Isolated cardiac amyloidosis. Utility of bone seeking tracers scintigraphy in differentiating the subtype of amyloid: A case report

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Background. **Three types of amyloid are responsible for cardiac amyloidosis. Differentiation of the subtype is critical for the disease progression and the therapeutic decision.**

Results. **Myocardial scintigraphy using Tc-PYP is able to differentiate the cardiac amyloid subtype with high sensitivity and specificity. The myocardial uptake of PYP is higher in patients with TTR amyloidosis.**

Conclusion. **Non-invasive tests for the detection of cardiac amyloidosis, like myocardial scintigraphy with bone seeking tracers, can play a major role in the diagnosis progression and therapeutic management of patients with cardiac amyloidosis.**

Key Words: Heart failure • SPECT • ^{99m}Tc

Abbreviations			
ATTR	Transthyretin-related amyloidosis	RV	Right ventricular
SSA	Senile systemic amyloidosis	LV	Left ventricular
AL	Light chain amyloidosis	H/CL	Heart to contralateral
CMRI	Cardiac magnetic resonance imaging	PYP	Pyrophosphate
TTE	Transthoracic echocardiogram	ATTRm	Hereditary transthyretin amyloidosis

INTRODUCTION

Cardiac amyloidosis is an infiltrative cardiomyopathy, caused by the deposition of insoluble fibrils in the myocardium. Clinically, signs and symptoms of cardiac amyloidosis often overlap with other causes of heart failure and electrocardiographic and echocardiographic findings may be not specific. Endomyocardial biopsy remains the gold standard for the definitive diagnosis. However, there is a need of non-invasive imaging modalities that can diagnose cardiac amyloid, differentiate subtypes, quantify the extent of infiltration, and monitor disease progression and response to treatment.[1–3]

We describe a case of cardiac amyloidosis in an elderly man who initially presented with worsening dyspnea and first revealed left bundle branch block. ^{99m}Tc PYP scintigraphy showed the significant uptake in the myocardium and the ATTR subtype of cardiac amyloidosis by qualitative and semiquantitative analysis, respectively.

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CASE REPORT

A 76-year-old man with a history of hypertension referred to the cardiologist with worsening dyspnea over the last one year. He had no family history of cardiovascular disease. His functional status was estimated to be New York Heart Association Class II (NYHA II).

An electrocardiogram (ECG) revealed sinus rhythm, HR 100 bpm, and left bundle branch block. A transthoracic echocardiogram (TTE) showed diastolic dysfunction, normal systolic function (preserved ejection fraction 60%), concentric left ventricular hypertrophy with intraventricular diastolic septal thickness 19 mm with granular sparkling, increased RV wall thickening, biventricular small chambers, and severe biatrial dilation (Figure 1).

Doppler-derived LV diastolic filling demonstrated a restrictive pattern with a trans-mitral early filling wave declaration time of 158 ms and an elevated E/A ratio 2:1 (Figure 2).

Due to these findings, a diagnosis suggestive of cardiac amyloidosis was considered probable. The patient underwent a complete work-up for systemic amyloidosis, serum protein electrophoresis, 24-hour urine protein electrophoresis, free light chain ratio, biochemical, and hematological analysis. No abnormal findings revealed. The next step was an abdominal fat biopsy with no presence of amyloid. One year later, the patient underwent a salivary gland biopsy that was also negative for amyloid deposits. A diagnosis of isolated cardiac amyloidosis was considered and a further work-up was performed. The patient underwent cardiac magnetic resonance imaging (CMRI). A delayed contrast enhancement (DCE), as a result of slow washout of gadolinium from the damaged myocardium was revealed, giving a differential diagnosis between cardiac amyloidosis and cardiomyopathies. Myocardial biopsy followed and amyloid deposits were found. However, immunohistochemical study of the biopsied tissue failed to identify the amyloid type.

