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Case Report

Wild-Type Transthyretin Cardiac Amyloidosis, Atypical Presentation. Case Report

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Abstract: Cardiac amyloidosis is characterized by the extracellular deposition of misfolded proteins. Currently, there are more than 30 proteins that can form amyloid fibrils in vivo, 9 of which accumulate in the myocardium. A 70-year-old male with a history of supraventricular tachycardia, type 2 diabetes, systemic arterial hypertension, and prostatic adenocarcinoma. As part of the treatment for bone metastases due to a history of cancer, a Tc99m methylenediphosphonate bone scan was performed, revealing an abnormal increase in myocardial bone turnover. A technetium-99 (Tc99) and pyrophosphate cardiac scan was performed, yielding a positive result for infiltrative process (AC-ATTR), Perugini 3, and H/CL ratio of 1.52. Based on cardiac scan findings of infiltrative process, absence of a polyclonal light chain spike, and a negative ATTR gene, the diagnosis of ATTRwt cardiac amyloidosis was reached.

Keywords: Amyloidosis, Transthyretin, Wild-Type.

INTRODUCTION

Systemic amyloidosis is a broad spectrum of diseases resulting from the misfolding of proteins that aggregate into amyloid strands in sheets [2]. This deposition of large amounts of amyloid fibrils can alter tissue architecture and cause organ dysfunction [1].

In cardiac amyloidosis (CA), this extracellular deposition of misfolded proteins has the pathognomonic histological property of green birefringence when observed under cross-polarized light after staining with Congo red. These proteins have an unstable structure, causing misfolding, aggregation, and deposition. Currently, there are more than 30 proteins that can form amyloid fibrils in vivo, of which 9 accumulate in the myocardium, and classification is based on the precursor protein [3,4].

CLINICAL CASE

We present the following case of a 70-year-old male, a retired teacher, with no significant family history. His personal medical history includes an episode of supraventricular tachycardia 20 years ago, with no current follow-up or treatment, a diagnosis of type 2 diabetes and systemic arterial hypertension since 2020 under control, and prostatic adenocarcinoma since 2019, which required total prostate resection.

His current condition began in January 2023, where, due to the approach for bone metastases due to a history of cancer, a bone scan with technetium-99 (Tc99) methylenediphosphonate was performed, which detected an abnormal increase in myocardial bone turnover related to amyloidosis.

On physical examination, the patient's blood pressure was 110/75 mmHg, heart rate was 54 beats per minute, respiratory rate was 20 per minute, and SpO2 was 92%. He was conscious and oriented, with no jugular vein engorgement. At the cardiovascular level, the patient showed a precordium with apical shock at the level of the fifth intercostal space and the left clavicular midline. Heart sounds were rhythmic, with S1 and S2 sounds present, adequate intensity, and decreased frequency. No murmurs or other aggregates were auscultated.

A 12-lead electrocardiogram showed sinus rhythm, a heart rate of 55 beats per minute, a QRS axis of 60°, a PR interval of 140 ms, and a QRS complex of 80 ms. There were no signs of ventricular enlargement. He had a repolarization disorder in the left ventricle, a QT interval of 450 ms, and a QTc of 426 ms.

Transthoracic echocardiography showed a non-dilated left ventricle with concentric hypertrophy, a 15 mm septum, inferoseptal, anterolateral, anterior, inferior, and inferoseptal hypokinesia, with a left ventricular ejection fraction of 47%. LV Sparklin was observed, global longitudinal strain -16.4%, and grade I diastolic dysfunction **(Figure 1 y 2)**.

