ISSN 2692-5877
DOI: 10.46998/IJCMCR.2022.23.000563

International Journal of
Clinical Studies & Medical Case Reports

Case Report

# Wild-Type Transthyretin Cardiac Amyloidosis: A Portuguese Case Report

**Fábia Cruz[1],*, Diana Brites[2], Sara Sintra[3] and Maria Eugénia André[4]**

*[1]Resident, Department of Internal Medicine, Centro de Responsabilidade Integrada de Medicina Interna, Hospital Amato Lusitano, Unidade Local de Saúde de Castelo Branco, Portugal*

*[2]Resident, Department of Internal Medicine, Centro de Responsabilidade Integrada de Medicina Interna, Hospital Amato Lusitano, Unidade Local de Saúde de Castelo Branco, Portugal*

*[3]Hospital Assistant, Department of Internal Medicine, Centro de Responsabilidade Integrada de Medicina Interna, Hospital Amato Lusitano, Unidade Local de Saúde de Castelo Branco, Portugal*

*[4]Senior Graduate Assistant, Department of Internal Medicine, Centro de Responsabilidade Integrada de Medicina Interna, Hospital Amato Lusitano, Unidade Local de Saúde de Castelo Branco, Portugal*

***Corresponding author:** Fábia Cruz, Resident, Department of Internal Medicine, Centro de Responsabilidade Integrada de Medicina Interna, Hospital Amato Lusitano, Unidade Local de Saúde de Castelo Branco, Portugal

**Received:** December 07, 2022 **Published:** December 28, 2022

## Abstract

Formerly a rare disease, cardiac amyloidosis has been progressively recognized due to advanced diagnostic techniques and increased suspicion among clinicians.

The authors present a 76-year-old male with comorbidities, progressive signs and symptoms and laboratorial, electrocardiographic, echocardiographic, cardiac magnetic resonance with gadolinium contrast, scintigraphy and genetic study findings in favor of wild-type transthyretin cardiac amyloidosis. After the diagnosis the patient started tafamidis and he was referred to a cardiac amyloidosis center.

Through this case report, the authors want to highlight the diagnostic evaluation of cardiac amyloidosis.

**Keywords:** Amyloidosis; Hypertrophic cardiomyopathy; Carpal Tunnel Syndrome; Atrial Fibrillation; Tafamidis

## Introduction

Although considered a rare disease, recent data suggest that cardiac amyloidosis is underappreciated as a cause of common cardiac diseases or syndromes. Recent advances in cardiac imaging, diagnostic strategies and therapies have improved the recognition and treatment of cardiac amyloidosis [1].

A prompt diagnosis is essential to enable timely treatment, as therapy is more effective in the early stages of the disease [1].

## Case Presentation

The authors report the case of a 76-year-old male with atrial fibrillation, arterial hypertension, lumbar spinal stenosis and family history of sudden death of his father and brother at 60 and 40 years, respectively. During the last year the patient reported increasing tiredness with small efforts, orthopnea, swollen lower extremities, skin bruising and decreased sensibility of both hands. At the outpatient clinic the patient presented with jugular vein distention, hepatojugular reflux, irregular S1 and S2 cardiac auscultation, rales on right basal lung auscultation, abdominal distention and lower extremity edema.

Electromyography showed serious bilateral median nerve compression at carpal canal suggesting bilateral carpal tunnel syndrome. Echocardiogram showed bi-atrial dilatation (left atrial 50.4ml/m2, right atrial 32ml/m2), concentric left ventricular hypertrophy (posterior wall thickness 19mm and intraventricular septal thickness 20.8mm), mild aortic stenosis (1.53cm2), granular sparkling texture of the myocardium, preserved ejection fraction (54%), reduced global longitudinal left ventricular strain (-10%), Doppler E/e' ratio of 18.86 and TAPSE of 14.13mm **(Figure 1)**. Abdominal ultrasound showed a small amount of ascites. Electrocardiogram (ECG) showed atrial fibrillation, low QRS voltage, Q waves in V1-V2 and ventricular extrasystoles **(Figure 2)**. Serum free light chain ratio was normal and serum and urine immunofixation electrophoresis was negative for monoclonal paraproteins. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was elevated with 9856.00pg/mL, as was cardiac troponin with 350ng/L. He had a proteinuria of 137.3mg/24h. An abdominal fat-pad biopsy was negative for Congo red stain.

