

CASE PRESENTATION

Cardiac Amyloidosis: from Heart Failure to Multiple Myeloma, a Case Report

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ABSTRACT

Cardiac amyloidosis is an underdiagnosed condition associated with a poor prognosis, likely leading to heart failure, malignant arrhythmias and death. A high index of suspicion should be maintained in regards to clinical, electrocardiographic and echocardiographic changes, as the "gold standard" for diagnosis, endomyocardial biopsy is often unavailable. Another challenge resides in the limited treatment options, with a relative contraindication to the use of betablockers, calcium channel blockers, angiotensin-converting enzyme inhibitors and digoxin. We are presenting the case of a patient with heart failure, in whom echocardiography with speckle tracking and cardiac magnetic resonance played an important role in diagnosing cardiac amyloidosis and underlying multiple myeloma. Despite a poor prognosis based on biomarkers (troponin and NTproBNP) and global longitudinal strain, as well as ineligibility for stem cell transplant the patients survived for another 5 years.

Keywords: cardiac amyloidosis, AL amyloidosis, multiple myeloma, heart failure, HFpEF.

REZUMAT

Amiloidoza cardiacă este o patologie subdiagnosticată cu prognostic infaust ce poate evolua către insuficiență cardiacă, aritmii maligne și deces. Suspiciunea diagnostică trebuie să fie bazată pe o multitudine de modificări clinice, electro și ecocardiografice deoarece „standardul de aur”, biopsia endomiocardică este o procedură invazivă, indisponibilă în majoritatea centrelor. O altă limitare legată de această patologie o constituie paleta restrânsă a tratamentului simptomatic prin contraindicația betablocantelor, a blocantelor de canal calcic, a inhibitorilor de enzimă de conversie și a digoxinului. Prezentăm cazul unei paciente internate cu fenomene de insuficiență cardiacă, la care ecocardiografia cu speckle tracking și rezonanța magnetică cardiacă au jucat un rol important în diagnosticul de amiloidoză cardiacă și, ulterior, de mielom multiplu. Particularitatea cazului rezidă în evoluția de lungă durată (deces la circa 5 ani de la diagnostic) în condițiile unor valori persistent crescute ale biomarkerilor (troponină și NTproBNP) și a unui strain longitudinal scăzut, dar și a afectării multi-organ ce a dus cu sine contraindicația transplantului medular.

Cuvinte cheie: amiloidoză cardiacă, amiloidoza AL, mielom multiplu, insuficiență cardiacă, IC cu fracție de ejeție preservată.

INTRODUCTION

Cardiac amyloidosis (CA) is an underdiagnosed condition caused by insoluble deposits of misfolded proteins in the extracellular matrix of all cardiac structures. Amyloidosis in itself is an umbrella term for a heterogeneous assortment of diseases as many different proteins may become misfolded and give rise to amyloid. However, most cases of cardiac amyloidosis can be attributed to only two types of amyloid: light-chain amyloidosis (AL) caused by immunoglobulin light-chains, thus occurring most commonly in patients with plasma cell dyscrasias, and transthyretin amyloidosis (ATTR) where a precursor of albumin becomes

misfolded. Furthermore, ATTR can be subdivided into the hereditary form, associated with a gene defect, and wild-type, occurring in older patients in whom the transthyretin gene is unaffected but the protein still becomes misfolded^{1,2}.

The clinical presentation of amyloidosis is variable and depends on amyloid distribution. Heart failure is a common finding, as well as orthostatic hypotension and syncope. ECG clues to cardiac amyloidosis are low QRS voltage in the limb leads and a pseudoinfarct pattern in the precordial or inferior leads. Due to amyloid build-up, conduction disturbances may become apparent and patients can present with atrioven-

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tricular block, atrial fibrillation or flutter, ventricular ectopy or prolonged QT interval¹⁻³. There are many subtle extracardiac signs associated with amyloidosis, which may aid in differentiating between AL and ATTR. While gastrointestinal symptoms, sweating and erectile dysfunction are common for both, peripheral neuropathy, carpal tunnel syndrome and lumbar spinal stenosis are more prevalent in ATTR, and periorbital ecchymoses ("raccoon eyes"), macroglossia and chronic kidney disease in AL².