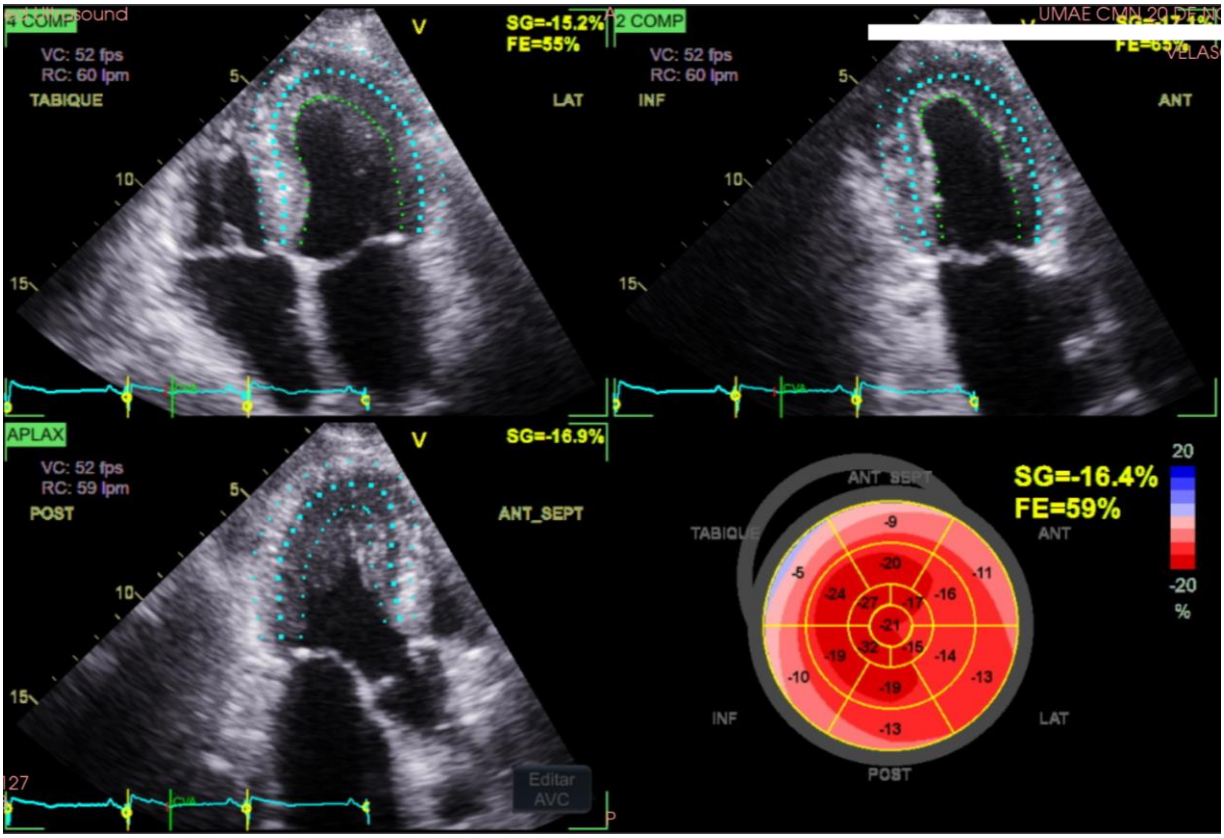

Figure 1: Apical four-chamber, two-chamber, and three-chamber views, to obtain longitudinal tension, show the "cherry-on-top" image, reflecting the decrease in tension at the basal and middle segments. A characteristic pattern of cardiac amyloidosis

The most significant initial laboratory studies showed Lambda light chains 17.8 mg/L, Kappa light chains 23 mg/L, Kappa/lambda ratio 1.29, NT-proBNP 128 pg/ml, and ATTR gene sequencing was negative.

