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https://doi.org/10.1016/j.recesp.2023.10.001

Diagnosis of transthyretin amyloidosis in patients with established cardiomyopathy

Diagnóstico de amiloidosis por transtirretina en pacientes con una miocardiopatía previa

To the Editor,

Cardiac amyloidosis (CA) is a serious, progressive disease that is more common than previously thought. Early diagnosis is crucial, as treatment can alter prognosis.[1–3] CA can coexist with more common cardiomyopathies and remain unnoticed for years, affecting overall prognosis.[4] Familiarity with the typical signs and symptoms of CA (red flags) can lead to an earlier diagnosis.[1,2] We present 3 cases of CA that were not initially suspected.

The first case involved a 73-year-old man with triple-vessel coronary artery disease treated with surgical revascularization. Following an echocardiogram showing left ventricular hypertrophy (20 mm), the patient was referred for cardiac magnetic resonance imaging (MRI), which confirmed the hypertrophy and showed anteroseptal mesocardial late gadolinium enhancement (LGE). There was no family history of hypertrophic cardiomyopathy (HCM). Next-generation sequencing (NGS) of sarcomeric genes and phenocopies detected a pathogenic variant in *TNNC1* (p.Ala8Val), confirming the diagnosis of HCM. Family members underwent genetic testing, but no other cases of HCM were detected. During follow-up, the patient developed signs of heart failure with a typical CA strain pattern and the Popeye sign. He had recently undergone surgery for lumbar spinal stenosis. A diagnosis of wild-type transthyretin (ATTRwt) CA was confirmed by

Table 1
Patient characteristics

	Initial cardiomyopathy, age at diagnosis	Genetic variant identified	Pathogenicity of variant according to ACMG	Relatives studied/ variant carriers, No.	Amyloidosis red flags	99mTc-DPD scintigraphy	EMB	Age at diagnosis of amyloidosis, y
Patient 1	Nonobstructive HCM (73 y)	*TNNC1* (p.Ala8Val)	Pathogenic	3/0	• Popeye sign • Lumbar spinal stenosis • Reduced LGS with apical conservation	Grade 3	Yes	77
Patient 2	Obstructive HCM (74 y)	*MYL3* (p.Met173Val)	Likely pathogenic	1/0	• Popeye sign • First-degree atrioventricular block • Diffuse LGE (MRI) • Abnormal gadolinium kinetics (MRI) • High native T_1 (1123 ms; Philips Ingenia 1.50 T) (MRI) • Increased ECF volume (66%) (MRI)	Grade 3	No	78
Patient 3	Titin cardiomyopathy (76 y)	*TTN* (p.Trp19433*)	Pathogenic	16/9	• Carpal tunnel syndrome • Lumbar spinal stenosis • Hypotension in previously hypertensive patient • Pseudoinfarct pattern and low voltages on ECG • Aortic stenosis • Mild pericardial effusion • Diffuse LGE (MRI) • Abnormal gadolinium kinetics (MRI) • High native T_1 (1103 ms; Philips Ingenia 1.50 T) (MRI) • Increased ECF volume (45%) (MRI)	Grade 1	No	78

^{99m}Tc-DPD, technetium-99m with 3,3-diphosphono-1,2-propanedicarboxylic acid; ACMG, American College of Medical Genetics; ECG, electrocardiogram; ECV, extracellular volume; EMB, endomyocardial biopsy; HCM, hypertrophic cardiomyopathy; LGS, global longitudinal strain; LTR, late gadolinium enhancement; MRI, magnetic resonance imaging.