Irrespective of precursor protein, amyloid deposits have a characteristic appearance when viewed under a microscope; when stained with Congo red, cells have an apple-green birefringence under polarized light. Endomyocardial biopsy followed by Congo red staining is the „gold standard’ in the diagnosis of cardiac amyloidosis. However, since access to the procedure is limited, cardiac involvement has been defined as either a positive heart biopsy and/ or an interventricular septum (IVS) thickness exceeding 12 mm in the absence of other causes of ventricular hypertrophy¹.

Echocardiography is, hence, the mainstay of diagnosis in patients with suspected cardiac amyloidosis. Aside from the thickened IVS with "granular sparkling", common findings also include dilated atria (may contain thrombi), a thickened interatrial septum, small to moderate pericardial effusion, mild valvular dysfunction (secondary to amyloid deposits in valvular structures), pulmonary hypertension and a restrictive mitral inflow pattern^{2,4}.

Modern imaging techniques such as 2D speckle tracking, cardiac magnetic resonance (CMR) and nuclear scintigraphy with technetium-labeled radiotracers are of particular help in the diagnostic of cardiac amyloidosis. Speckle tracking has become common place in echocardiography laboratories worldwide and a relative sparing of the longitudinal strain in the ventricular apex, an aspect commonly described as „cherry on top", is an easily recognizable feature of cardiac amyloidosis^{5,6}. Moreover, late gadolinium enhancement (LGE) and T1 mapping on CMR reveal another characteristic pattern, and cardiac uptake higher than grade 2 on nuclear scintigraphy in the absence of plasma cell dyscrasia is diagnostic for ATTR². A study performed on explanted hearts seems to tie in apical sparing of GLS with amyloid distribution predominantly in the basal and mid-cavity sections, also corresponding to the subendocardial pattern of LGE⁷.

The prognosis associated with cardiac amyloidosis depends on the type of amyloid involved. ATTR may

present with a milder phenotype, while AL has a rapid progression rate (0.19 - 2.02 mm/month has been cited)⁸. Evidently, an early and accurate diagnosis is important as a means to early treatment.

We present the case of a heart failure patient who on closer inspection exhibited stigmata associated with amyloid build-up and was thus diagnosed with multiple myeloma and cardiac amyloidosis.

CASE PRESENTATION

A 50-year-old woman with grade 3 arterial hypertension and diabetes mellitus is admitted for exertional dyspnea, palpitations and constitutional symptoms (weight loss and anorexia). On examination, the patient is afebrile, with a blood pressure of 120/70 mmHg, heart rate 73 bpm and SatO₂ 98% on breathing ambient air. She has macroglossia, nuchal petechiae, peripheral facial nerve paralysis, bilateral leg edema and an enlarged, tender liver.

Laboratory assays reveal a normal complete blood count, electrolytes, renal and liver function tests. Troponin (cTnT) is 0.092 ng/mL, within the normal range, though the NTproBNP value is highly elevated 6220 pg/mL (reference range: 0 – 125 pg/mL).

The ECG exhibits sinus rhythm with a trifascicular block (first degree atrioventricular block, right bundle branch block and anterior fascicular block), low QRS voltage, a pseudoinfarct pattern in the inferior leads and an isolated premature ventricular complex (PVC).

On echocardiography, biatrial enlargement, ventricular hypertrophy, and grade III diastolic dysfunction are evident (Figure 1, Figure 3 – panels 1-4), as well as a characteristic pattern of apical sparing of global longitudinal strain (GLS: -14.3%, Figure 2). CMR finds a patchy subendocardial and subepicardial pattern of LGE (Figure 3 – panels 5-8), an increased LV mass index (103 g/m²), a small pericardial effusion (0.9 cm) and a left ventricular ejection fraction of 57%, without intracardiac thrombi.

