Cardiac Amyloidosis, Follow the Trail Not to Miss the Diagnosis

Amiloidose Cardíaca, Seguir o Rasto para Não Falhar o Diagnóstico

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Abstract

Amyloidosis is a systemic disease caused by the extracellular deposition of insoluble fibrils of low molecular weight proteins, the most common of which are light chains (AL amyloidosis) and transthyretin (ATTR amyloidosis), the latter in acquired (wild type) or hereditary form. Despite being considered rare, its underdiagnosis is now recognized, meaning that a high index of suspicion is essential in order to modify the morbidity and mortality of patients affected by it.
The authors describe a case report of amyloidosis with cardiac involvement.

Keywords: Amyloidosis; Amyloid Neuropathies, Familial; Cardiomyopathies; Immunoglobulin Light-chain Amyloidosis

Resumo

A amiloidose é uma doença sistémica causada pelo depósito extracelular de fibrilas insolúveis de proteínas de baixo peso molecular, sendo as mais comuns as cadeias leves (amiloidose AL) e a transtirretina (amiloidose ATTR), esta última sob a forma adquirida (*wild type*) ou hereditária. Apesar de ser considerada rara, é hoje reconhecido o seu subdiagnóstico, pelo que é fundamental um elevado índice de suspeita no sentido de alterar a morbilidade e mortalidade dos doentes por ela afetados.
Os autores descrevem um caso clínico de amiloidose com envolvimento cardíaco.

Palavras chave: Amiloidose; Amiloidose de Cadeia Leve de Imunoglobulina; Cardiomiopatias; Neuropatias Amilóides Familiares

Introduction

Cardiac amyloidosis is a restrictive cardiomyopathy caused by the progressive extracellular deposition of amyloid fibrils in the heart, with poor outcomes if left untreated.[1,2] Although once considered a rare disease, nowadays it is well recognized as an underdiagnosed cause of common cardiac diseases or syndromes such as heart failure with preserved ejection fraction, aortic stenosis, or unexplained left ventricular hypertrophy (LVH), particularly in the elderly.[3-6]

The nomenclature for systemic amyloidosis includes an "A" for amyloid followed by an abbreviation of the protein that misfolds. Most cases correspond to monoclonal immunoglobulin light chain amyloidosis (AL) or transthyretin amyloidosis (ATTR), either in its hereditary (ATTRv) or acquired (ATTRwt) form. The ATTRwt form, which is associated with ageing, is currently considered the most frequent form of cardiac amyloidosis worldwide.[1,2]

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It is of most importance to diagnosis cardiac amyloidosis in order to change disease progression, the patients' prognosis, their symptoms and quality of life. ATTR cardiac amyloidosis specific treatment can stop or delay amyloid deposition and even for AL amyloidosis, the prognosis has significantly improved with effective therapies which reduces the production of the cardiotoxic light chains.[1,2]

Case Report

We present the case of a 75-year-old male patient with no relevant family history, with a medical history of type 2 diabetes *mellitus*, dyslipidaemia, hyperuricemia and severe aortic valve stenosis with aortic valve replacement with a Resilia Inspiris nº 23 bioprosthesis 4 years ago. He was medicated with acetylsalicylic acid 100 mg od, ezetimibe + simvastatin 10+40 mg od, glibenclamide 5 mg od and allopurinol 150 mg od. In NYHA class I, he underwent a transthoracic echocardiogram at the follow-up appointment which demonstrated the aortic biological prosthesis without signs of dysfunction and severe asymmetric septal left ventricular hypertrophy, with preserved biventricular systolic function and a grade II diastolic dysfunction; the strain analysis showed decreased global longitudinal strain without apical sparing (Fig. 1). There was a remarkable evolution of ventricular hypertrophy from mild to severe in 1 year. At physical examination, a bilateral Popeye sign secondary to a bilateral ruptured distal biceps tendon was seen. The 12-lead electrocardiogram recorded sinus rhythm with HR 74 bpm with marginal left ventricular hypertrophy criteria (Fig. 2). Cardiac magnetic resonance (CMR) imaging was performed which demonstrated asymmetric septal hypertrophy with a maximum thickness of 16 mm, fibrosis in the inferior interventricular junction and stria of septal fibrosis (Fig. 3).