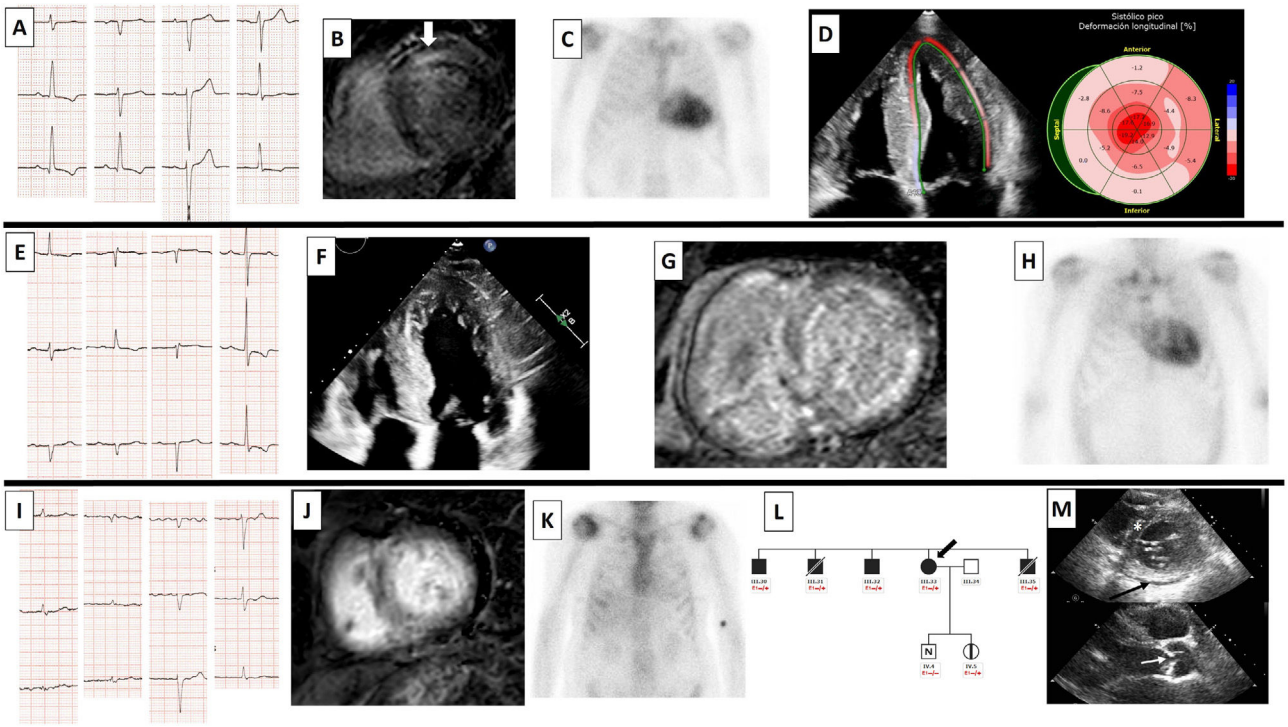

Figure 1. Patient 1. A: ECG. B: cardiac MRI with anteroseptal mesocardial late gadolinium enhancement (LGE) (white arrow). C: ^{99m}Tc-DPD cardiac scintigraphy showing grade 3 uptake. D: decreased global longitudinal strain with apical conservation. Patient 2. E: ECG. F: echocardiogram with apical 4-chamber views showing concentric thickening of left and right ventricles. G: cardiac MRI with abnormal gadolinium kinetics and diffuse, heterogeneous LGE in left and right ventricles. H: ^{99m}Tc-DPD cardiac scintigraphy showing grade 3 uptake. Patient 3. I: ECG with atrial fibrillation, low voltages, and pseudoinfarct pattern. J: cardiac MRI with diffuse LGE and abnormal gadolinium enhancement. K: ^{99m}Tc-DPD cardiac scintigraphy with grade 1-2 uptake. L: section of the family tree (arrow, patient 3; black, relative with titin cardiomyopathy; black square, affected male relative; black circle, affected female relative; diagonal line, deceased relative; white square, healthy male relative; N, normal; vertical line, healthy carrier; E1 –/+, heterozygous for *TTN* variant [p.Trp19433*]; E1 –/–, noncarrier). M: upper image with echocardiogram showing septal hypertrophy of 12 mm (asterisk) and mild pericardial effusion (arrow); lower image showing aortic valve thickening (arrow). ^{99m}Tc-DPD: technetium-99m with 3,3-diphosphono-1,2-propanedicarboxylic acid; ECG: electrocardiogram; MRI: magnetic resonance imaging; LGE, late gadolinium enhancement; *TTN*, titin.

technetium-99m-3,3-diphosphono-1,2 propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy (grade 3 uptake), while laboratory tests ruled out monoclonal proteins and genetic tests were negative. The patient developed a respiratory infection and died at the age of 79 years.

The second case of CA involved a 62-year-old hypertensive man with septal hypertrophy (15 mm) that had been attributed to hypertension for years. When the patient was aged 74 years, he developed dyspnea on exertion. An echocardiogram showed hypertrophy (23 mm), systolic anterior motion, and a subaortic gradient of 67 mmHg with the Valsalva maneuver. The patient was referred to the family heart disease unit, where he underwent NGS of sarcomeric genes and phenocopies. The results showed a likely pathogenic variant in *MYL3* (p.Met173Val), confirming the diagnosis of obstructive HCM. The patient was started on beta-blocker treatment, which relieved his obstructive symptoms. Genetic testing of family members detected no other cases of HCM. Two years later, the patient developed signs of heart failure, with an N-terminal pro-brain natriuretic peptide fraction of 3000 pg/mL, a restrictive diastolic pattern on the echocardiogram, and the Popeye sign in the right arm (this deformity had not been previously present). Cardiac MRI showed abnormal gadolinium kinetics and diffuse LGE in both ventricles, while cardiac ^{99m}Tc-DPD scintigraphy showed grade 3 uptake. Monoclonal proteins were ruled out and the patient was diagnosed with ATTRwt CA. He is currently under follow-up at the outpatient clinic.

