyloid cardiomyopathy – a diagnostic challenge

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Resumo

Os autores apresentam o caso de um doente de 71 anos, com antecedentes de hipertensão arterial e diabetes mellitus, admitido por dispneia e anasarca. O ecocardiograma apresentou dilatação bi-auricular, hipertrofia severa do ventrículo esquerdo (VE) e disfunção sistólica ligeira do VE. A tomografia computorizada abdominal mostrou hepatoesplenomegalia e ascite de grande volume. Reinternado dois meses depois por agravamento da sintomatologia. Repetiu ecocardiograma que revelou, de novo, um fluxo transmitral com padrão de tipo restritivo. O cateterismo cardíaco excluiu doença coronária. A biopsia endomiocárdica revelou lesões de fibro-elastose e hipertrofia nuclear, sem evidência inicial de material do tipo amilóide. A ressonância magnética cardíaca (RMC) revelou hipertrofia bi-ventricular e um padrão de realce tardio (RT) sugestivo de miocardiopatia infiltrativa (amiloidose). Realizou biopsia da gordura abdominal que identificou substância amilóide pelo método do Vermelho do Congo.

O diagnóstico de cardiomiopatia amilóide é difícil. Apesar da biopsia endomiocárdica ser o gold standard, a RMC tem surgido como método não-invasivo útil na determinação etiológica das miocardiopatias pela sua capacidade de caracterização tecidular através da técnica de RT.

Palavras chave: miocardiopatia restritiva, amiloidose, biopsia endomiocárdica, ressonância magnética cardíaca, realce tardio.

Abstract

The authors present the case of a 71-year-old male patient, with previous history of arterial hypertension and diabetes mellitus, admitted with dyspnoea and anasarca. The echocardiogram presented biatrial dilation, severe left ventricle (LV) hypertrophy and mild LV systolic dysfunction. Abdominal computed tomography scan revealed hepatosplenomegaly and large volume ascites. Readmitted two months later with symptoms worsening. A new echocardiogram was performed, revealing, besides the referred changes, a transmitral flow with a restrictive pattern. Cardiac catheterization excluded coronary disease. Endomyocardial biopsy revealed fibroelastosis lesions and nuclear hypertrophy, without initial evidence of amyloid deposition. Cardiovascular magnetic resonance imaging (CMRI) revealed bi-ventricular hypertrophy and a pattern of late gadolinium enhancement (LGE) suggestive of restrictive cardiomyopathy (amyloidosis). Abdominal fat biopsy identified amyloid substance by Congo red-stain.

The diagnosis of amyloid cardiomyopathy is difficult. Although endomyocardial biopsy is the gold standard, CMRI arises as a non-invasive method useful to determine cardiomyopathies etiology due to its capacity of characterizing tissue through LGE.

Key words: Restrictive cardiomyopathy; Amyloidosis; Endomyocardial biopsy; Cardiovascular magnetic resonance imaging; Late gadolinium enhancement.

INTRODUCTION

Restrictive myocardiopathy is a rare entity, being the less frequent kind of myocardiopathy. It is characterized by a limitation on the filling up and reduction of the diastolic volume or of both ventricles, preserving the systolic function. It can be idiopathic or associated to other diseases.[1]

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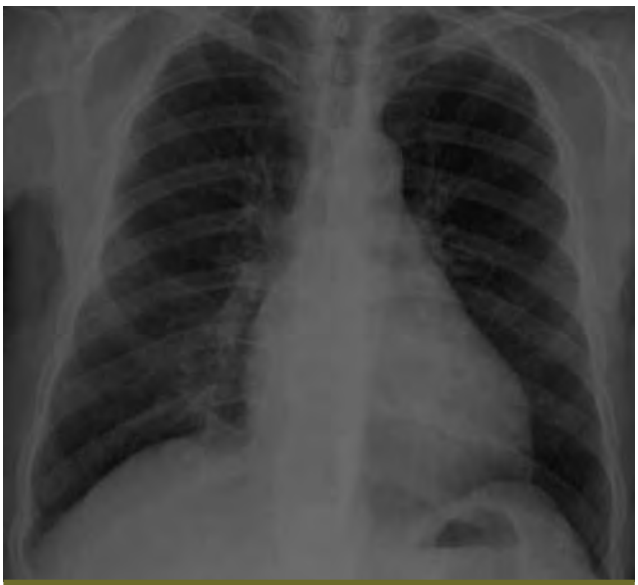
Amyloidosis is a clinical dysfunction caused by the extracellular deposit of an insoluble protein aggregate, with a characteristic configuration in the folded sheet B, presenting an apple green birefringence to polarized light, when stained with Congo Red. The range of involved organs can include the kidneys, heart, blood vessels, central and peripheral nervous system, liver, small intestine, colon, lung, eyes, skin and bone.[2]

