

# Cardiac amyloidosis in a patient with multiple myeloma

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**Abstract.** Amyloidosis is an infiltrative condition caused by extracellular deposits of amyloid which results from modified, insoluble proteins. The associated B lymphocyte dyscrasias in systemic amyloidosis (AL) include lymphoma, multiple myeloma and macroglobulinemia. The amyloid fibrils are formed from monoclonal immunoglobulins light chains of both lambda ( $\lambda$ ) and kappa ( $\kappa$ ) families, produced by proliferated plasmocytes. We present the case of a patient with multiple myeloma (MM), who developed amyloidosis secondary to light chains deposits within the myocardium. The main symptoms and signs were due to right sided heart failure. In order to confirm the diagnosis, imaging test were performed (echocardiography and cardiac MRI) followed by oral mucosa tissue biopsy and subcutaneous abdominal fat by fine-needle aspiration. The diagnosis of multiple myeloma was established at the Hematology Clinic in Cluj-Napoca.

**Key Words:** amyloidosis, echocardiography, MRI, multiple myeloma

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## Introduction

Amyloidosis includes a heterogeneous group of conditions, usually of unknown etiology, that have as basic mechanism the extracellular storage of autologous proteins with a fibrillary ultrastructure and specific tinctorial features. Isolated cardiac involvement is rare, cardiac amyloidosis usually being part of a systemic condition (Elliott et al 2014; Maleszewski 2015). The case of a patient with MM who developed cardiac amyloidosis secondary to light chains deposits at the level of the myocardium is presented.

## Case report

67 year old female patient with no significant pathological history was hospitalized in our service for dyspnea on mild exertion, fatigue, bilateral lower extremities edema. The patient experienced an insidious onset of symptoms that progressively aggravated within the last 7 days. The associated symptoms were equilibrium disorders, unsystematic vertigo and weight loss (approximately 5 kg in 3 months). Physical examination revealed altered general condition, pale tears, periorbital purpura, macroglossia, hypotension, signs of right-sided heart failure (turgescence jugular vein, edema at the lower limb, hepatomegaly), bilateral basal pleural syndrome.

The EKG revealed a sinus rhythm, heart rate - 90/min, diffuse microvoltage, 1st degree AVB and anterior pseudoinfarction. Thoracic X ray showed bilateral pleural effusion and lung

stasis. Echocardiography visualized biventricular hypertrophy, mild/moderate asymmetric pericardial effusion (Fig.1), biatrial dilatation, a thickened, granular, sparkling interventricular septum (IVS), moderate mitral insufficiency (Fig.2), preserved left ventricular (LV) systolic function (Fig.3), restrictive mitral flow (Fig.4), moderate secondary pulmonary hypertension, severe tricuspid insufficiency (Fig.5, Fig.6). Echocardiography was done using a Philips Affiniti 50G device.

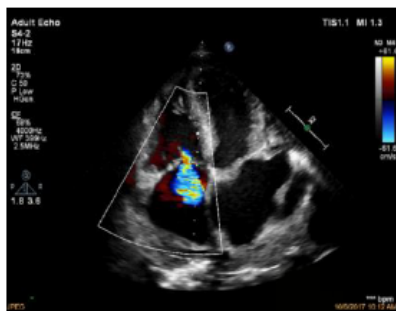
Laboratory evaluation revealed increased levels of NT pro-BNP (5718 pg/ml), hypoproteinemia, hypogamaglobulinemia and proteinuria. These results were followed by immunofixation electrophoresis for serum and urine proteins, which showed monoclonal lambda chains. The  $\kappa/\lambda$  light chains ratio was altered, which raised the suspicion of a monoclonal gammopathy and led to a bone marrow biopsy.

Bone marrow analysis revealed 50% plasmocytes with significant alterations: abnormal morphology, gigantic plasmocytes with large or double nuclei, intercellular bridges, thus confirming the MM diagnosis. The skull X-ray did not reveal osteolytic lesions.

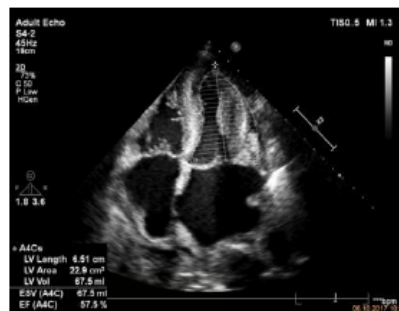
Based on clinical and imaging findings a restrictive cardiomyopathy caused by amyloidosis was suspected. Thus a cardiac MRI was performed to complete the investigations. MRI examination was performed using a General Electric Signa Explorer 1.5T MRI device. Cardiac MRI revealed an inhomogeneous appearance of LV and a diffuse late phase contrast enhancement within the myocardium, that did not correspond to an arterial territory.



