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CASE REPORT

"Two is Company, Three is a Crowd" – A Case Presentation of Cardiac Amyloidosis, Hypertrophic Cardiomyopathy Plus Coronary Heart Disease

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Abstract

A 76-year-old man was referred to our appointment with complaints of exertional dyspnea. He had a medical history consisting of chronic coronary syndrome, hypertrophic cardiomyopathy, and an implantable cardioverter-defibrillator for primary prevention. A transthoracic echocardiogram revealed features suspicious for cardiac amyloidosis. Haematologic and genetic tests were negative, and scintigraphy was positive, confirming wild-type transthyretin amyloidosis, not eligible for tafamidis. Several months later with optimized medical therapy, he had two worsening heart failure events.

This clinical case highlights the importance of differential diagnosis. Our patient had both hypertrophic cardiomyopathy and transthyretin amyloidosis, a rare association that constitutes a diagnostic and treatment challenge.

Keywords: Cardiac amyloidosis, ATTR amyloidosis, Hypertrophic cardiomyopathy, Differential diagnosis, Case report

1. History of presentation

A 76-year-old man with a fair functional status despite an important past medical history was referred to our Cardiology appointment.

At our appointment, he complained of exertional dyspnea for less than ordinary activity (New York Heart Association Functional Classification [NYHA] III). No extracardiac symptoms were observed. Crackles on pulmonary auscultation were detected. Furthermore, he referred one single ICD shock few days before, which was considered an appropriate therapy.

1.1. Past medical history

He was previously followed at another hospital and was diagnosed with coronary heart disease with a stent implanted in the median left anterior descending artery at the age of 58. At the age of 68, he was diagnosed with non-obstructive hypertrophic cardiomyopathy (HCM), with a suggestive cardiac magnetic resonance (CMR) revealing late gadolinium enhancement (LGE) in the hypertrophied areas and systolic anterior motion of the mitral valve, and with a positive genetic test for the heterozygous pathogenic variant *CSRP3*:c.128 del,p(Ala43Valfs*165). An alpha-galactosidase A genetic analysis was negative. Left ventricular ejection fraction was reported as normal. Furthermore, he had received an implantable cardioverter-defibrillator (ICD) a year later for primary prevention. Other relevant past medical history consisted of atrial fibrillation, arterial hypertension, type 2 diabetes, chronic kidney disease and obstructive sleep apnea under continuous positive airway pressure therapy. He was polymedicated with esomeprazol 20 mg, furosemide 40 mg, bisoprolol 2.5 mg, apixaban 5 mg twice a day, empagliflozin 10 mg, alopurinol 100 mg, atorvastatin 40 mg,

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spironolactone 12.5 mg, enalapril 2.5 mg and two bronchodilators.

There was no family history of cardiac disease, including HCM or sudden cardiac death.

1.2. Differential diagnosis

As the patient was experiencing symptoms compatible with heart failure, further cardiac workup was needed. An electrocardiogram (ECG), a transthoracic echocardiogram and blood analysis were requested. Oral furosemide dose was also increased, and an early reevaluation was scheduled.

1.3. Investigations

However, before attending the second Cardiology appointment, the patient had one episode of acute heart failure due to a respiratory tract infection, requiring hospitalization in the Internal Medicine department. Afterward, the patient remained in NYHA class II-III.

An ECG revealed right ventricular pacing (Fig. 1), and blood analysis showed a normal hemogram, elevated creatinine (1.8 mg/dL), and N-terminal brain natriuretic peptide of 19600 pg/mL. A transthoracic echocardiogram showed severe ventricular hypertrophy with granular sparkling of the myocardium, reduced global longitudinal strain despite preserved left ventricular ejection fraction, low myocardial velocities, reduced longitudinal right ventricular function, atrial enlargement, calcified subvalvular aortic and mitral apparatus, and mild pericardial effusion (Figs. 2 and 3, Clip 1).

At this point, suspicion was raised for a possible diagnosis of cardiac amyloidosis (CA) and further tests were requested. Immunofixation and free light chain assay were negative and bone tracer cardiac scintigraphy (99 mTc 3,3-diphosphono-1,2-propanodicarboxylic acid) positive (Perugini grade 3) (Fig. 4). As genetic testing was negative, wild-type transthyretin amyloidosis (ATTRwt) was confirmed (Fig. 5).