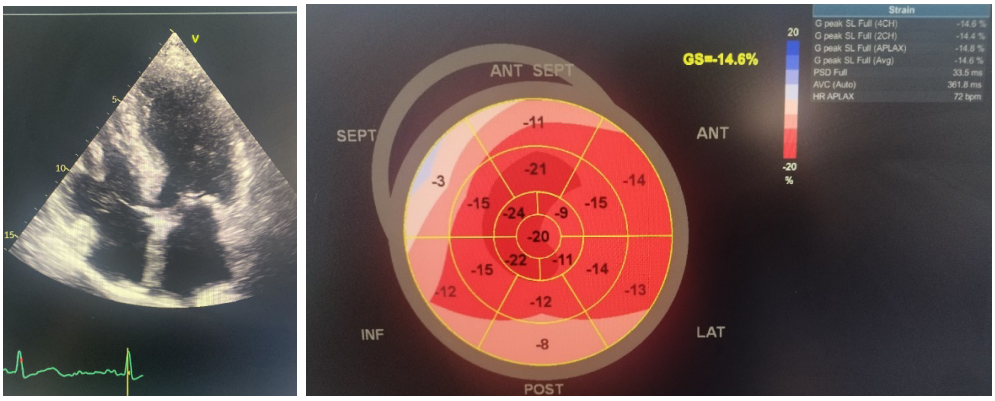

Figure 1. Echocardiogram showing septal left ventricular hypertrophy in apical 4 chamber view and the bull's-eye plot from strain imaging.

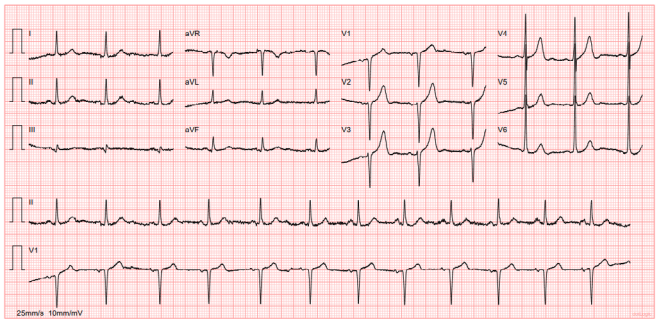

Figure 2. 12-lead electrocardiogram.

A Tc-99m-DPD scintigraphy was requested, which showed grade 3 myocardial uptake of the radiotracer with a visual score of 3 (Fig. 4). A clonal dyscrasia was excluded by serum free light chain assay and serum and urine protein electrophoresis with immunofixation. Laboratorial results did not demonstrate significant changes, including renal function and proteinuria. Genetic testing for the transthyretin gene was negative. Electromyography of the median and cubital nerves of the upper limbs was performed with evidence of severe bilateral carpal tunnel syndrome.

The patient is going to start tafamidis.

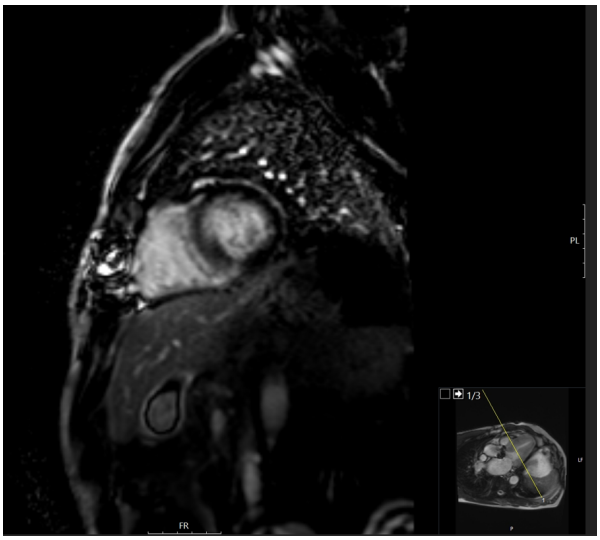

Figure 3. Cardia MR – Inversion-recovery sequence - short axis - showed the presence of late gadolinium enhancement in the inferior inerventricular junction and stria of septal fibrosis.