Upon hematology referral, IgA λ -secreting multiple myeloma is confirmed by bone marrow aspirate: over 50% plasmacytes and Mott cells, as well as a subcutaneous fat biopsy positive for amyloid.

Throughout the hospital stay, the patient develops paroxysmal atrial fibrillation and atrial flutter with variable block (Figure 4). She is started on amiodarone and apixaban 5 mg b.i.d., as well as diuretics (furosemide 40 mg b.i.d and spironolactone 50 mg o.d). She also receives treatment for multiple myeloma (cyclophosphamide/ bortezomib/ dexamethasone). Due to mul-

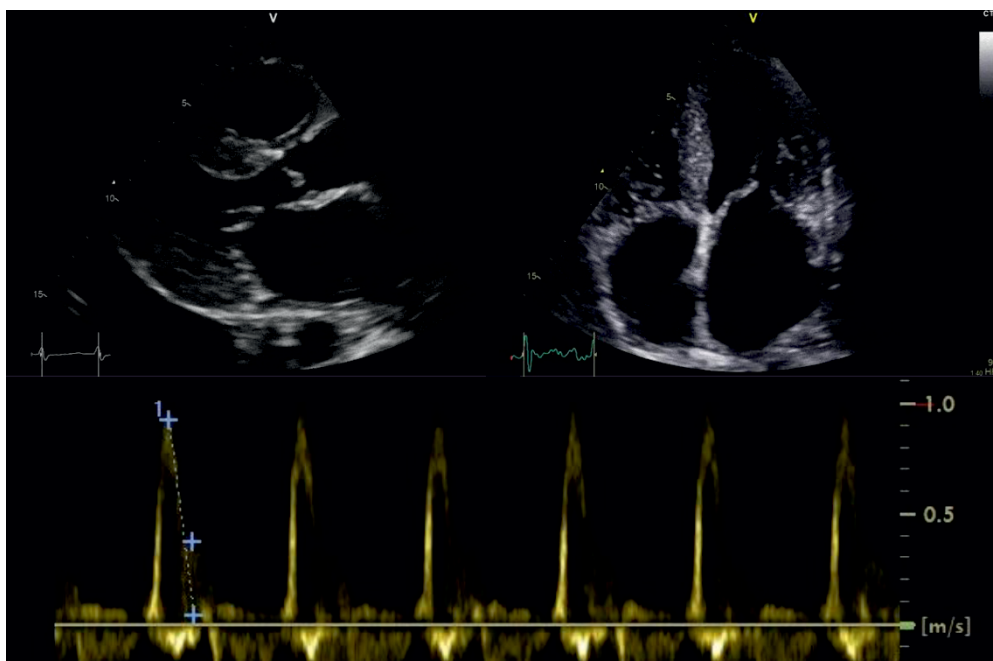


Figure 1. Echocardiography in a patient with multiple myeloma and cardiac amyloidosis showing thickened ventricular myocardium with granular sparkling, dilated atria and pleural effusion (panels A&B), as well grade 3 diastolic dysfunction (panel C).