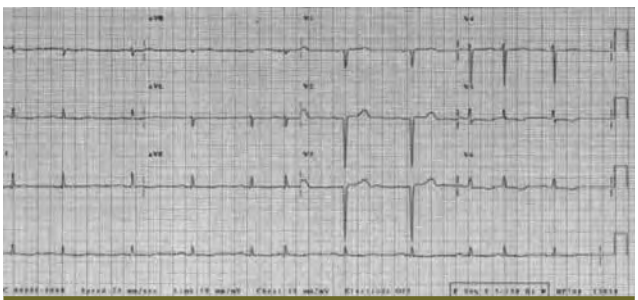
Cardiac amyloidosis is the most frequent cause of restrictive myocardiopathy;1 it can be primary (AL) hereditary or more rarely, associated to inflammatory diseases, or more rarely, associated to inflammatory diseases (AA).[2]

The more frequent clinic manifestations are heart failure and conduction changes.[2]



Thorax Teleradiography on admission.

FIG. 1

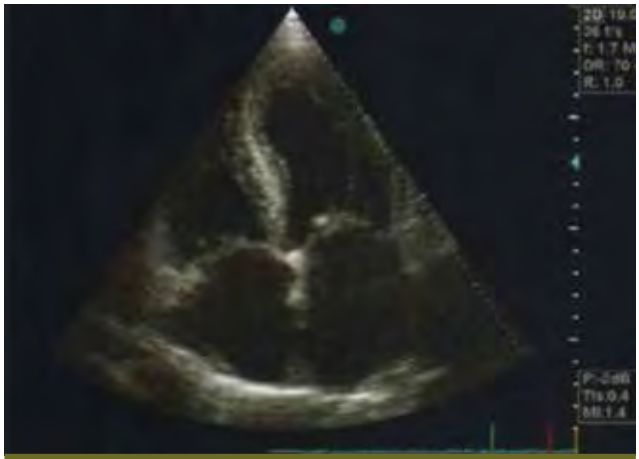


ECG on admission. qS Pattern in V1-V3.

FIG. 2

Whatever its etiology, myocardial infiltration by amyloid substance gives a worst prognosis.[2]

There are several non-invasive supplementary diagnostic tests to identify the cardiac involvement by amyloidosis: transthoracic ultrasound (TTU), electrocardiogram (ECG), heart magnetic resonance (HMR) and the scintigraphy with P amyloid component serial and radio marked. Because no test on its own is enough to make the diagnosis, it is necessary to conjugate the findings with the clinic and with the histological identification of amyloid infiltration in another place. Yet, often it is necessary to resort to the test considered the *gold standard* to the diagnosis: endomyocardial biopsy.[2]



ETT (apical incidence 4 chambers). Biatrial dilation, ventricular cavities, Left ventricle concentric hypertrophy, with "glossy" myocardium.