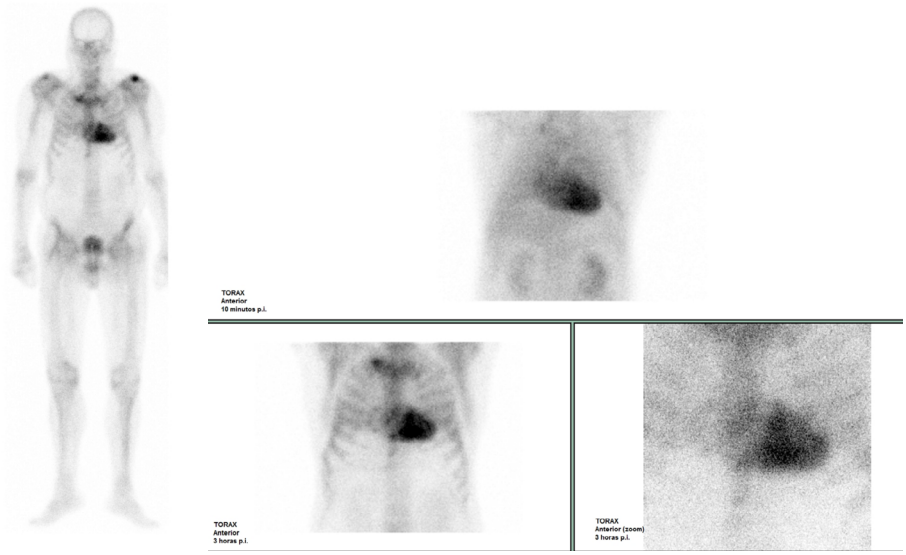

Figure 4. Tc-99m-DPD scintigraphy showing myocardium uptake with a visual score of 3.

Discussion

Cardiac amyloidosis is characterized by the extracellular deposition of misfolded proteins that aggregate into b-sheet amyloid fibrils in the ventricular myocardium with the pathognomonic histological property of green birefringence when viewed under cross-polarized light after staining with Congo red. Imaging techniques and monoclonal light chain testing allow for accurate non-invasive diagnosis of ATTR-CM according with the clinical context, without the need for confirmatory endomyocardial biopsies.[1,2] Most cases correspond to monoclonal immunoglobulin light chain amyloidosis (AL) or transthyretin amyloidosis (ATTR), either in its hereditary (ATTRv) or acquired (ATTRwt) form, being the ATTRwt subtype considered the most frequent one worldwide.

Although once considered a rare disease, nowadays it is well recognized as an underdiagnosed cause of common cardiac diseases or syndromes such as heart failure with preserved ejection fraction, aortic stenosis, or unexplained LVH, particularly in the elderly.[3,4] TTR misfolding and aggregation appear to increase with aging, as autopsy series of patients over 80 years of age indicate that 25% have TTR amyloid deposits, not always with clinical manifestations.[6-8]

The majority of patients with ATTR-CM do not receive a timely diagnosis. In a survey of patients with ATTR-CM, diagnosis was made within 6 months of symptom onset in only 35% of those with ATTRv and 46% of those with ATTRwt. Many patients see more than 5 physicians being correctly diagnosed because: it is assumed that amyloidosis is rare; there is an overlap with other more "common" diseases; and the multisystemic signs and symptoms wrongly assumed as "not related", such as musculoskeletal, neurologic, gastrointestinal (GI), and renal manifestations.[5,6] In this clinical case of left ventricular hypertrophy, in a less severe initial phase, it was assumed to be attributed to the pressure overload in the context of severe aortic stenosis. In other cases the increased left ventricular wall thickness may be mistaken for hypertensive heart disease or hypertrophic CM.