A cardiac magnetic resonance imaging (MRI) was performed, revealing 4-chamber right ventricle findings of 36.5 mm diastolic diameter and 27.6 mm systolic diameter, 2.6 mm free wall thickness, 30 mm tricuspid annulus with mild regurgitation, 34.5 mm mitral annulus, mild thickening of its edges, and mild regurgitation. In 3-chamber left ventricle with 44.5 mm diastolic diameter and 31 mm systolic diameter, no alterations in the segmental systolic thickening of the left ventricle were observed, with qualitatively preserved biventricular systolic function. No hyperintensity areas were observed on T2-weighted sequences. On inversion recovery sequences after administration of contrast medium, late enhancement of the ischemic pattern was observed with the following distribution: diffuse global subendocardial predominantly in the basal and middle thirds. The findings included amyloid cardiomyopathy, diffuse late subendocardial enhancement, and mild mitral and tricuspid regurgitation **(Figure 3).**

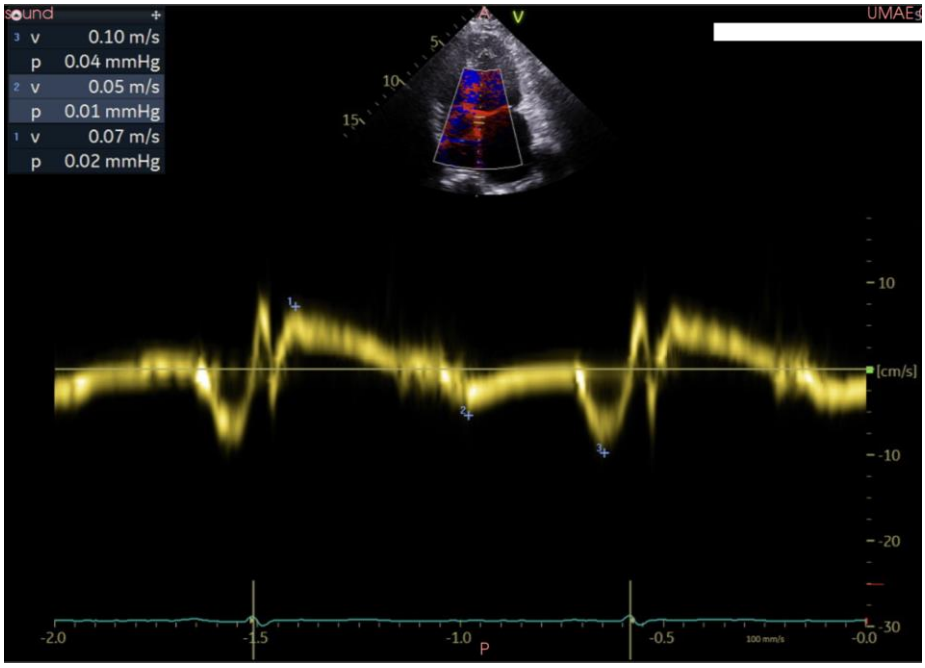

Figure 2: In the apical four-chamber view, tissue Doppler shows a decrease in the septal "e" wave by 5 m/s

To support the diagnostic suspicion, a nuclear medicine study was performed with a Tc99 and pyrophosphate cardiac scan, yielding a positive result for an infiltrative process (AC-ATTR), Perugini 3, and an H/CL ratio of 1.52 **(Figure 4).** Given the imaging findings, the cardiac scan was compatible with an infiltrative process at the cardiac level and the absence of a polyclonal peak with light chains, ruling out the AC-AL subtype, and the ATTR gene was negative. The conclusion was reached: ATTRwt cardiac amyloidosis.

The patient was followed up in an outpatient clinic, followed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) and cardiopulmonary exercise testing (CPET). The patient reported New York Heart Association (NYHA) functional class I. Therefore, it was decided to start tafamidis 61 mg every 24 hours.