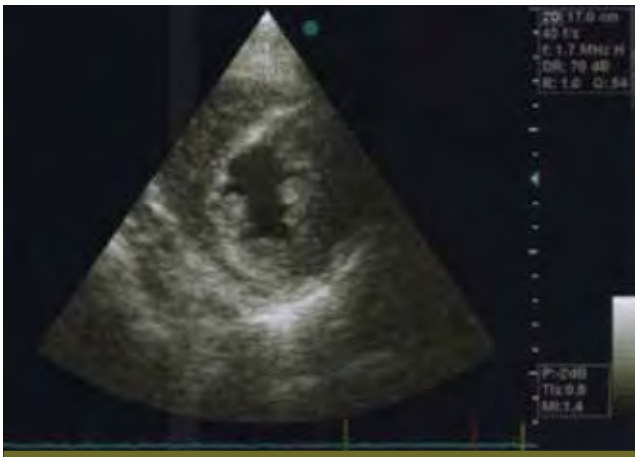
FIG. 3

CASE REPORT

The authors present a case of a 71-year-old man, with a background of high blood pressure and type 2 diabetes *mellitus* known for 10 years, without relevant family background and with a heart failure condition evolving for two years. Admitted into the Internal Medicine Service due to dyspnea and anasarca. *Fig. 1* and *2* express, respectively, the thorax teleradiography and the ECG carried out on admission. To clarify the clinical condition, the patient underwent a TTU which has revealed a biatrial dilation, LV severe hypertrophy and LV mild systolic dysfunction [ejection fraction (FE): 52%]. Left ventricle hypertrophy was interpreted in the context of hypertensive cardiopathy, and in the absence of important ventricular dysfunction, it was investigated the abdominal compartment through computerized tomography which has revealed hepatosplenomegaly and a high volume ascites. A liver biopsy was carried out, which did not show any specific changes. He had shown a gradual improvement with diuretic therapeutic, being discharged and referred to the Cardiology clinic.

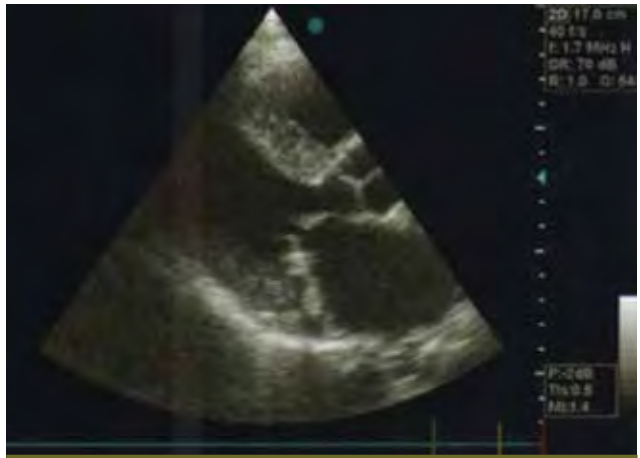
He was observed as an outpatient four months after admission. He showed a worsening of the symptomatology, having been admitted in the Cardiology Service.

He has repeated the TTU (*Fig. 3-6*) revealing again a transmitral flow with a pattern of a restrictive type.



TTU (short axis incidence). Severe grade concentric hypertrophy on the left ventricle.

FIG. 4



TTU (parasternal long axis). Hipertrofia do septo interventricular.

FIG. 5

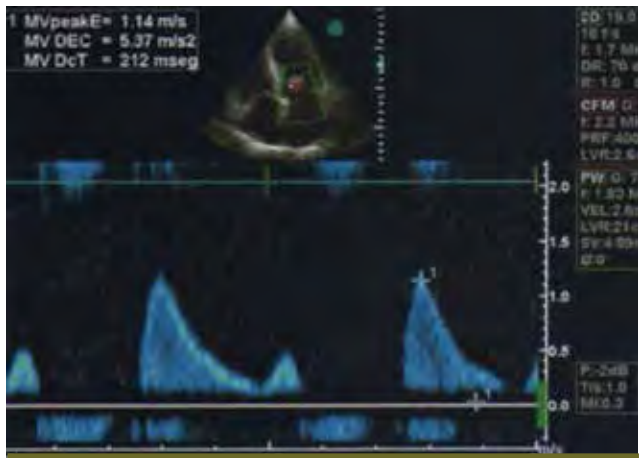
Therefore, and before a hypertrophic myocardiopathy of unclear etiology, an endomyocardial biopsy was carried out revealing fibroelastosis lesions and nuclear hypertrophy, without deposition of material of the amyloid type. In the same procedure, coronarography was carried out, excluding a coronary disease with meaning in angiography.