The diagnosis of cardiac amyloidosis requires a high index of suspicion and the clinician must have in mind "red flags" that are associated with the cardiac amyloidosis phenotype for many reasons: specific laboratory and imaging tests are required to reach the diagnosis and it can imply a specific treatment that can modify patient's prognosis, symptoms and quality of life.[1,2] Cardiac amyloidosis clinical clues/red flags can be divided into cardiac features (increased left ventricular wall thickness without an evident cause, heart failure, atrial fibrillation or conduction system disease, elevated cardiac biomarkers such as high sensitivity troponin or natriuretic peptides) and extracardiac manifestations such as carpal tunnel syndrome, spinal stenosis, hip or knee replacement, prior shoulder surgery, proteinuria, or peripheral/autonomic neuropathy).[1,2] Cardiac amyloidosis should be suspected in patients with increased LV wall thickness in the presence of cardiac or extracardiac red flags and/or in specific clinical situations, particularly in patients >65 years of age (Fig. 5).[1]

The red flags in this patient were progressive left ventricular hypertrophy without an evident cause (it was not severe when he had severe aortic stenosis), the progression of hypertrophy without a clear explanation in a patient with a past history of aortic stenosis and Popeye sign. Musculoskeletal manifestations, such as spontaneous biceps tendon rupture and spinal stenosis, are unique to ATTR amyloidosis.

As in this case, it is common to see discordant QRS voltage for degree of increased left ventricular wall thickness on imaging.

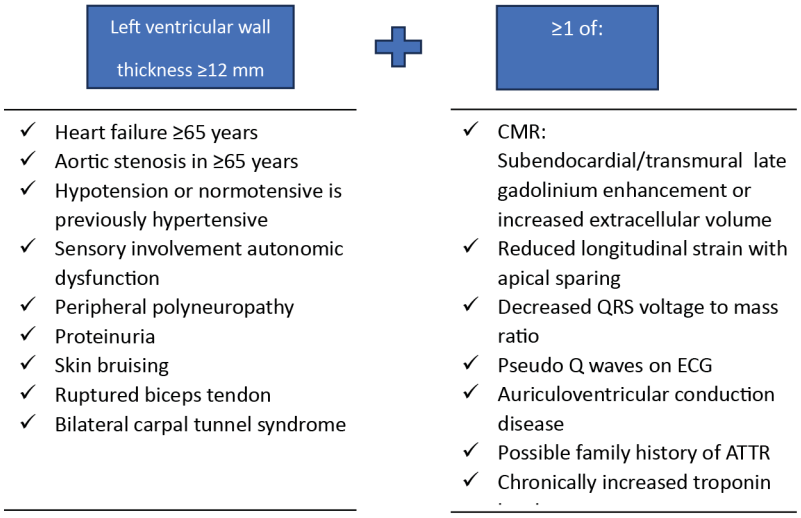

Figure 5. Clues/red flags for cardiac amyloidosis.

Cardiac amyloidosis can be diagnosed using both invasive and non-invasive diagnostic criteria, being non-invasive criteria accepted only for ATTR. Invasive criteria include demonstration of amyloid fibrils within cardiac tissue or, alternatively, demonstration of amyloid deposits in an extracardiac biopsy accompanied either by characteristic features of cardiac amyloidosis on echocardiography or CMR. Non-invasive criteria include typical echocardiographic/CMR findings combined with planar and single-photon emission computed tomography (SPECT) grade 2 or 3 myocardial radiotracer uptake in 99mtechnetium--pyrophosphate (99mTc-PYP) or 3,3-diphosphono-1,2 propanodicarboxylic acid DPD or hydroxymethylene diphosphonate (HMDP) scintigraphy and exclusion of a clonal dyscrasia by all the following tests: serum free light chain assay, serum and urine protein electrophoresis with immunofixation.[9]

Echocardiographic diagnostic findings include increased left ventricular wall atrioventricular valve/right ventricle free wall/interatrial septum thickening, diastolic dysfunction, decreased mitral annular systolic velocity (s'), biatrial enlargement, and decreased global longitudinal strain with relative apical sparing (not seen in our patient).[2]

In this case report magnetic resonance imaging (MRI) did not show a diffuse subendocardial or transmural late gadolinium enhancement, typical but not always present in amyloidosis cardiomyopathy.