The third case of CA involved a 75-year-old woman with hypertension and a history of familial dilated cardiomyopathy due to a titin (*TTN*) variant (p.Trp19433*). She had atrial fibrillation with a nondilated left ventricle and a left ventricular ejection fraction (LVEF) of less than 30%. She was a carrier of a pathogenic familial *TTN* variant. Neurohormonal treatment increased LVEF to 50%. When she was 78 years old, the patient experienced clinical deterioration not attributable to the LVEF at the time and intolerance to neurohormonal antagonists due to hypotension. ECG findings included low voltages and the pseudoinfarct pattern; the echocardiogram showed mild pericardial effusion, moderate aortic stenosis, and a septal thickness of 12 mm. She underwent ^{99m}Tc-DPD scintigraphy, with uptake reported as grade 1-2, and laboratory tests, which ruled out monoclonal proteins. She refused to undergo biopsy for histologic confirmation. Cardiac MRI showed increased extracellular fluid volume and native T_1 values, diffuse LGE, and abnormal gadolinium kinetics. Sanger sequencing of the *TTR* gene was negative. Based on the above findings, the patient was diagnosed with ATTRwt CA. She is currently under outpatient follow-up and has stable dyspnea on slight exertion.

The clinical characteristics of the 3 patients are summarized in table 1. Some of their test findings are shown in figure 1.

The 3 cases described in this report show that a previous diagnosis of cardiomyopathy does not rule out CA. All 3 patients had clinical and echocardiographic red flags for CA while under follow-up for HCM or titin cardiomyopathy. Cardiologists should always be alert to possible red flags for CA in patients older than 65 or 70 years, especially in the presence of left ventricular hypertrophy or worsening symptoms.[4–6] An existing diagnosis of cardiomyopathy should not preclude tests for CA, as both conditions can clearly coexist.

FUNDING

No funding was received for this study.

ETHICAL CONSIDERATIONS

Approval from the local ethics committee was not needed due to the characteristics of the study. The authors confirm that they received written informed consent from the patients for the publication of the text and images included in this article. Sex and gender were reported in accordance with the Spanish Sex and Gender Equity in Research (SAGER) guidelines.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tools were used for this study.

AUTHORS' CONTRIBUTIONS

E. Martín-Álvarez, R. Barriales-Villa, and J.M. Larrañaga-Moreira designed the study, prepared the figures, and wrote the manuscript. G. Barge-Caballero, M.G. Crespo-Leiro, and B. Souto-Caínzos critically reviewed the manuscript.

CONFLICTS OF INTEREST

J. M. Larrañaga Moreira, M. G. Crespo Leiro, and R. Barriales Villa report have received funding from Pfizer for attending conferences.

M. G. Crespo Leiro received funding from Pfizer at her institute for participating in a clinical trial.

R. Barriales Villa has performed consultancy work for Pfizer, Alnylam, and Akcea.

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Use of SGLT2i in patients with transthyretin amyloid cardiomyopathy: prevalence and safety in a Spanish prospective cohort

Uso de iSGLT2 en pacientes con amiloidosis cardiaca por transtirretina: prevalencia y seguridad en una cohorte prospectiva en España

To the Editor,

Few data are available on the usefulness of drugs typically used to treat heart failure (HF) in patients with transthyretin cardiac amyloidosis (ATTR-CA). Of these medications, the most pertinent drug class is possibly sodium-glucose cotransporter type 2 inhibitors (SGLT2i) because they are indicated for both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).[1] The latter is the form with the most frequent clinical presentation in ATTR-CA patients.[2] The proven diagnostic benefit of this class of medications in all ejection fraction types, as well as its diuretic effect and favorable hemodynamic profile, suggests that it could be a good therapeutic option in patients with ATTR-CA. However, because this population is systematically excluded from clinical trials of SGLT2i, its effectiveness and safety profile in ATTR-CA are unknown. Accordingly, we examined the prevalence of SGLT2i use and the safety of the drugs in a cohort of patients with ATTR-CA.

We established a prospective registry of all patients diagnosed with ATTR-CA in our center between January 1, 2018, and July 31, 2022, and identified all patients who received any treatment with an SGLT2i. All adverse events potentially associated with this drug class were recorded via a retrospective review of electronic medical records from the date of treatment initiation to discontinuation, patient death, or end of the observation period, established at November 30, 2022. Participant follow-up was conducted in the Heart Failure Unit at least every six months. All