Is Wild-type Transthyretin Cardiac Amyloidosis Still Considered a Rare Disease?

Luis Enrique Sanchez Siancas[1]
Hospital III Suarez-Angamos Essalud,[1] *Lima – Peru*

Introduction

Amyloidosis is a disease characterized by extracellular deposition of insoluble proteins resulting in organ dysfunction. There are more than 30 known proteins capable of aggregating into amyloid fibrils; among these, amyloidosis due to light chain (AL) immunoglobulin and transthyretin amyloidosis (ATTR) represent 98% of cardiac amyloidosis.[1] Transthyretin (TTR) is a tetrameric protein whose function is to transport thyroxine and retinol-binding protein. It is primarily produced in the liver, with smaller quantities found in the choroid plexus and retinal pigment epithelium.[2]

There are two distinct forms of ATTR: hereditary, caused by pathogenic mutations that destabilize the protein, and acquired, also known as wild-type (wtATTR), which results from the accumulation of wtATTR protein.[3] Regarding clinical manifestations of ATTR, in the case of the hereditary type, they depend on the genetic variant involved and can lead to cardiac and extracardiac involvement, including sensory-motor peripheral neuropathies, autonomic neuropathies, gastrointestinal manifestations, among others. In the case of wtATTR, cardiac involvement is the predominant manifestation, characterized by heart failure, conduction disorders, and arrhythmias.[4] The gold standard for diagnosis of cardiac amyloidosis is the demonstration of apple-green birefringence in polarized light microscopy of Congo red-stained tissue.[5] However, confirmatory biopsy is no longer necessary for a diagnosis when the following criteria are met: heart failure with an echocardiogram or cardiac magnetic resonance imaging consistent with amyloidosis, a grade 2 or 3 uptake on radionuclide scintigraphy with 99m-Technetium-labeled 3,3-*diphosphono-1,2-propanodicarboxylic acid* or pyrophosphate (PYP), and absence of a detectable monoclonal gammopathy.[6] There are currently new disease-modifying therapeutic options available for both hereditary and acquired ATTR. Among the available drugs are selective TTR stabilizers, such as tafamidis, and genetic silencers, such as inotersen or patisiran, which provide the most significant benefit in the early stages of the disease.[7]

Keywords

Amyloidosis; Prealbumin; Rare Diseases.

Mailing Address: Luis Enrique Sanchez Siancas •
Hospital III Suarez-Angamos Essalud. Avenida Angamos Este, 261. Postal code: 15074. Lima – Peru.
E-mail: lesanchezsiancas@gmail.com
Manuscript received June 3, 2024; revised July 4, 2024; accepted July 29, 2024
Editor responsible for the review: Marcelo Tavares

DOI: https://doi.org/10.36660/abcimg.20240050i

Case report

A 62-year-old man without established cardiovascular disease and risk factors was referred to our hospital. He had been experiencing symptoms for the past 5 months, including dyspnea classified as New York Heart Association (NYHA) Class II, paresthesia in the lower limbs, and syncopal episodes.

On physical examination, his blood pressure was 80/50 mmHg, heart rate was 62 beats per minute, respiratory rate was 20 breaths per minute, and oxygen saturation was 97%. There were no signs of peripheral hypoperfusion or edema in the limbs. Vesicular breath sounds were clear in both lung fields with a few crepitations. On cardiovascular examination, rhythmic heart sounds of good intensity were noted, without murmurs or jugular vein distension. The electrocardiogram showed sinus rhythm, left anterior hemiblock, and first-degree atrioventricular block with a PR interval of 240 milliseconds.

Transthoracic echocardiography revealed diffuse left ventricular hypertrophy, with a maximum interventricular septum thickness of 18 mm (Figure 1). Left ventricular ejection fraction (LVEF) and right ventricular systolic function were preserved (LVEF 58%). There was biauricular dilation (indexed left atrial volume 51 mL/m^2, left atrial area 19 cm^2), with mild tricuspid regurgitation. Diastolic dysfunction type III was observed with increased left ventricular filling pressures and a low probability of pulmonary hypertension. Speckle tracking analysis in the left ventricle showed impairment of subendocardial fibers with global longitudinal strain (GLS) of -14%, more pronounced impairment in medial and basal segments, and relative preservation of apical segments (Figure 2). Relative apical sparing (RELAPS) was 1.06, the septal apical-to-base longitudinal strain ratio (SAB) was 12.5, and the ejection fraction-GLS ratio (EFSR) was 4.14.