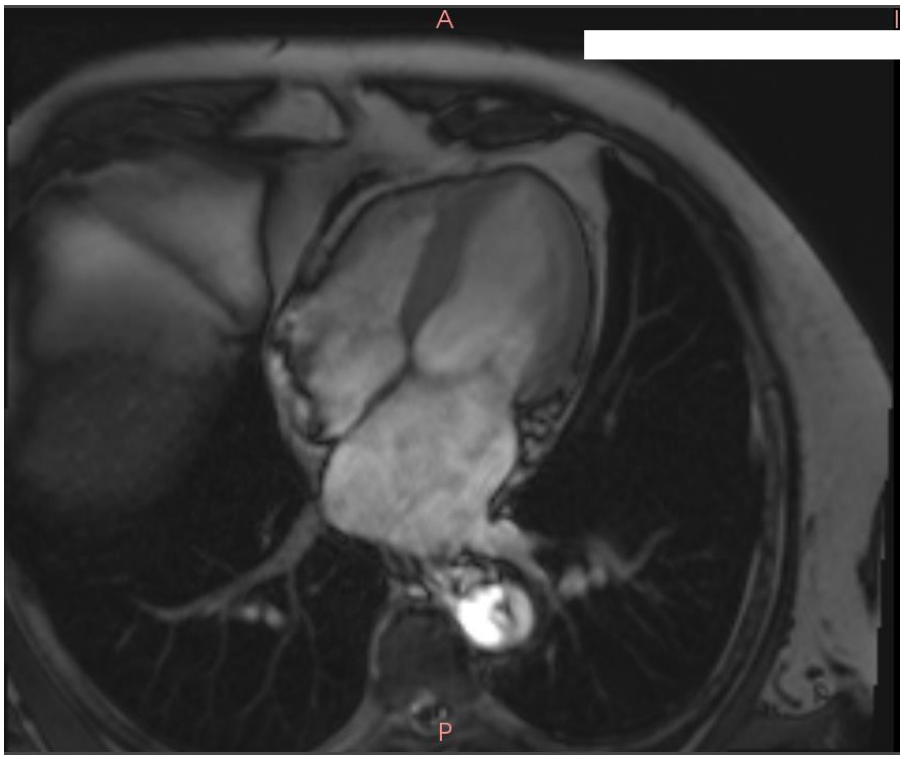

Figure 3: Cardiac magnetic resonance imaging in 3-chamber cine, showing thickening at the level of the interventricular septum, characteristic of cardiac amyloidosis

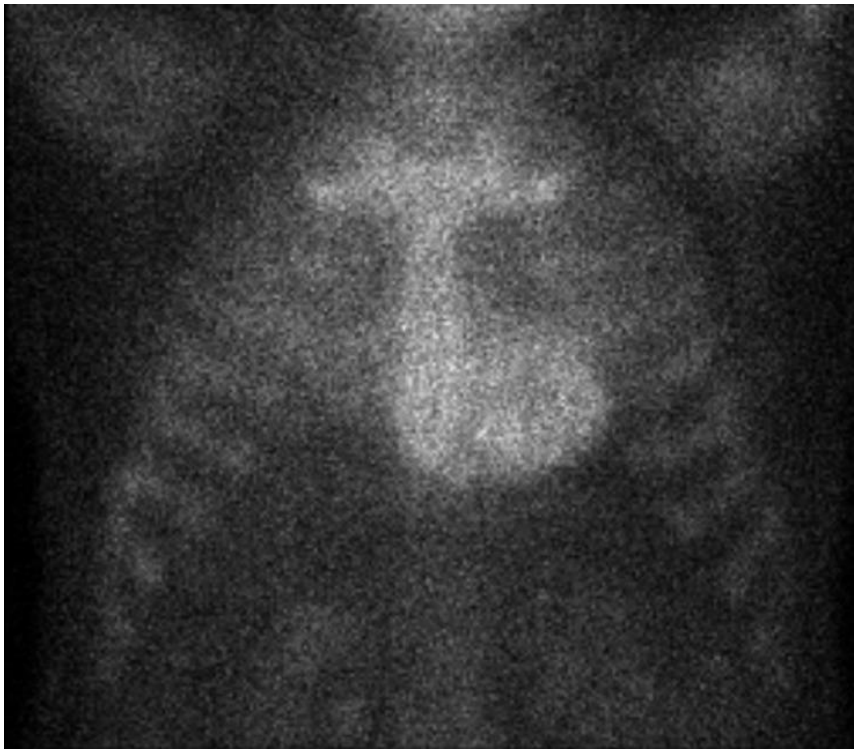

Figure 4: Cardiac scan with Tc99 and pyrophosphates. Perugini 3, H/CL index 1.52

DISCUSSION

AC causes a wide range of symptoms, and the condition is classified into two main types: transthyretin cardiac amyloidosis (ATTR-AC), which in turn has two subtypes: hereditary (ATTRh) and wild-type (ATTRwt), and immunoglobulin light chain cardiac amyloidosis (ILC-AC) [6].