In the absence of a histology diagnosis, a heart MNR (*Fig. 7*) was performed revealing biventricular hypertrophy and a RT pattern suggesting amyloidosis infiltrative myocardiopathy.

Due to the high level of suspicion of heart commitment by amyloidosis, he was subject to vacuum biopsy of the abdominal fat which has identified amyloid substance by Congo Red method.

The patient was referred to the Internal Medicine outpatient clinic. In the study carried out, a normal serum ratio κ/λ (1.55), with normal serum and urinary proteins immunoelectrophoresis/immunofixation should be highlighted; the bone marrow immunophenotypic study was normal. He died two months later.

Facing a systemic amyloidosis diagnosis, confirmed by abdominal fat biopsy, associated with clinic and imageology findings of restrictive myocardiopathy with suggestive PRT on the heart NMR, it was requested the revaluation of the fragment of the endomyocardial biopsy searching for amyloid material. The histochemical study of Congo Red has shown an amorphous substance, birefringent under polarized light, confirming the cardiac amyloidotic infiltration



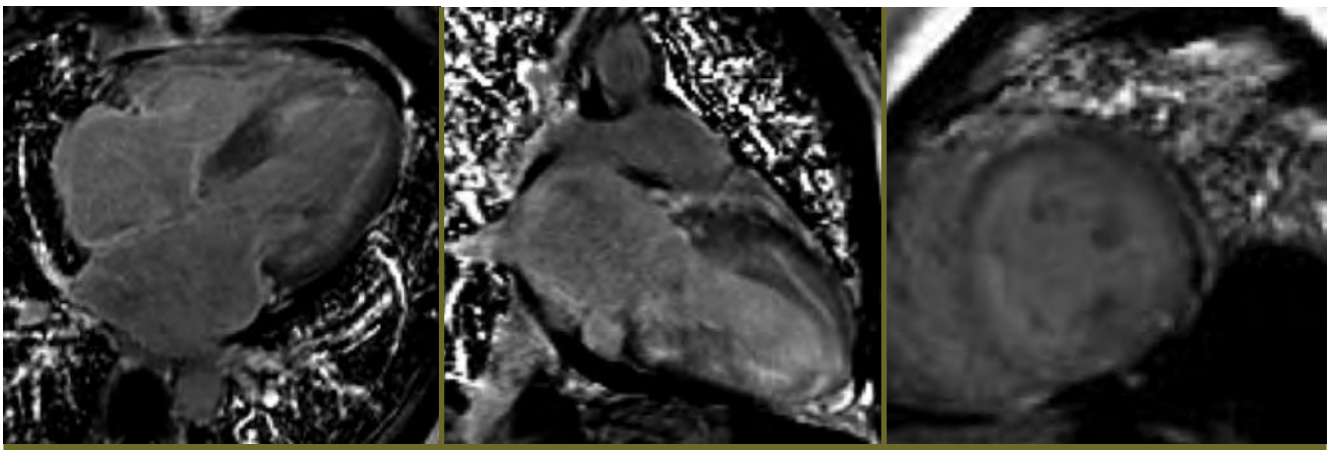
TTU (Doppler study). Transmitral flow, with an E/A relationship of 2.5 (diastolic dysfunction of restrictive type).

FIG. 6

(*Fig. 8-9*); the immunohistochemical study has revealed to be an amyloid protein AL λ.

DISCUSSION

The case described shows how difficult it is the *ante-mortem* diagnosis of the cardiac involvement in amyloidosis. In fact, the unspecific character or the symptoms associated with the disease (mainly right heart failure) leads to delays in the diagnosis, that is achieved in the later stages of the disease in which the organ dysfunction is present, restricting the treat-



Heart NMR – Late contrast: diffuse subendocardial pattern (from the left to the right: four chambers, two chambers, short axis)

FIG. 7

ment efficacy. The early diagnosis is crucial for the improvement of the morbidity and mortality,[2,3,4] but implies a high level of clinical suspicion.