Myocardial scintigraphy using ^{25m}Ci ^{99m}Tc-PYP was performed in order to establish the type of amyloidosis. Planar image of anterior thorax with the heart centered in the field of view was obtained 1 hour post injection with a dual head Philips Forte Jet Stream γ camera. A semiquantitative visual scoring of cardiac retention (0: absent cardiac uptake, 1: mild uptake less than bone, 2: moderate uptake equal to bone, 3: high uptake greater than bone), and a semiquantitative analysis of heart retention was calculated by drawing a

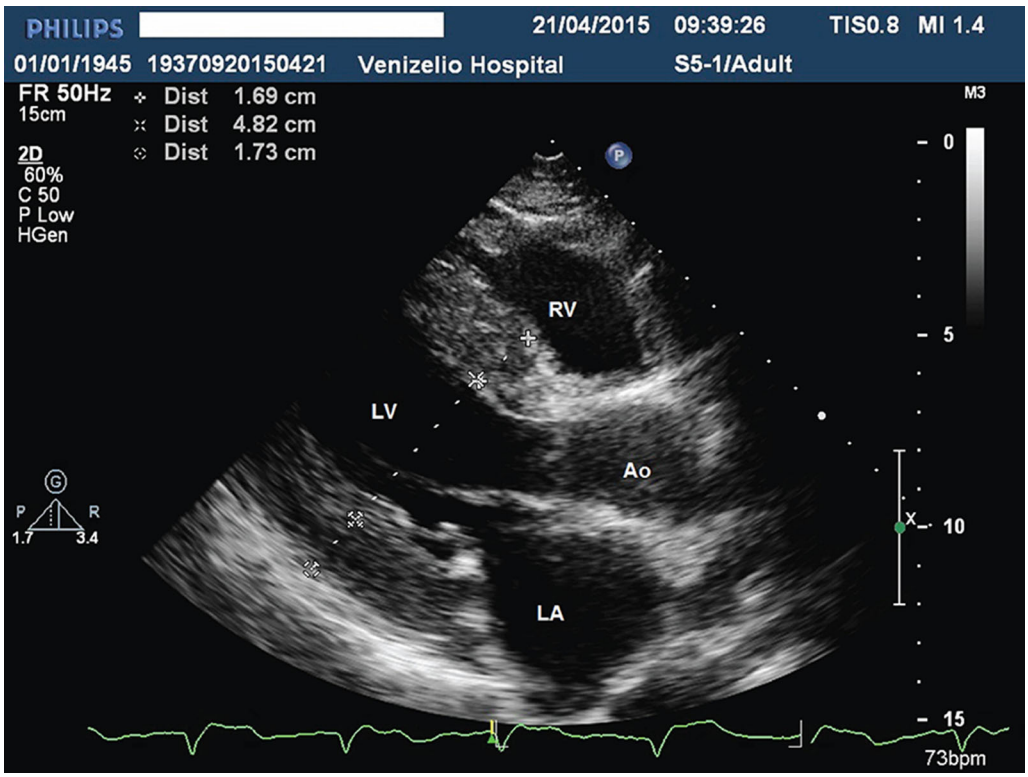

Figure 1. Transthoracic echocardiogram shows concentric LV hypertrophy with the typical granular sparkling texture, especially in the interventricular septum. *LA*, left atrium; *LV*, left ventricle; *RA*, right atrium; *RV*, right ventricle.