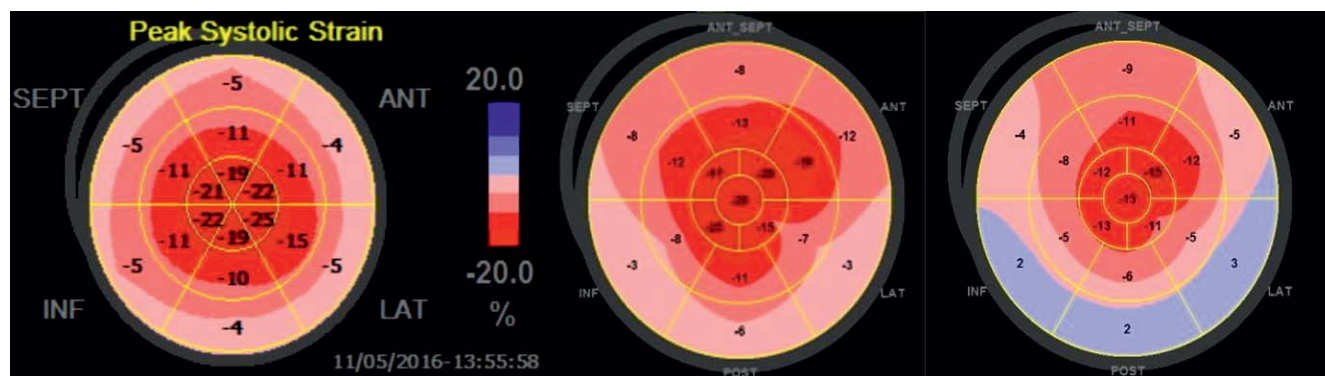


Figure 2. Global longitudinal strain (GLS) deterioration throughout the years (2016-2019) in a patient with multiple myeloma and cardiac amyloidosis, showing a “cherry on top” pattern i.e. relative apical sparing.

tiorgan involvement, she is not a candidate for stem cell transplantation.

Over the next 5 years, she is hospitalized multiple times for similar symptoms, each time presenting with slightly elevated troponin (0.05 – 0.092 ng/mL) and high NTproBNP (4810 – 18300 pg/mL), as well as a decreasing GLS albeit preserving the apical strain (-14.3% to -8.1% - Figure 2). Eventually, multiple myeloma progression, sepsis and intractable heart failure lead to the patient’s death.

DISCUSSIONS: TREATMENT AND PROGNOSIS

Up until recently, there were very few available treatment options for cardiac amyloidosis. Among them, autologous stem cell transplant (SCT) preceded by high-dose melphalan is considered effective, with mortality rates below 5% and good survival, though only applicable to 20% of newly diagnosed AL patients⁹. Heart transplantation has been attempted in patients with CA, regardless of etiology, and proved an effective

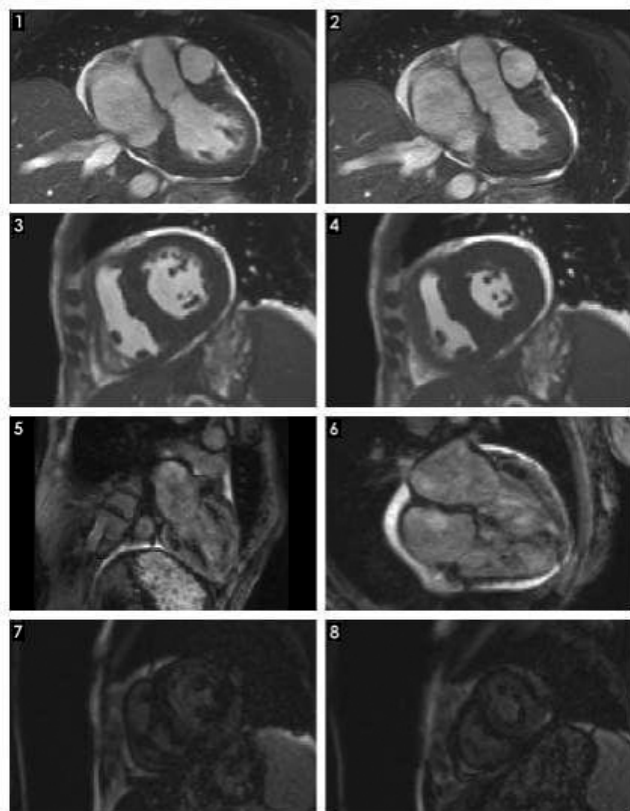


Figure 3. Cardiac magnetic resonance in a patient with multiple myeloma and cardiac amyloidosis showing thickened left ventricular walls (circle) and interatrial septum, as well as dilated atria (star). CMR revealed a patchy subendocardial and subepicardial pattern of LGE (panels 5-8), an increased LV mass index, a small pericardial effusion (0.9 cm) and a left ventricular ejection fraction of 57%, without intracardiac thrombi.

ve option in patients with minimal extracardiac involvement¹⁰.