Indeed, CMR is neither necessary nor sufficient for establishing the diagnosis of cardiac amyloidosis as a standalone test and cannot distinguish between AL-CM and ATTR-CM.[2] In the other hand, CMR can be useful in identifying findings suggestive of other infiltrative/inflammatory or restrictive CMs, including sarcoidosis, hemochromatosis, or Fabry disease, as well as hypertrophic cardiomyopathy.

The cardiac amyloidosis diagnosis combines the search for a monoclonal protein and bone scintigraphy. Scintigraphy using technetium-based compounds (pyrophosphate [Tc-PYP] and diphosphono-1,2-propanodicarboxylic acid[Tc-DPD] have emerged as an important imaging tool in the non-invasive diagnosis of ATTR-CM, with cardiac uptake that is consistent with ATTR-CM (grade 2 or 3 uptake). However, it should always be considered that in up to 10% of AL-CM can have this uptake.[10] In Portugal, the usual protocol is the planar scintigraphy using Tc-DPD.

AL amyloidosis can be excluded through a monoclonal protein screen including serum free light chain assay (with monoclonality assumed by an abnormal ratio) and a serum/urine immunofixation test. Serum/urine protein electrophoresis should not be used to exclude monoclonal protein given its lower accuracy relative to immunofixation for AL amyloidosis. If no monoclonal protein is identified by immunofixation and the serum free/light chain ratio is in the normal range, then AL amyloidosis has been excluded with a negative predictive value of 99%.[2]

Because DPD/PYP scan cannot distinguish between wild type and mutated ATTR, a TTR genetic testing was performed, which was negative. TTR genetic testing is recommended in all transthyretin amyloid cardiomyopathy (ATTR-CM) patients regardless of age, as 5% of ATTR-CM patients ≥70 years (and 10% among females) have ATTRv.[11]

Once cardiac amyloidosis is suspected, the goal is to obtain an early and rapid diagnosis as early initiation of therapy can prevent further amyloid deposition and further end-organ damage. The treatment of cardiac amyloidosis includes treating and preventing complications and stopping or delaying amyloid deposition by specific treatment. There is no evidence

to support the use of standard heart failure therapy, which often is not well tolerated, apart from diuretics.[1]

In patients with cardiac amyloidosis, conduction defects, tachyarrhythmias, and sudden cardiac death (SCD) are common. Cardiac amyloidosis is characterized by infiltration of the conduction tissue, so the threshold for actively looking for conduction tissue disease to justify symptoms such as syncope our pre-syncope should be low, although currently conventional indications should be used for pacing in this group of patients.[12] The role of implantable cardioverter-defibrillator (ICD) in cardiac amyloidosis for SCD prevention is not clearly known.[2]

Transthyretin stabilization and reduction of its production are the basis of TTR cardiac amyloidosis treatment. Tafamidis reduced all-cause mortality and cardiovascular hospitalizations in ATTR, with the largest benefit in patients at NYHA functional class I and II. [13]

Conclusion

Cardiac amyloidosis is a progressive disease with poor outcomes if left untreated. Although once considered a rare disease, nowadays it is well recognized it is underdiagnosed as a cause of common cardiac diseases or syndromes such as unexplained LVH.

Once cardiac amyloidosis is suspected, the goal is to obtain an early and rapid diagnosis as early initiation of therapy can prevent further amyloid deposition and further end-organ damage. The diagnostic algorithm combines the search for a monoclonal protein and bone scintigraphy, followed by TTR genetic testing to distinguish between the ATTRwt and ATTRv in those with definite diagnosis of ATTR cardiac amyloidosis.

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