Although considered a rare disease, recent data suggest that cardiac amyloidosis is underestimated as a cause of common cardiac diseases or syndromes [3].

In Mexico and Latin America, the clinical and genetic characteristics of subjects with ATTR were published in 2017 by the THAOS (Transthyretin Amyloidosis Outcomes Survey) group. Data from 2,887 subjects from Mexico, Argentina, and Brazil were reviewed. It was observed that the male/female ratio was close to 50%, and that genetic variants differed between countries. In Argentina and Brazil, the most common variant was Val30Met, while in Mexico it was Ser50Arg. Regarding the amyloidosis phenotype (neurological, cardiac, or mixed involvement), neurological involvement was the most common in all three countries, followed by the mixed phenotype [10].

The protein transthyretin is responsible for the transport of the thyroid hormone thyroxine (T4) and the retinol (vitamin A) binding protein. It is produced primarily in the liver, but also in the choroid plexus and retinal pigment epithelium. In AC-ATTR, it undergoes pathological misfolding and aggregates into amyloid fibrils and is deposited in multiple tissues, causing irreversible damage [7].

It manifests primarily as cardiomyopathy and polyneuropathy. Cardiomyopathy can cause heart failure, arrhythmia, and death, while ATTR deposition in nerves causes peripheral or small fiber autonomic polyneuropathy. ATTR deposition in the ligaments manifests as carpal tunnel syndrome and cervical or lumbar spinal stenosis [5].

The diagnosis of AC requires a detailed clinical history and physical examination, including laboratory studies and cardiac imaging [6]. The electrophysiological manifestations of AC are poorly understood. Although atrial arrhythmias, particularly atrial fibrillation (AF), are well documented, there is less published data on ventricular arrhythmias and atrioventricular (AV) node disease [8].

Conventional echocardiographic findings indicate that AC should be suspected whenever there is an increase in LV wall thickness ≥12 mm in the absence of other underlying causes or if this finding is disproportionate to the underlying cause. The “typical” increased myocardial echogenicity (“mottled,” “bright,” hyperreflective “texture” of the myocardium) is neither specific nor sensitive for amyloidosis, as it can occur in other causes of hypertrophy, such as end-stage renal

disease and other infiltrative cardiomyopathies. It raises suspicion of CA when combined with severely reduced LV longitudinal function [9].

The most reliable method for diagnosis is tissue biopsy, with the exception of ATTR, which can be diagnosed without a tissue biopsy, provided that certain criteria are met. Periumbilical fat biopsy is commonly used due to its minimally invasive nature, but the main limitation of this procedure is its relatively low diagnostic sensitivity, especially in ATTRwt, and therefore cannot be used to exclude it [7].

Regarding treatment as of 2022, tafamidis is the only drug approved by the US Food and Drug Administration (FDA) for the treatment of ATTR cardiac amyloidosis. It acts as a stabilizer of TTR, slowing its dissociation and, therefore, the formation of fibrils and cardiac deposits. Early diagnosis is crucial, as tafamidis slows disease progression but does not necessarily cause its regression. The FDA-approved doses are tafamidis 61 mg or tafamidis meglumine 80 mg [2].

CONCLUSION

We present the case of an older male patient with AC with an atypical presentation, clinically with NYHA functional class I, diagnosed as an incidental finding. The diagnosis was reached based on cardiac imaging findings, ruling out LA-AC due to normal light chains, and hATTR-AC due to negative ATTR gene sequencing.

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