Cardiac Magnetic Resonance imaging (CMR) with gadolinium contrast revealed concentric left ventricular hypertrophy (14mm), mild interatrial septum hypertrophy (5mm), bi-atrial dilatation, diffuse subendocardial late gadolinium enhance-





DOI: 10.46998/IJCMCR.2022.23.000563

ment in ventricular and atrial walls and right pleural effusion **(Figure 3)**. 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scintigraphy revealed intense cardiac uptake grade 3: myocardial uptake greater than bone with reduced bone uptake **(Figure 4)**.

Based on the patient's comorbidities, signs and symptoms with laboratorial, ECG, echocardiogram, CMR and scintigraphy findings, with absence of monoclonal proteins, the diagnosis of transthyretin cardiac amyloidosis was done. Genetic study, to distinguish hereditary from wild type protein, confirmed the absence of mutations in c.128G>A p.(Ser43Asn). c.142G>A p.(Val48Met) and c.148G>A p.(Val50Met). Thereby, final diagnosis was wild-type transthyretin cardiac amyloidosis.

After 6 months of his first internal medicine consultation the patient initiated tafamidis and was referred to a cardiac amyloidosis center. Meanwhile, carpal tunnel decompression was done.

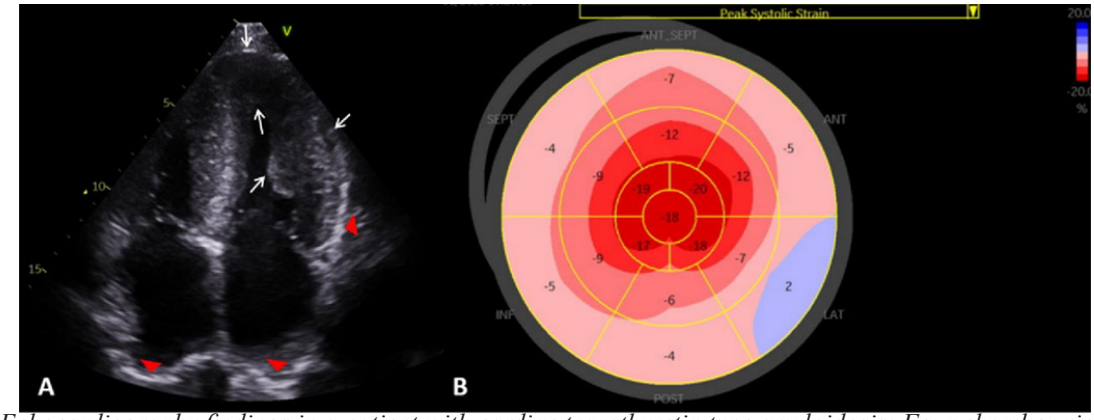


*Figure 1: Echocardiography findings in a patient with cardiac transthyretin type amyloidosis: Four chamber view (A) showing granular sparkling texture of the myocardium (red arrow head), concentric left ventricular hypertrophy (white arrows) and atrial dilatation. (B) Left ventricular longitudinal strain.*