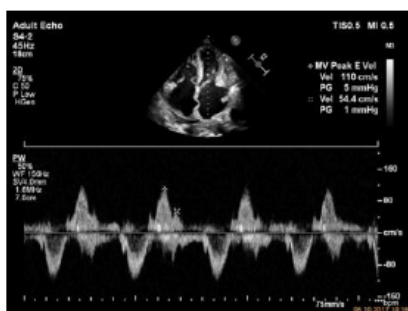
**Fig.1** Transthoracic echocardiography, long axis parasternal view, 2D examination, biventricular hypertrophy, asymmetric pericardial effusion



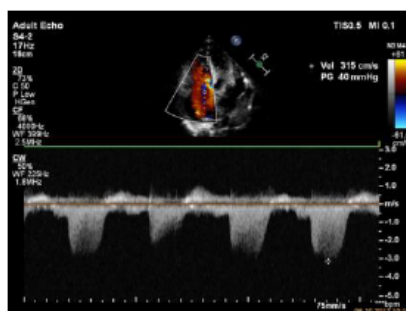
**Fig.2** Transthoracic echocardiography, apical 4 chambers view, 2D examination, granular, sparkling aspect of the IVS, severe tricuspid insufficiency



**Fig.3** Transthoracic echocardiography, apical 4 chambers view, 2D examination, efficient LV with an >50% EF



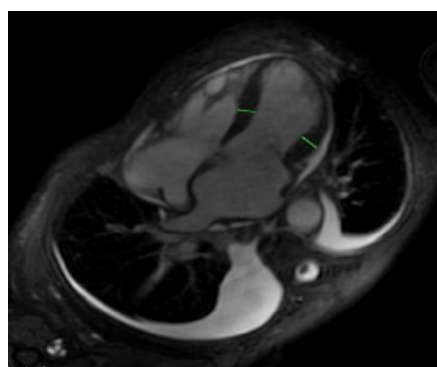
**Fig.4** Transthoracic echocardiography, apical 4 chambers view, pulsed wave Doppler of the mitral valve: restrictive diastolic dysfunction.



**Fig.5** Transthoracic echocardiography, apical 4 chambers view, continuous wave Doppler examination of the tricuspid valve: severe tricuspid insufficiency; RV-RA gradient = 40 mm Hg, PAP=60 mmHg.



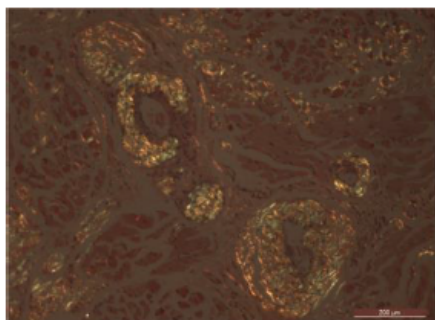
**Fig.6** Transthoracic echocardiography, 2D examination, subcostal view: dilated IVC (27 mm), reduced inspiratory collapse < 50%.



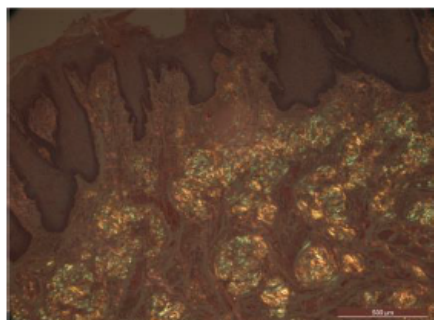
**Fig.7** Cardiac MRI, FIESTA CINE 4C sequence: Thickened LV lateral wall (12mm in diastole). Pericardial effusion. Bilateral pleural effusion.



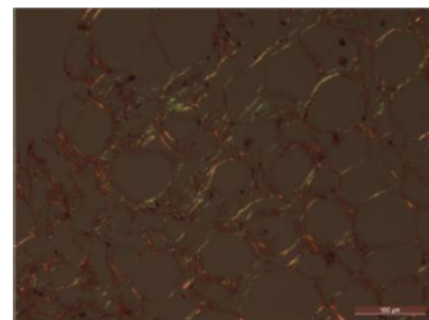
**Fig.8a and 8b.** 2D MDE Short axis sequence: inhomogeneous LV myocardium, late-phase contrast enhancement within the myocardium (not confined to a certain vascular territory), IVS, lateral and anterior ventricle wall (a), transmural enhancement in some areas at the level of the apical septum (b) – MRI findings suggest infiltrative cardiomyopathy, within context of amyloidosis; on CINE IR (lock Locker) the signal of the myocardium is canceled at a lower TI than that of the blood.



**Fig.9** Biopsy of the tongue mucosa - squamous epithelial layer and at the level of the chorion, infiltrating the muscle fibers of the tongue; amyloid deposits with "apple green" birefringence in red Congo coloration, examined with a 4x a 10x focus.



**Fig.10** Between the muscle fibers there are also vessels with circumferential amyloid deposits, showing "apple green" birefringence through the 10x focus.



**Fig.11** Biopsy of the adipose tissue with fine amyloid intercellular deposits, showing "apple green" birefringence through the 20 x focus.

These aspects were suggestive for infiltrative cardiomyopathy, most likely due to amyloidosis (Fig. 7, Fig. 8a and 8b).