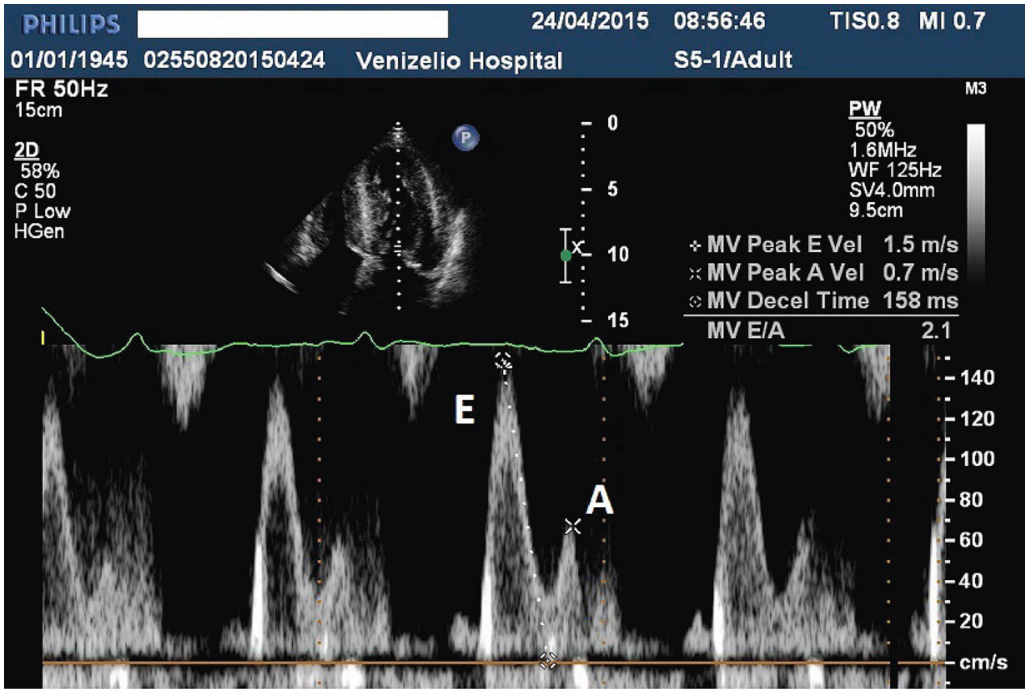

Figure 2. Doppler-derived LV diastolic filling showed a trans-mitral early filling wave declaration time of 158 ms and an elevated E/A ratio 2:1.

region of interest (ROI) over the heart and on the contralateral chest. The fraction of mean counts in the heart ROI-to-contralateral chest ROI was calculated as the heart-to-contralateral (H/CL) ratio (Figure 3). In this patient, scintigraphic findings revealed a very intensive tracer uptake in the heart region compared to bone tissue (score 3). The (H/CL) ratio was 1,9 (reference value $>$ 1,5). The above findings were suggestive of transthyretin-related (TTR) cardiac amyloidosis.

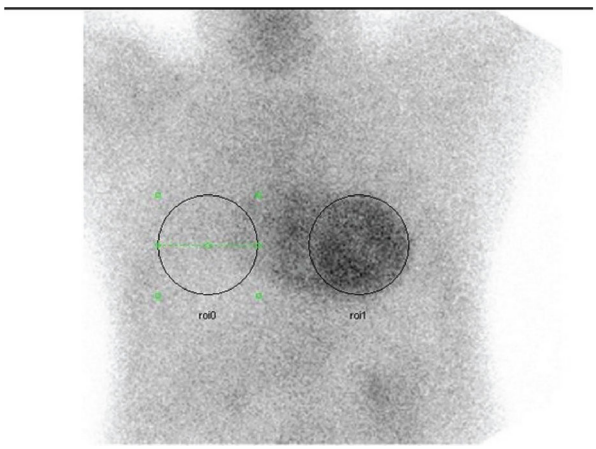

Figure 3. ^{99m}Tc-PYP planar myocardial imaging, taken at 1 hour after injection, revealed diffuse intense ^{99m}Tc-PYP uptake (score 3). Quantitative analysis of heart retention → (H/CL) ratio = 1,9. *H*, heart; *CL*, contralateral.

The management of the patient was symptomatic and the therapy included only diuretics. Two years later, the patient presented with progressive dyspnea on exertion and lower extremity edema. He was classified as New York Heart Association Class III (NYHA III) and there was no significant differentiation of his therapy.

DISCUSSION

Amyloidosis is a systemic or localized disease, characterized by extracellular deposition of anomalous fibrillar proteins in a variety of tissues. Amyloid deposits cause both tissue architecture disruption and direct cytotoxic effects due to the amyloidogenic precursor proteins.[1]

Cardiac amyloidosis is an underappreciated and underdiagnosed cause of heart failure.[2] Three types of amyloid with different clinical courses are responsible for the majority of cardiac involvement (1) light chain (AL) amyloidosis, (2) senile systemic amyloidosis (SSA), and (3) hereditary forms caused by a mutation of TTR (TTRm). Differentiation of the subtype of cardiac amyloidosis is critical for the therapeutic decision.[3]