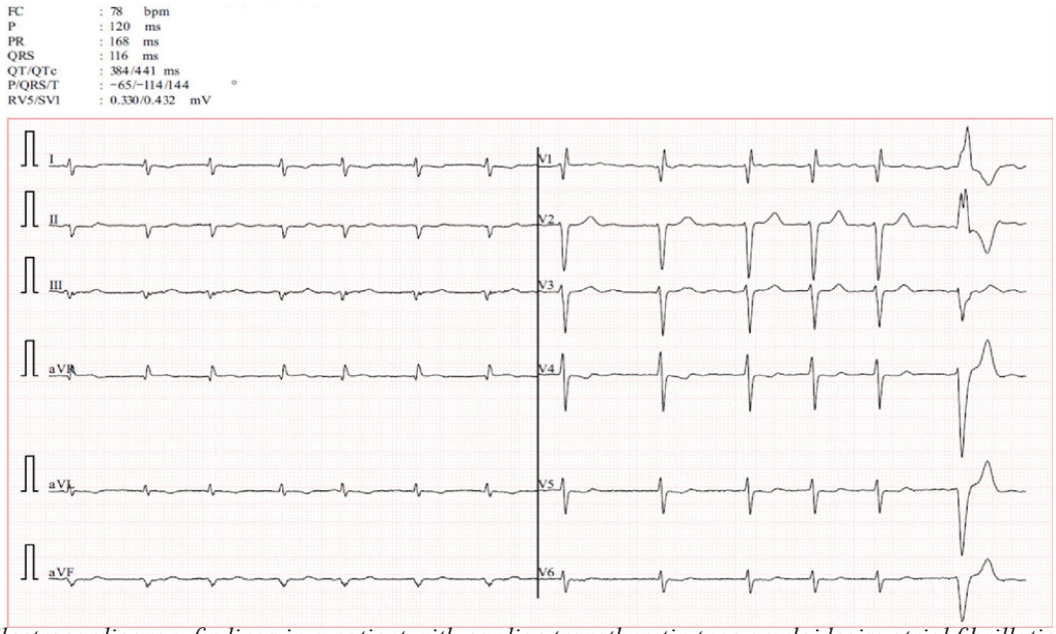


*Figure 2: Electrocardiogram findings in a patient with cardiac transthyretin type amyloidosis: atrial fibrillation, decreased QRS voltage to degree of left ventricular thickness in V1 and Q waves in V1-V2.*

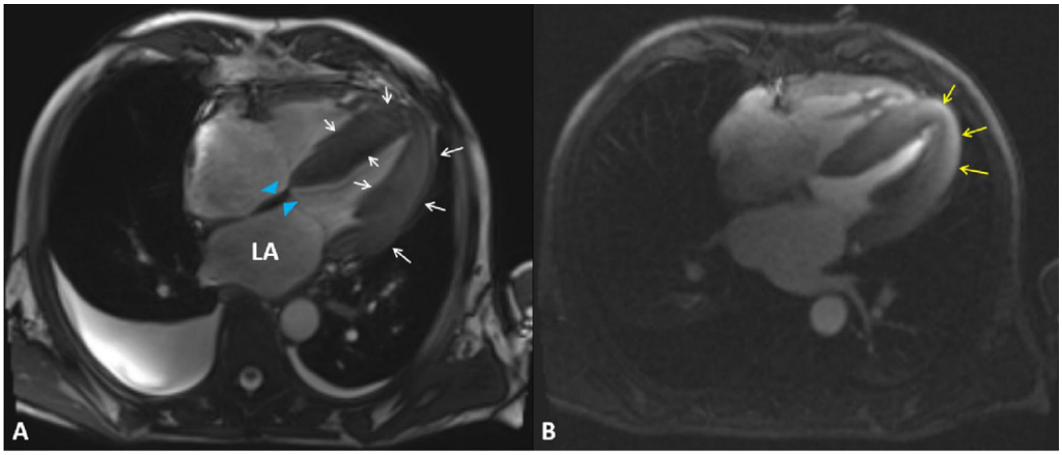


*Figure 3: Cardiac magnetic resonance with gadolinium contrast findings in a patient with cardiac transthyretin type amyloidosis: Axial view (A) showing concentric left ventricular hypertrophy (14mm) (white arrows), interatrial septum hypertrophy (5mm) (blue arrow head) and atrial dilatation (left atrium with 34 cm2); (B) Diffuse subendocardial late gadolinium enhancement (yellow arrows) in left ventricular wall.*

**Citation:** Fábia Cruz*, Diana Brites, Sara Sintra and Maria Eugénia André. Wild-Type Transthyretin Cardiac Amyloidosis: A Portuguese Case Report. *IJCMCR. 2022; 23(3): 003*