The differential diagnosis included other forms of restrictive cardiomyopathy: familial (familial amyloidosis, hemochromatosis, Anderson-Fabry Disease, glycogenosis, pseudoxanthoma elasticum, desminopathy), non-familial (amyloidosis A, scleroderma-associated cardiomyopathy, endomyocardial fibrosis, cardiac carcinoid syndrome, post-radiation cardiomyopathy, toxic medication induced cardiomyopathy) (Elliott et al 2014). Systemic amyloidosis was histologically confirmed by oral mucosa and subcutaneous fat biopsy (red Congo and polarized light exams) (Fig.9, Fig.10, Fig.11).

The Holter Electrocardiography monitoring excluded the presence of severe, intermittent rhythm and conduction disorders which frequently occur in patients with restrictive cardiomyopathy.

As a result of the physical and multidisciplinary examinations the following diagnosis was established: Multiple myeloma with light lambda chains, IInd degree Salmon-Durie, ISS II. Systemic amyloidosis (cardiac, renal). Non-familial restrictive cardiomyopathy. Moderate mitral insufficiency. Severe tricuspid insufficiency. Moderate secondary pulmonary hypertension. Mild pericardial effusion. Ist degree atrio-ventricular block. NYHA III Congestive heart failure. Nephritic syndrome.

The therapy was initiated according to protocols for MM, specifically BCD (Bortezomib/ proteasome inhibitor 1.3 mg/mp days 1,4,8,11, Cyclophosphamide 500 mg/mp days 1,8,15 and Dexamethasone 20 mg iv days 1,4,8,11) (Nuvolone et al 2018). Also, treatment for cardiac failure was administered according to the European guidelines (Ponikowski et al, 2016). We followed the treatment recommendations for heart failure with preserved ejection fraction. The patient required diuretic treatment for the improvement of her systemic congestion. The administration of diuretics (Furosemide 40-100 mg/day and Spironolactone 50-100 mg/day) was limited by the presence of arterial hypotension. The drugs were administered in fractionated doses and in a progressive manner, under blood pressure control. The presence of arterial hypotension did not allow vasodilators (angiotensin-converting enzyme inhibitors) to be administered. Due to the low cardiac rate, no beta blockers were administered.

The patient received the first three doses of the first chemotherapy cycle, but the evolution has been unfavorable, with bilateral lower extremities edema worsening, both cardiac failure and hypoproteinemia secondary to renal involvement. Diuretics and albumin were administered, yet the evolution continued to be unfavorable leading to the patient's death 3 months after the diagnosis.

## Discussion

The diagnosis algorithm in cardiac amyloidosis consists in the identification of clinical signs (right cardiac failure, syncope, orthostatic hypotension), EKG (pseudoinfarction, microvoltage) and echocardiography signs (restrictive cardiomyopathy). Amyloidosis etiology is suggested by echocardiographic findings such as thickening of the IVS, which appears granular and sparkling (Maleszewski 2015; Kourelis et al 2015). These elements were present in our patient's case. To establish the positive diagnosis it is necessary to perform a cardiac MRI and biopsy of the rectal and oral mucosa as well as of the subcutaneous fat, examinations that were performed in our patient and confirmed the diagnosis (Di Bella et al 2014).

In amyloidosis patients it is important to determine the amyloidosis type because the clinical manifestations and the prognosis depend on the source of the protein that generates the amyloidosis (Flodrova et al 2018; Li et al 2018; Chen et al 2018). Risk group evaluation is based on NT pro BNP and systolic blood pressure (SBP). Our patient belonged to the moderate risk group (NT-proBNP < 8500 ng/L and SBP < 100 mm Hg) (Kumar et al, 2012).

The therapeutic approach is based on the treatment of the cardiac failure and of the MM. The treatment of the MM was administered according to international protocols, including new agents (proteasome inhibitors), cyclophosphamide, corticoid therapy (Nuvolone et al 2018).

Patients survival with MM and secondary systemic amyloidosis is appreciated to be 1-2 years, while in amyloidosis associated with heart failure, the survival is 4-6 months (Drew et al 2010).

## Conclusions

The prognosis for amyloidosis patients can be improved by an early-as-possible diagnosis which should allow for an early initiation of the specific treatment. In our case, the diagnosis was made in the last stage of the disease because of the late presentation of the patient, when she had systemic involvement. The suspicion of cardiac amyloidosis was suggested by the clinical and paraclinical examinations (ECG, echocardiography, and cardiac MRI). The final diagnosis was established following the histopathological and haematological examinations.

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### Citation

Chiorescu RM, Stoia MA, Pârvu A, Georgiu C, Barta A, Chiorescu S, Manole S. Cardiac amyloidosis in a patient with multiple myeloma. *HVM Bioflux* 2018;10(4):196-199.

### Editor

Ștefan Cristian Vesa

### Received

6 November 2018

### Accepted

16 November 2018

### Published Online

16 December 2018

### Funding

None reported

### Conflicts/ Competing Interests

None reported