The measurement of free AL in blood was performed, with a Kappa/Lambda ratio of 0.34, which is within the normal range (0.26-1.65). Cardiac scintigraphy with technetium-99m PYP showed moderate myocardial uptake (Perugini grade 2) (Figure 3). Cardiac magnetic resonance revealed myocardial edema assessed by T2 STIR and T2 mapping sequences, diffuse interstitial fibrosis with an increased extracellular volume of 59%, and diffuse subendocardial fibrosis assessed by late gadolinium enhancement and native T1 mapping (Figure 4). The genetic study yielded negative results for pathogenic variants in the TTR gene.

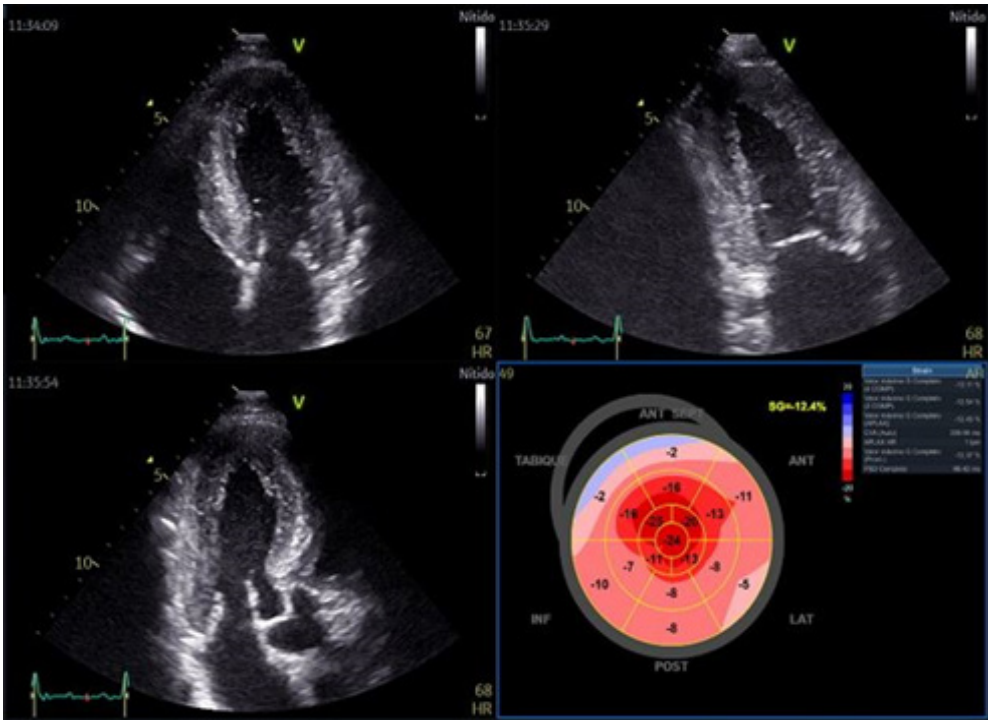

Figure 1 – *Transthoracic echocardiogram showing severe concentric ventricular hypertrophy in apical views and apical sparing in longitudinal strain bull's eye plot.*