List of abbreviations

ATTRwt	wild-type transthyretin amyloidosis
CA	cardiac amyloidosis
CMR	cardiac magnetic resonance
ECV	extracellular volume
HCM	hypertrophic cardiomyopathy
ICD	implantable cardioverter-defibrillator
LA	left atrium
LGE	late gadolinium enhancement
NYHA	New York Heart Association

1.4. Management

Due to extension of disease and comorbidities, this patient was considered ineligible for tafamidis. Despite optimized medical therapy, the patient experienced two worsening heart failure episodes several months later, approximately one month apart, due to progression of his disease. He required inpatient treatment and clinically improved after intravenous diuretics, being discharged after 6 and 7 days, respectively. In the second event, thoracentesis was performed due to persistent right pleural effusion.

His medications were reviewed with the aim of discontinuing hypotensive drugs, increasing diuretics, and simplifying the regimen. He is currently

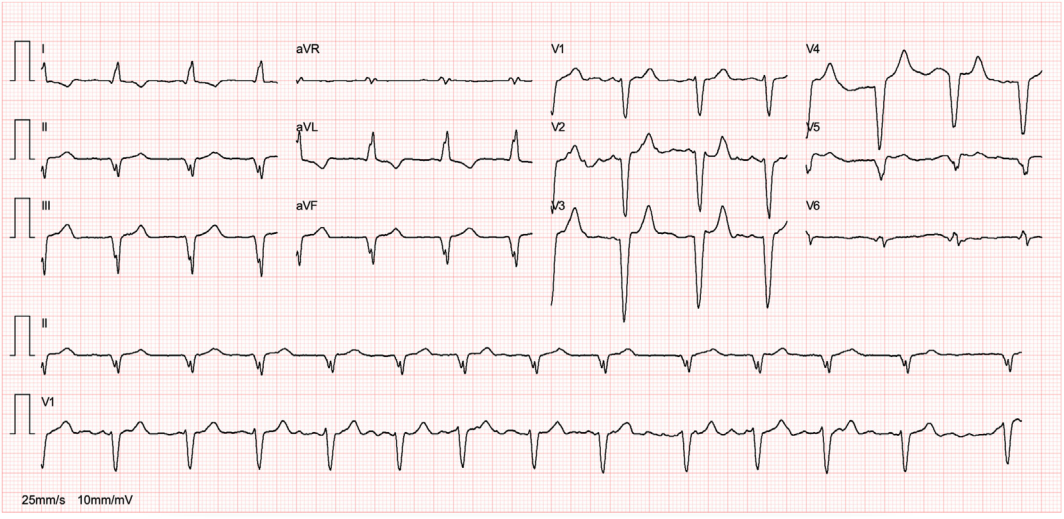

Fig. 1. ECG revealing right ventricular pacing.

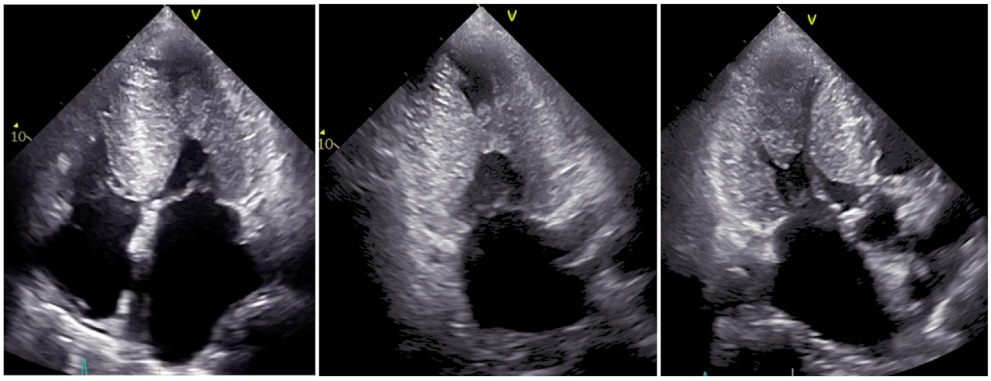

Fig. 2. Transthoracic echocardiogram with severe left ventricular hypertrophy.