However, in 2019¹¹ and 2020¹², tafamidis, an oral TTR stabilizer, was approved for use by the FDA and EMA respectively. Tafamidis binds transthyretin tetramers and prevents formation of amyloid and, according to the ATTR-ACT trial, leads to a 30% reduction in mortality and cardiovascular hospitalization for patients with wild-type and hereditary ATTR, while also improving quality of life and functional capacity¹³.

As for AL, in early 2021¹⁴, the FDA granted accelerated approval to Darzalex Faspro, Janssen Biotech Inc. (daratumumab plus hyaluronidase) in a combined regimen with bortezomib, cyclophosphamide and dexamethasone. Daratumumab is an anti-CD38 antibody previously approved in the treatment of multiple myeloma¹⁵, and according to the ANDROMEDA (NCT03201965) trial, cardiac response was attained in 8 out of 13 patients at the 12-month follow-up¹⁶.

Atrial fibrillation in the setting of cardiac amyloidosis carries a greater risk for systemic embolism, thus indicating anticoagulation regimens irrespective of CHA₂DS₂-VASc score. A postmortem analysis on patients with cardiac amyloidosis showed a higher thrombotic burden of AL despite maintenance of sinus rhythm and a preserved left ventricular ejection fraction, compared to ATTR. It has been hypothesized that hypercoagulability, endothelial dysfunction,

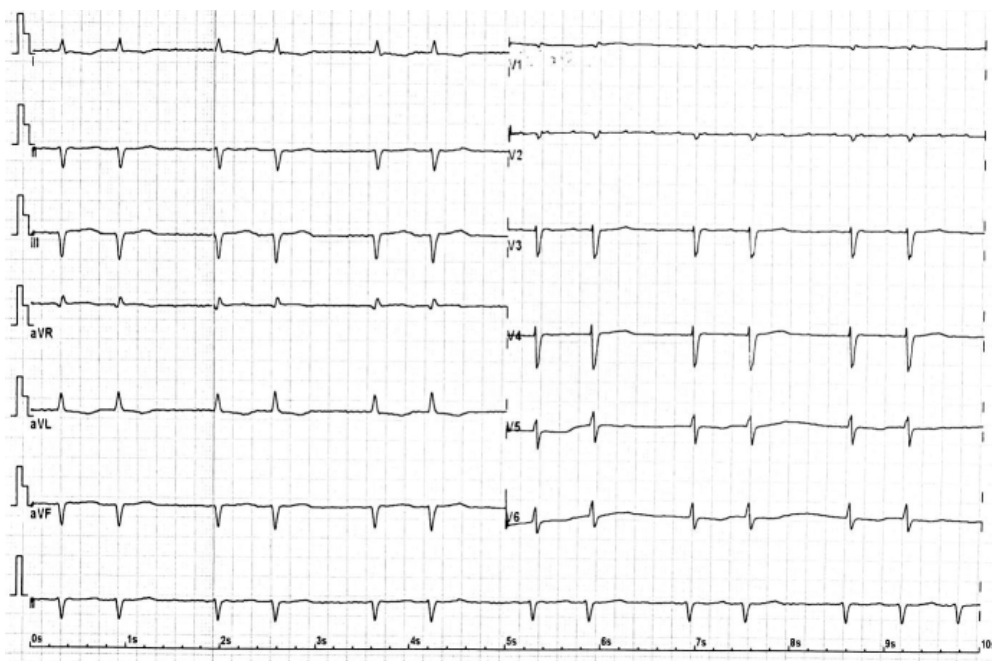


Figure 4. ECG of a patient with multiple myeloma and cardiac amyloidosis, showing atrial flutter with a variable atrioventricular block: 2:1 and 4:1, a pseudoinfarct pattern in the inferior leads and low QRS voltage in the limb leads (precordial leads are at half amplitude due to machine calibration).