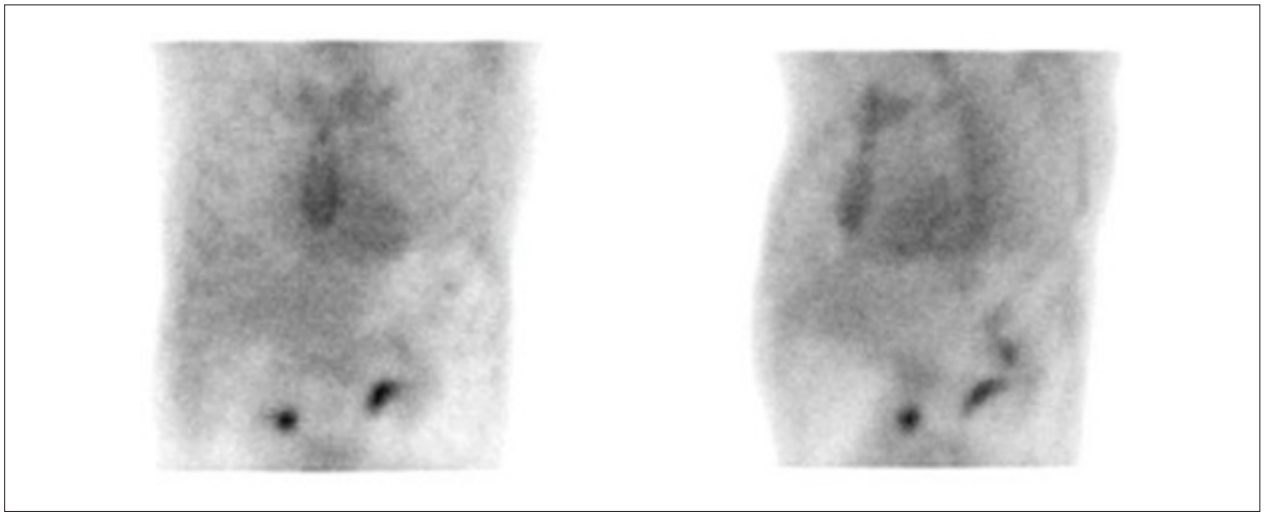

Figure 2 – *Perugini grade 2 myocardial uptake on cardiac scintigraphy (anterior and left anterior oblique view).*

Discussion

We reported the case of an older patient who sought cardiology outpatient care due to symptoms of heart failure, autonomic dysfunction, and peripheral neuropathic involvement.

Echocardiography is an important tool for diagnosing the disease. There are echocardiographic parameters that can be helpful in differentiating cardiac amyloidosis from other conditions that cause ventricular hypertrophy, such as RELAPS > 1, SAB > 2.1, and EFSR > 4.1.[8-10] In our patient, the SAB value was 12.5, with a RELAPS of 1.06 and an EFSR of 4.8, which are suggestive of cardiac amyloidosis. Additionally, cardiac magnetic resonance was performed, which revealed diffuse subendocardial fibrosis associated with increased native T1 mapping values and extracellular

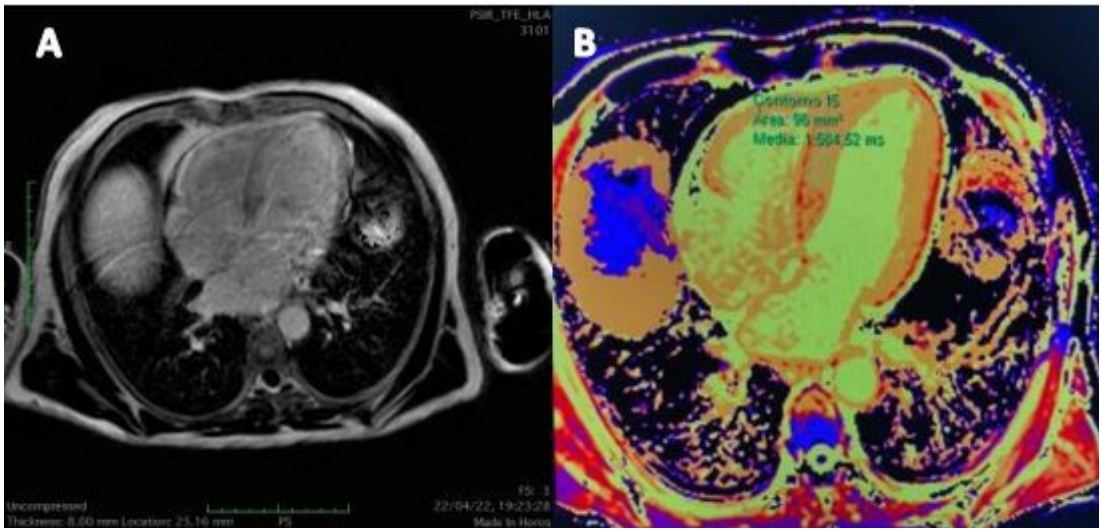

Figure 3 – *Cardiac magnetic resonance imaging. A) Four chamber view with diffuse subendocardial late gadolinium enhancement; B) elevated T1 mapping.*

volume, which are considered characteristic parameters for cardiac amyloidosis.[11]

Cardiac scintigraphy is crucial for defining the presence of ATTR without the need for endomyocardial biopsy. In our patient, PYP scintigraphy showed myocardial uptake at Perugini grade II.[12] Additionally free AL measurement in the blood yielded a normal Kappa/Lambda ratio of 0.34.