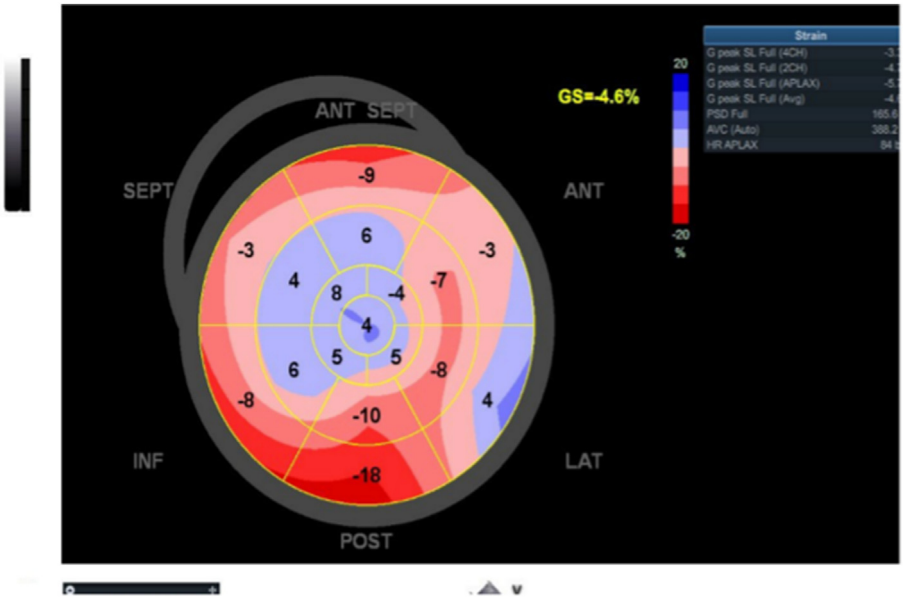

Fig. 3. Reduced longitudinal strain - two-dimensional speckle-tracking transthoracic echocardiogram.

medicated with esomeprazol 20 mg, furosemide 80 mg, bisoprolol 5 mg, rivaroxaban 15 mg, empagliflozin 10 mg, alopurinol 100 mg, atorvastatin 40 mg, spironolactone 12.5 mg, sertraline 50 mg and two bronchodilators. Although aware of the prognosis of the disease, the patient is motivated to comply with all treatments.

2. Discussion

Differential diagnosis of HCM phenotype is of uttermost importance in clinical practice. HCM is a relatively common heart condition [1,2] genetically based [1]. Clinical assessment and imaging are crucial to the best management of this disease [1], specially concerning ICD for primary prevention [2]. New treatments are needed and mavacamten is still under investigation [2]. Nowadays, mortality due to this disease is uncommon, mainly related to non-obstructive patients with end-stage disease or comorbidities [2].

Other conditions such as CA are associated with left ventricular hypertrophy that may mimic HCM [3]. CA is caused by accumulation of amyloid fibrils in interstitial space between myocytes [3,4]. There are nine known types of CA (AA, AApoAI, AApoAII, AApoAIV, Ab2M, AFib, AGel, AL, ATTR) [4], with AL and ATTR accounting for most of CA cases [3,4]. Both European and American Cardiology Societies have recently proposed similar algorithms to diagnose CA and its type [3,4]. These are primarily based on clinical suspicion, signs, symptoms and basic workup suspicious for this disease, further complemented with haematologic tests, bone tracer scintigraphy and ATTR genetic testing [3,4]. Clinical suspicion in our patient was