Before the clinical findings and electro and ultrasound, the diagnosis hypothesis of infiltrative myocardiopathy would be the most likely. A heart catheter with coronarography was carried out to exclude coronary disease (as there were electrocardiographic changes compatible with a previous infarction) and endomyocardial biopsy was performed.

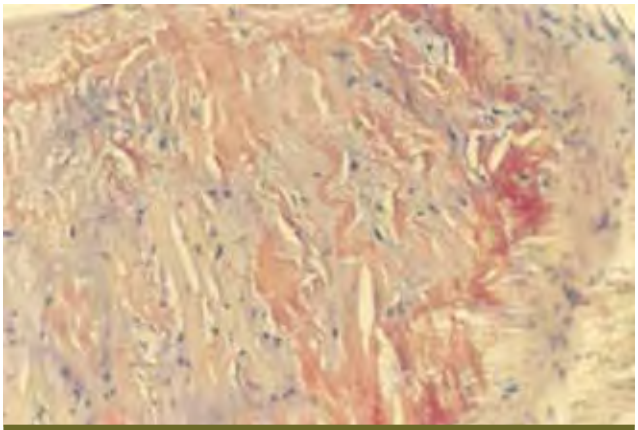
The coronary angiography did not show a significant coronary disease, what was to expect, as amyloidosis seldom affects the epicardial coronary vessels.[2]

The endomyocardial biopsy remains the *gold standard* for the diagnosis of cardiac amyloidosis.[1,2,3,4] However, in the case presented, the research of amyloid substance was negative.

At this time, the heart NMR, with RT technique, enabled a tissue characterization, reinforcing the hypothesis of myocardium infiltration by amyloid substance. On this aspect, two exceptions are made: firstly, being the diagnosis of heart amyloidosis a histological diagnosis and, being the sensitivity of the endomyocardial biopsy virtually 100% (as the amyloid deposit has a diffuse pattern in the heart muscle),[2] it is questionable why the research of amyloid substance was negative; secondly, in the absence of a myocardial histologic result, it should be questioned whether image exams are enough to state a diagnosis and, among these, which is the heart NMR role.

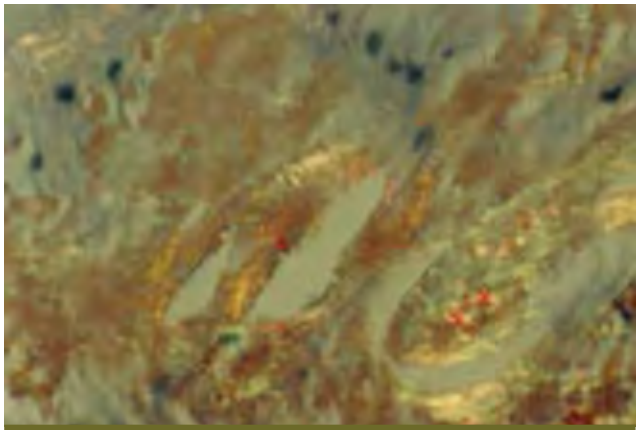
The evaluation of histological sections to research amyloid material depends on several factors. The staining method by Congo Red remains the *gold standard* to detect amyloid deposits.[4] Therefore, factors as the observer experience, a good technique of fixation, an appropriate staining protocol (alkaline Red Congo) and the use of sections of 5-10 µm[(4)] are determinant to a correct evaluation. It was not possible to identify the reason why the first histological evaluation was negative for amyloidosis, presuming to be the influence of factors presented as a cause of such result.