**DOI:** *10.46998/IJCMCR.2022.23.000563*

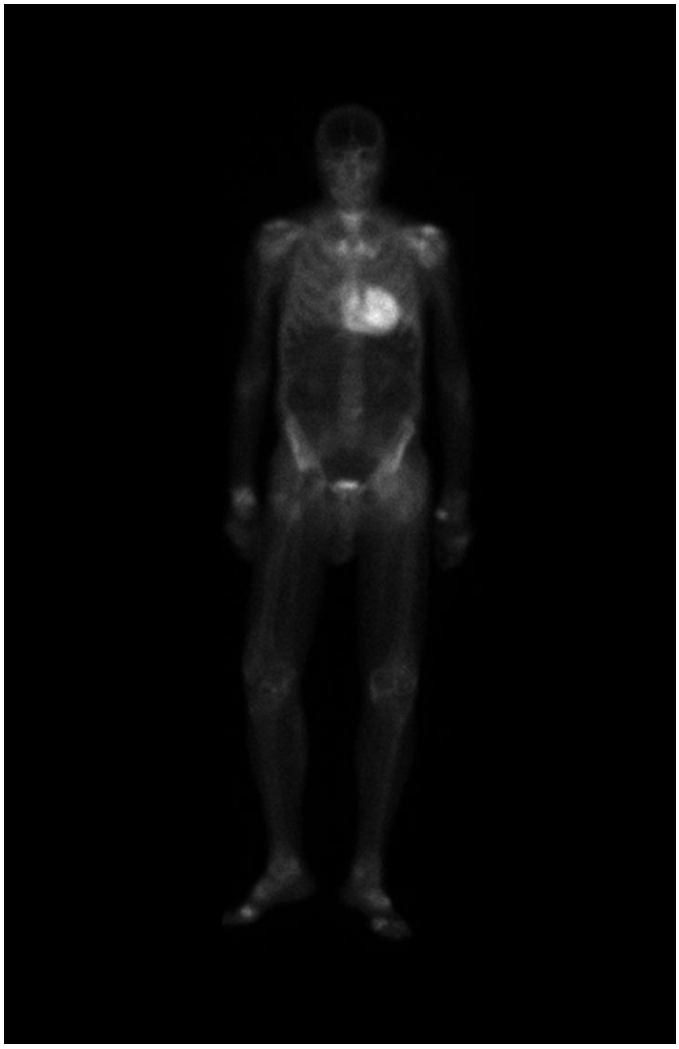

*Figure 4: 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scintigraphy findings in a patient with cardiac transthyretin type amyloidosis: Grade 3 - myocardial uptake greater than bone with reduced bone uptake.*

## Discussion

Cardiac Amyloidosis (CA) is a progressive, potentially fatal and infiltrative cardiomyopathy caused by extracellular deposition of transthyretin-derived insoluble amyloid fibrils in the myocardium [1-4].

The infiltrative process results in biventricular wall thickening with concentric ventricular remodeling and low cardiac output. The subsequent elevation of pressure in the atria is associated with atrial dilatation. The conduction system is also frequently disrupted, with atrial arrhythmias and atrioventricular conduction delays being common [5].

The two most prevalent forms of CA are: light chain immunoglobulin (AL) and transthyretin (ATTR) amyloidosis [5, 6]. ATTR includes the wild-type (>90% of cases) and the hereditary or variant type (<10% of cases) [6].

Wild-type ATTR-CA is almost exclusively a disease of older adults with male preponderance [7]. 16% of patients with severe aortic stenosis undergoing aortic valve replacement have transthyretin cardiac amyloidosis [8,9].

Age >65 years and heart failure along with a left ventricular wall thickness > or =12mm at echocardiography are major criteria for the suspicion of CA [6].

Cardiac amyloidosis typically appears within a constellation of extracardiac signs and symptoms: involvement of soft tissues leads to an increased incidence of bilateral carpal tunnel syndrome, spinal stenosis or spontaneous biceps tendon rupture [7], as well as proteinuria, peripheral polyneuropathy, dysautonomia, macroglossia, deafness and skin discoloration and bruising [1].

Cardiac involvement in amyloidosis typically presents with heart failure symptoms and signs with prominent features of right ventricular failure (peripheral congestion) including lower extremity edema, jugular vein distention, hepatic congestion, ascites and dyspnea [4]. Possible family history may also raise suspicion [1].

In addition, NT-proBNP may be disproportionately high (> 3000 pg/mL) due to direct compression of cardiomyocytes and stress caused by raised filling pressures and troponin elevation (> 0.05 ng/mL) may be persistent. On ECG, the findings are a decreased QRS voltage to mass ratio, pseudo-Q waves and AV conduction disease. On echocardiogram, granular sparkling texture of the myocardium, atrial dilatation, pericardial effusion, aortic stenosis, increased wall and valve thickness, preserved ejection fraction, reduced global longitudinal left ventricular strain (< -15%), Doppler E/e' ratio >11 and TAPSE ≤19mm can be found. On CMR, there is a subendocardial/transmural late gadolinium enhancement or increased extracel-

lular volume [1, 5].

Early recognition remains essential to afford the best treatment efficacy [7]. A timely definitive diagnosis should be obtained as patient outcomes depend largely on early initiation of therapy [1].

Invasive diagnostic criteria apply to all forms of cardiac amyloidosis whereas non-invasive criteria are accepted only for ATTR [1]. Cardiac ATTR amyloidosis can be diagnosed in the absence of histology in the setting of typical echocardiographic/CMR findings when radionuclide bone scintigraphy shows Grade 2 or 3 myocardial uptake of radiotracer (Grade 2: similar myocardial and bone uptake. Grade 3: myocardial uptake greater than bone with reduced/absent bone uptake) and clonal dyscrasia is excluded (by all the following tests: serum free light chain assay, serum and urine protein electrophoresis with immunofixation) [1].