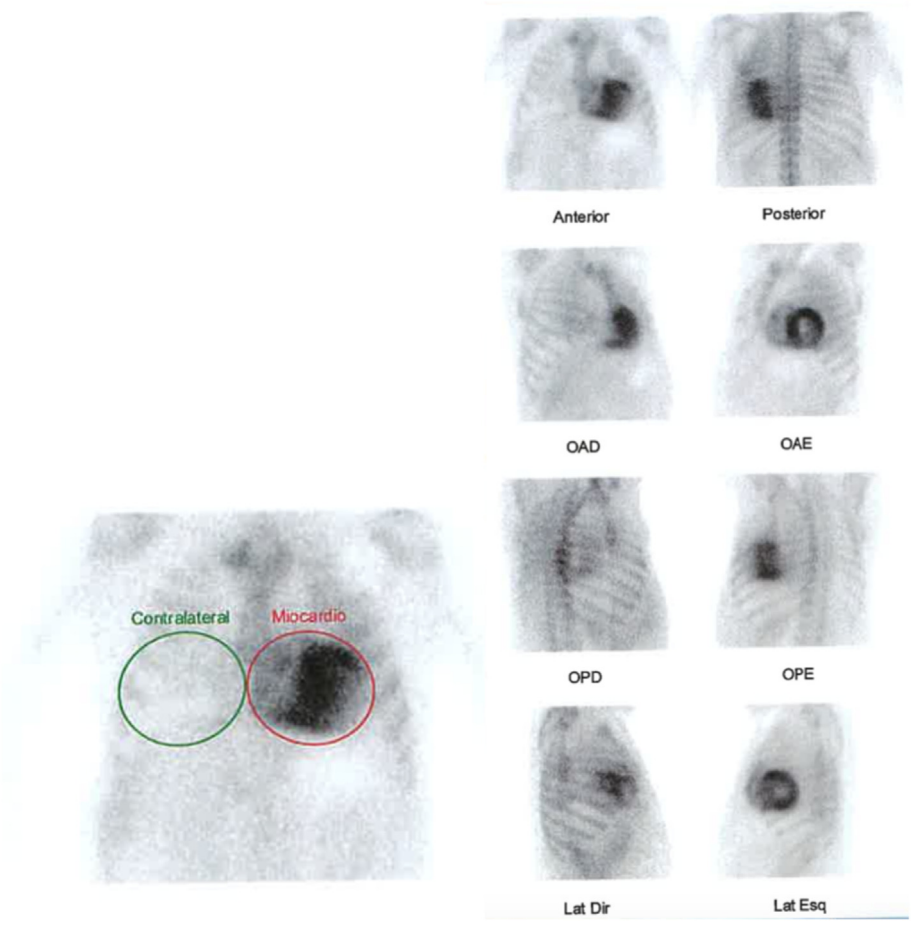

Fig. 4. Positive bone tracer cardiac scintigraphy.

challenging, not only due to the absence of extracardiac red flags, but also because of the past diagnose of HCM. Several echocardiographic red flags were reported (granular sparkling of myocardium, increased ventricular wall and valvular thickness and pericardial effusion), while apical sparing was not observed, probably due to the ischemic heart disease. Although bone tracer scintigraphy may have false positives in certain situations, such as other types of amyloidosis, recent myocardial infarction, rib fractures, blood pool or hydroxychloroquine toxicity [4], these conditions were excluded in our patient.

In cases of negative genetic testing, ATTR is named “wild-type”, as in our patient. In the last years, ATTR amyloidosis has been increasingly diagnosed among patients with heart failure with preserved ejection fraction and aortic stenosis [4].

Nevertheless, multimodality imaging is crucial in differential diagnosis of HCM phenotype. Besides the suspicious echocardiographic findings abovementioned, impaired LA function assessed by speckle tracking echocardiography [5], and global left ventricular myocardial work indexes [6] may have a role in CA diagnosis, but larger studies are needed [6]. Nevertheless, some authors consider CMR as the best exam for this purpose, providing more accurate information regarding morphological characteristics, myocardial T1 mapping, extracellular volume (ECV) and LGE [7]. Thickened ventricular and LA walls, pericardial effusion, diffuse subendocardial LGE, “early darkening” sign after LGE, and diffusely increased myocardial T1 and ECV are suggestive of CA. Nevertheless, atypical patterns are also described, and a definite diagnosis should be integrated with patient history [7]. Although the authors did not have access to the images of the CMR described, as they were from another hospital, the report available was not suggestive of CA. Furthermore, LGE increases with amyloid deposition [7] and CA was probably at an early stage at the time of CMR.

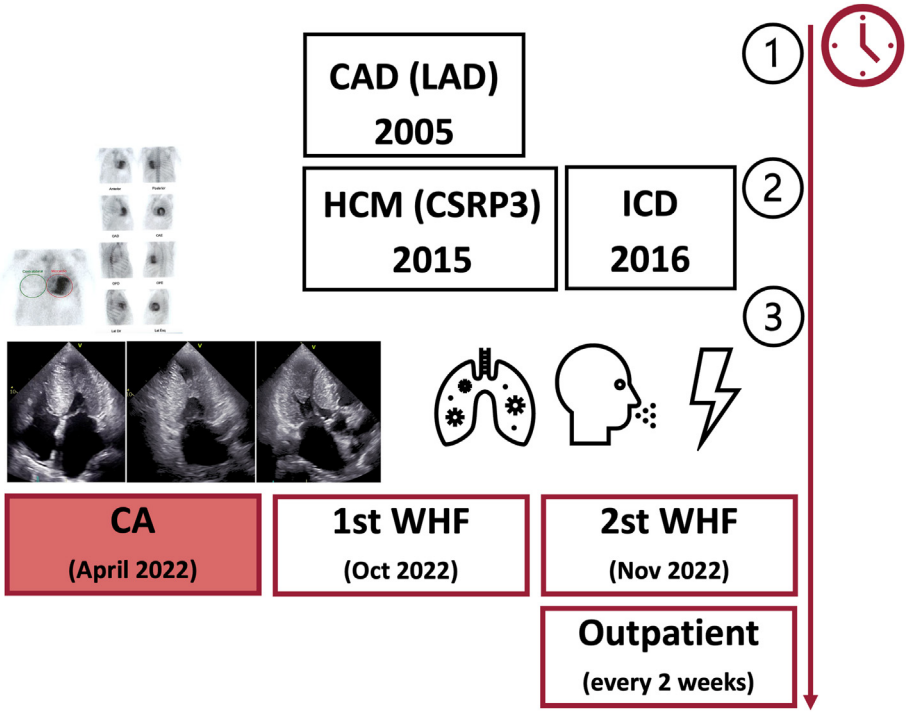

Fig. 5. Timeline (central figure). Abbreviations: CAD - coronary artery disease; LAD - left anterior descending; WHF - worsening heart failure.