reduced atrial contractility and endomyocardial damage via light-chain toxicity contribute to the increased thromboembolic risk^{17,18}. Though to a lesser degree, ATTR is also associated with a high risk of thrombosis especially when compared to the general population. It has been advocated that all CA patients undergoing cardioversion be evaluated by transesophageal echocardiography, irrespective of prior anticoagulation and time from arrhythmia onset¹⁸⁻²¹. Moreover, arrhythmias complicating cardioversion seem to be more prevalent among cardiac amyloidosis patients, though success rates are comparable with the general population¹⁹.

To date, there is no preferred oral anticoagulation agent²². A review of 290 ATTR patients did not find a statistically significant difference between DOACs and warfarin regarding either thrombotic events or major bleeding, though patients in the warfarin group who developed complications (either thrombotic or related to major bleeding) were more likely to have a labile INR²². As stated, patients in sinus rhythm may hide atrial thrombi and discussion on whether cardiac amyloidosis in the absence of atrial fibrillation warrants anticoagulation is ongoing²¹. The safest option in terms of both thrombotic and bleeding risk may be left atrial appendage occlusion followed by half-dose DOAC (most commonly used were apixaban and dabigatran²³).

Therapies with evidence in treating heart failure may be poorly tolerated or downright detrimental to patients with cardiac amyloidosis. Due to the restrictive cardiomyopathy, as ventricular filling becomes impaired, cardiac output is only maintained through tachycardia, so betablockers, with their negative inotropic and chronotropic effects should be avoided. Angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers and calcium channel blockers may worsen orthostatic hypotension and careful dose titration is warranted. Digoxin binds to amyloid fibrils, thus increasing the risk of toxicity even at normal serum concentrations. Loop diuretics require albumin-binding, so patients with nephrotic syndrome and hypoalbuminemia from renal amyloid may require higher doses. Furthermore, intravenous should be the preferred route of administration of furosemide since enteral edema in the setting of anasarca and amyloid infiltration of the gut alter drug absorption^{18,21,24}.

Biomarkers such as troponin and NTproBNP have been proposed as outcome predictors in light-chain amyloidosis. Based on a paper published in 2004, troponin and NTproBNP cutoffs (cTnT < 0.035 µg/L,

NTproBNP < 332 ng/L) have been used as a means to stratify AL patients and predict mortality²⁵. The difference between involved and uninvolved free light-chain has since been added to account for clonal burden, as well as an update in troponin and NTproBNP cutoffs (cTnT < 0.025 ng/mL, NTproBNP < 1.800 pg/mL) to give a more accurate prognosis²⁶. Other staging systems have been developed, based on BNP rather than NTproBNP, to be used in patients with advanced renal dysfunction (chronic kidney disease stage 4 or 5), but larger cohorts are required to validate the findings²⁷. Global longitudinal strain (cutoff 17%) has also been proffered not only as a prognostic means but one with the ability to further refine stratification based on biomarkers^{28,29}. Perhaps due to poor survival, to date there are no studies demonstrating evolution of GLS in AL patients ineligible for stem cell transplantation. In contrast, ATTR does not exhibit the same relationship between troponin and survival, most likely since light-chain amyloid also has a direct myocytotoxic effect^{30,31}.

CONCLUSION

Cardiac amyloidosis is still an underdiagnosed condition, but with the advent of imaging modalities like speckle tracking, cardiac magnetic resonance and nuclear scintigraphy, as well as new therapies like tafamidis for transthyretin amyloidosis and daratumumab for light-chain amyloidosis, it is now more important than ever to maintain a high index of suspicion and diagnose patients as soon as possible.

Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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