Heart NMR is a non-invasive powerful tool to support the heart amyloidosis suspicion, as it is a volumetric technique defining with precision the size, volume, function and mass of cardiac cavities, with the capacity of characterizing intrinsic interstitial abnormalities, through an RT technique.[6] Until such method emerged, the diagnosis of heart amyloidosis, in the absence of endomyocardial biopsy, was presumed based in the histological documentation of amyloid infiltration in another organ, associated to the clinical combination (Symptoms of Heart Failure Class ≥ 2 New York Heart Association) with electro and echocardiographic findings [2,3,5] – low voltage in the limbs derivations ($\leq 0{,}5$ mV) and an increase on the LV mass with thickening of the ventricular wall (> 12 mm). Often, the Left Ventricle EF is normal or slightly depressed until a later stage of the disease, albeit severe HF symptoms may emerge. Apart of such findings, the "glossy" aspect of the myocardium in TTU is very characteristic in the heart amyloidosis.[2] The heart NMR is particularly useful in the differential



Endomyocardial biopsy (x200): Red Congo stain.

FIG. 8



Endomyocardial biopsy (x400): Red Congo Stain under polarized light.

FIG. 9

diagnosis between the ventricular wall thickening by myocardial infiltration vs. ventricular hypertrophy caused by high blood pressure. RT technique shows a diffuse contrast pattern, subendocardial, circumferential, characteristic of amyloidotic infiltration.[6] These typical changes in RT are due to the expansion of the interstitial compartment by the infiltration of the amyloid protein.[2,5,6]

Vogelsberg *et al*.[3] comparing the heart NMR with a endomyocardial biopsy to detect heart amyloidosis, came to the conclusion that the first present a sensitivity and specificity of 80% to 94%, respectively, with a positive predictive value of 92% and a negative predictive of 85%. With the confirmation of such data, through other studies, the diagnosis of heart amyloidosis could be confirmed in the presence of clinical criteria and the RT pattern typical in the Heart NMR, being the endomyocardial biopsy just necessary in cases where the identification of the type of the amyloid protein is necessary for the therapeutic orientation.

Apart of this, to provide direct information of the space allocation of the amyloid in the myocardium, the heart NMR contrasting can help a prognosis value and being used in the treatment *follow-up*.[2,3]

CONCLUSION

The myocardial infiltration by amyloid substance is a rare entity, representing a diagnostic challenge, as its clinical characteristics overlap heart failure frequent causes. The early diagnosis is often difficult, being already established in later stages of heart failure, affecting the treatment.

At present, the endomyocardial biopsy remains as the auxiliary exam to state the diagnosis. However, with the advent of heart NMT with RT technique, the identification of a typical infiltrative pattern may turn this technique into the diagnosis tool to confirm cardiac amyloidosis, avoiding the resource to biopsy. Although the Vogelsberg et al. results are encouraging, they are based in series with small samples, related with the rarity of the pathology. To carry out multicentric studies with a higher number of subjects can confirm such results and thus, validating the use of RT technique to a diagnosis confirmation of amyloid myocardiopathy. ■

References

1. Nihoyannopoulos P, Dawson D. Restrictive cardiomyopathies. Eur J Echocardiogr. 2009; 10(8): iii 23-33.

2. Desai H, Aronow W, Peterson S, Frishman W. Cardiac Amyloidosis Approaches to Diagnosis and Management. Cardiol Rev. 2010;18(1):1-11.

3. Vogelsberg H, Mahrholdt H, Deluigi C, Yilmaz A, Kispert E, Greulich S, Klingel K, Kandolf R, Sechtem U. Cardiovascular Magnetic Resonance in Clinically Suspected Cardiac Amyloidosis noninvasive imaging compared to endomyocardial biopsy. J Am Coll Cardiol, 2008; 51:1022-1030.

4. Picken M. Amyloidosis – Where Are We Now and Where Are We Heading?. Arch Pathol Lab Med 2010; vol 134: 545-551.

5. Ruberg F, Appelbaum E, Davidoff R, Ozonoff A, Kissinger K, Harrigan C, Skinner M, Manning W. Diagnostic and Prognostic Utility of Cardiovascular Magnetic Resonance Imaging in Light-Chain Cardiac Amyloidosis. Am J Cardiol. 2009; 103(4): 544–549.

6. Maceira A, Joshi J, Prasad S et al. Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation 2005;111:122–124.