CA treatment is complex. Fluid overload is managed with loop diuretics and mineralocorticoid receptor antagonists, and they are considered the pillars of the treatment [3]. Further management of concomitant cardiac comorbidities and complications, such as, atrial fibrillation, conduction disorders, aortic stenosis and ventricular arrhythmias is needed [4], as well as a multidisciplinary team [3,4] (e.g Neurology, Gastroenterology, Haematology, Nephrology, Palliative care) for other non-cardiac comorbidities [3]. Regarding disease specific treatments, tafamidis has shown positive results in ATTR cardiac amyloidosis [4], but its administration is not widely available. Tafamidis may delay progression of the disease but does not result in its regression [3], and this patient was considered to be at a "point of no return" due to the severity of the disease and comorbidities.

2.1. Follow-up

Since discharge the patient remains in NYHA III-IV class, requiring regular outpatient management with intravenous diuretic administration in the Cardiology Department, with a reserved prognosis.

3. Conclusion

This patient had both confirmed hypertrophic cardiomyopathy and wild-type ATTR amyloidosis, an association that makes the case a diagnosis and treatment challenge. Due to comorbidities and the irreversibility and severity of the disease, optimised medical therapy and palliative care was offered to the patient.

3.1. Learning objectives

- Even when the diagnosis seems clear, the clinician should not remain calm. Differential diagnosis is crucial in patients with HCM phenotype.
- HCM is a relatively common heart condition genetically based with a mortality lower than 1%/year. On the other hand, CA is increasingly diagnosed and its treatment is complex.
- This case highlights an association between HCM and CA.

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Author contribution

Conception and design of Study: CMG, MC, CD, FS, JM. Literature review: CMG, MC, CD, FS, JM. Acquisition of data: CMG, MC, CD, FS, JM. Analysis and interpretation of data: CMG, MC. Research investigation and analysis: CMG, FS. Data collection: CMG, CD. Drafting of manuscript: CMG, MC, CD, FS, JM. Revising and editing the manuscript critically for important intellectual contents: CMG,

MC, CD, FS, JM. Data preparation and presentation: CMG, FS. Supervision of the research: CMG, JM. Research coordination and management: CMG, JM.

Ethics information

Written informed consent was obtained from the patient for publication of this case report, including accompanying images.

Conflict of interest

The authors have no conflicts of interest.

References

[1] Maron BJ, Desai MY, Nishimura RA, Spirito P, Rakowski H, Towbin JA, et al. Diagnosis and evaluation of hypertrophic cardiomyopathy. J Am Coll Cardiol 2022;79(4):372–89. https://doi.org/10.1016/j.jacc.2021.12.002.

[2] Maron BJ, Desai MY, Nishimura RA, Spirito P, Rakowski H, Towbin JA, et al. Management of hypertrophic cardiomyopathy. J Am Coll Cardiol 2022;79(4):390–414. https://doi.org/10.1016/j.jacc.2021.11.021.

[3] Kittleson MM, Ruberg FL, Ambardekar AV, Brannagan TH, Cheng RK, Clarke JO, et al. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis. J Am Coll Cardiol 2023;81(11):1076–126. https://doi.org/10.1016/j.jacc.2022.11.022.

[4] 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 diseases. Eur Heart J 2021;42(16):1554–68. https://doi.org/10.1093/eurheartj/ehab072.

[5] Monte IP, Faro DC, Trimarchi G, de Gaetano F, Campisi M, Losi V, et al. Left atrial strain imaging by speckle tracking echocardiography: the supportive diagnostic value in cardiac amyloidosis and hypertrophic cardiomyopathy. J Cardiovasc Dev Dis 2023;10(6). https://doi.org/10.3390/jcdd10060261.

[6] de Gregorio C, Trimarchi G, Faro DC, De Gaetano F, Campisi M, Losi V, et al. Myocardial work appraisal in transthyretin cardiac amyloidosis and nonobstructive hypertrophic cardiomyopathy. Am J Cardiol 2023;208:173–9.

[7] Licordari R, Trimarchi G, Teresi L, Restelli D, Lofrumento F, Perna A, et al. Cardiac magnetic resonance in HCM phenocopies: from diagnosis to risk stratification and therapeutic management. J Clin Med 2023;12(10). https://doi.org/10.3390/jcm12103481.