Scintigraphy has a specificity and positive predictive value for TTR-CA of up to 100% (able to identify pre- symptomatic disease) [5,6]. In contrast, CMR has a sensitivity and specificity of 85% and 92%, respectively [6].

Treatment of CA involves two areas: treatment and prevention of complications and comorbidities, the most common are aortic stenosis, heart failure, thromboembolism, atrial fibrillation, conduction disorders and ventricular arrhythmias. and stopping or delaying amyloid deposition by specific treatment [1]. Tafamidis should be generally considered the agent of choice in wtTTR-CA patients because it reduced all- cause mortality and cardiovascular hospitalizations, mainly in those patients with NYHA class I and II at baseline. [1, 6]. Functional improvement occurred within 6 months, whereas the decrease in mortality took nearly 2 years to occur [6].

Advances in cardiac imaging and improved awareness among physicians have facilitated the diagnosis of cardiac amyloidosis over the last decade. Involvement of the heart in the setting of amyloidosis carries an adverse prognosis. Timely diagnosis is of the greatest importance for appropriate treatment modalities that may crucially modify the natural history of the disease [4].

In this case, the patient (>65-year-old male) showed multiple signs and symptoms during the last year with negative serum free light chains, negative serum and urine immunofixation and negative ATTR mutation in association with laboratorial, electrocardiographic, echocardiographic, cardiac magnetic resonance with gadolinium contrast and scintigraphy findings in favor of wild-type transthyretin cardiac amyloidosis. After the diagnosis the patient started tafamidis and he was referred to a cardiac amyloidosis center.

## Conclusion

Cardiac amyloidosis, which has previously been underrecognized and considered to be rare, has been increasingly recognized as a cause of heart failure with preserved ejection fraction among elderly patients, changing its course from incurable to treatable [2].

It is crucial for clinicians to be aware of this clinical entity for early diagnosis and proper treatment [2].

## Learning Points

1. Cardiac amyloidosis should be suspected in age >65 years and heart failure along with a left ventricular wall thickness > or =12mm at echocardiography;
2. Cardiac ATTR amyloidosis can be diagnosed in the absence of histology in the setting of typical echocardiographic/CMR findings when radionuclide bone scintigraphy shows Grade 2 or 3 myocardial uptake of radiotracer and clonal dyscrasia is excluded;
3. Timely diagnosis is importante for appropriate treatment modify the natural history of the disease;

**Patient's consent:** Written informed consent was obtained for the publication in this case report and accompanying images;
**Funding:** The authors declare that no funding was received for this article;
**Declaration of Competing Interest:** None of the authors have any conflicts of interest to disclosure
**Authors Contribution:**
Fábia Cruz: acquisition of data, drafting the article and literature revision
Diana Brites: acquisition of data and literature revision
Sara Sintra: critical revision
Maria Eugénia André: guarantor

## References

1. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, et al; Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diasease, 2021; 42(16): 1554-1568.
2. Yamamoto H, Yokochi T. Transthyretin cardiac amyloidosis: an update on diagnosis and treatment; European Society of Cardiology Heart Failure, 2019; 6: 1128-1139.
3. Manolis A, Manolis TA, Melita H. Cardiac amyloidosis: An underdiagnosed/underappreciated disease; European Journal of Internal Medicine, 2019; 67: 1-13.
4. Papingiotis G, Basmpana L, Farmakis D. Cardiac amyloidosis: epidemiology, diagnosis and therapy. E- Journal of Cardiology Practice, 2021; 19: 19-21.
5. Martinez-Naharro A, Hawkins PN, Fontana M. Cardiac amyloidosis. Clinical Medicine, 2018; 18(2): 30-35.
6. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal, 2021; 42(36): 3599-3726.
7. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. Journal of the American College of Cardiology, 2019; 73(22): 2872-2891.
8. Fabbri G, Serenelli M, Cantone A, Sanguettoli F, Rapezzi C. Transthyretin amyloidosis in aortic stenosis: clinical and therapeutic implications. European Heart Journal Supplements, 2021; 23: 128-132.
9. Penalver J, Ambrosino M, Jeon HD, Agrawal A, Kanjanahattakij N, Pitteloud M, et al. Transthyretin Cardiac Amyloidosis and Aortic Stenosis: Connection and Therapeutic Implications. Current Cardiology Reviews, 2020; 16: 221-230.