Finally, genetic testing was negative for pathogenic variants in the TTR gene, confirming the diagnosis of wtATTR.

Conclusions

wtATTR was previously considered a rare disease. However, this perception has been changing in recent years due to the new diagnostic methods available and an increased understanding of the disease. The case described in this report emphasizes the importance of encouraging cardiologists to identify patients who are still underdiagnosed.

Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, statistical analysis, obtaining financing, writing of the manuscript and critical revision of the manuscript for intellectual content: Siancas LES.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Maleszewski JJ. Cardiac Amyloidosis: Pathology, Nomenclature, and Typing. Cardiovasc Pathol. 2015;24(6):343-50. doi: 10.1016/j.carpath.2015.07.008.
2. Vieira M, Saraiva MJ. Transthyretin: A Multifaceted Protein. Biomol Concepts. 2014;5(1):45-54. doi: 10.1515/bmc-2013-0038.
3. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019;73(22):2872-91. doi: 10.1016/j.jacc.2019.04.003.
4. Dispenzieri A, Coelho T, Conceição I, Waddington-Cruz M, Wixner J, Kristen AV, et al. Clinical and Genetic Profile of Patients Enrolled in the Transthyretin Amyloidosis Outcomes Survey (THAOS): 14-Year Update. Orphanet J Rare Dis. 2022;17(1):236. doi: 10.1186/s13023-022-02359-w.
5. Ash S, Shorer E, Ramgobin D, Vo M, Gibbons J, Golamari R, et al. Cardiac Amyloidosis-A Review of Current Literature for the Practicing Physician. Clin Cardiol. 2021;44(3):322-31. doi: 10.1002/clc.23572.

6. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation. 2016;133(24):2404-12. doi: 10.1161/CIRCULATIONAHA.116.021612.

7. Zhou J, Li Y, Geng J, Zhou H, Liu L, Peng X. Recent Progress in the Development and Clinical Application of New Drugs for Transthyretin Cardiac Amyloidosis. J Cardiovasc Pharmacol. 2023;82(6):427-37. doi: 10.1097/FJC.0000000000001478.

8. Phelan D, Collier P, Thavendiranathan P, Popović ZB, Hanna M, Plana JC, et al. Relative Apical Sparing of Longitudinal Strain Using Two-dimensional Speckle-tracking Echocardiography is Both Sensitive and Specific for the Diagnosis of Cardiac Amyloidosis. Heart. 2012;98(19):1442-8. doi: 10.1136/heartjnl-2012-302353.

9. Liu D, Hu K, Niemann M, Herrmann S, Cikes M, Störk S, et al. Effect of Combined Systolic and Diastolic Functional Parameter Assessment for Differentiation of Cardiac Amyloidosis from Other Causes of Concentric Left Ventricular Hypertrophy. Circ Cardiovasc Imaging. 2013;6(6):1066-72. doi: 10.1161/CIRCIMAGING.113.000683.

10. Pagourelias ED, Duchenne J, Mirea O, Vovas G, van Cleemput J, Delforge M, et al. The Relation of Ejection Fraction and Global Longitudinal Strain in Amyloidosis: Implications for Differential Diagnosis. JACC Cardiovasc Imaging. 2016;9(11):1358-9. doi: 10.1016/j.jcmg.2015.11.013.

11. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, et al. Magnetic Resonance in Transthyretin Cardiac Amyloidosis. J Am Coll Cardiol. 2017;70(4):466-77. doi: 10.1016/j.jacc.2017.05.053.

12. Perugini E, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, et al. Noninvasive Etiologic Diagnosis of Cardiac Amyloidosis Using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic Acid Scintigraphy. J Am Coll Cardiol. 2005;46(6):1076-84. doi: 10.1016/j.jacc.2005.05.073.