Cardiac amyloid infiltration affects the systolic-diastolic function, the microvascular flow distribution, and the electrical conduction. Amyloid fibrils are

concentrated in the ventricles and atria, perivascularly and in the valves.[1] In AL amyloidosis, amyloid is produced from clonal light chains. The heart is affected in close to 50% of cases. It has rapid progression and median survival < 6 months in untreated patients.[4] ATTRm amyloidosis has a much lower rate of cardiac involvement. The ECG appearance is very similar to advanced AL cardiac amyloidosis, but is associated with less heart failure and a much better long-term survival. The VAL122IL is the commonest mutation of transthyretin seen clinically with heart involvement. Right-sided heart failure predominates.[5] Senil systemic amyloidosis (SSA) results from the cardiac deposition of amyloid derived from wild-type transthyretin and presents as congestive heart failure. Non-cardiac involvement is rare. It is thought to be an aging-related disorder, similar to AB deposition in the brain, is almost exclusively a disorder of men > 70 years old, with a median of survival 7,5 years from the onset of heart failure. Right-sided or biventricular heart failure, left ventricular thickening with normal ventricular cavity size, atrial fibrillation, bifascicular block on the ECG, and progression to complete AV block are common findings.[5]

Endomyocardial biopsy remains the gold standard for definitive diagnosis of cardiac amyloid. However, complications appear in 6% of patients with cardiac amyloidosis and include arrhythmia, perforation with pericardial tamponade, accidental arterial puncture, and pneumothorax. However, negative biopsy findings do not rule out amyloidosis because amyloid deposition is often patchy.[6]

Nowadays, various non-invasive tests for the detection of cardiac amyloidosis are used. Echocardiography has been considered the gold standard non-invasive method. The typical findings are the increased LV wall thickness. Patients with ATTR amyloidosis tend to have greater degrees of LV thickness when compared to those with AL amyloidosis. Its sensitivity in early stages of cardiac amyloidosis is low and the definition of amyloid subtypes is not feasible.[7]

Cardiac magnetic resonance imaging (CMRI) can detect amyloid infiltration before wall thickening with the advantage to detect early stages of disease. Although the global subendocardial circumference-delayed contrast enhancement is the most frequent pattern specific for amyloidosis, the focal pattern cannot be considered specific.[1]

Nuclear imaging modalities include bone seeking tracers, tracers for the sympathetic innervation of the myocardium, and amyloid specific tracers.[8] ^{99m}Tc 3,3 diphosphono 1,2-propanodicarboxylic acid (DPD) is the most studied bone seeking tracer for the imaging of cardiac amyloidosis. Its sensitivity and specificity for diagnosing ATTR cardiac amyloidosis are 100% and 88%, respectively.[9] Unfortunately, it is not now available for clinical use due to not approvement by the FDA.[8] ^{99m}Tc pyrophosphate(PYP) was first described in 1983 in patients with cardiac amyloidosis.[10] It is believed that the uptake of pyrophosphate in the myocardium of these patients may be related to high calcium levels in amyloidosis.

Recently, it was described that the myocardial uptake of PYP in patients with ATTR amyloidosis is significantly higher than in patients with AL amyloidosis. The H/CL ratio $> 1,5$ distinguishes ATTR from AL cardiac amyloidosis with a 97% sensitivity and 100% specificity . The higher calcium levels in ATTR hearts, the greater density of small microcalcifications, the long duration over which amyloid deposition is occured may be related with the higher uptake of PYP in ATTR cardiac amyloidosis.[11]

While liver transplantation is the current standard therapy for familial amyloid polyneuropathy (FAP), there are several limitations in cardiac amyloidosis. The progression of cardiac amyloidosis may continue after liver transplantation, because there is continuing deposition of wild-type TTR at extra-hepatic sited, including the heart.[3] Current management remains symptomatic. Supporting therapies include ACE inhibitors, diuretics, cardiovascular medications, and anticoagulation for atrial fibrillation. Biventricular pacing should be a consideration if atrioventricular block occurs.[3,12]

CONCLUSION

Planar myocardial scintigraphy using ^{99m}Tc PYP could be able to establish the diagnosis of cardiac amyloidosis and to provide useful information about the cardiac amyloidosis subtype and the therapeutic management.

Disclosure

O. Bourogianni, E. Papadaki, E. Foukarakis and S. Koukouraki as authors of this case report have nothing to declare.

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