Letters to the Editor

Diagnosing transthyretin amyloidosis in patients with known genetic cardiomyopathies – opportunities and open questions

Amiloidosis por transtirretina diagnosticada en pacientes con una miocardiopatía previa - oportunidades y preguntas abiertas

To the Editor,

We had the pleasure to read the article by Martín-Álvarez et al., recently published in your journal. It interestingly depicts the potential overlap of an acquired cardiomyopathy wild-type transthyretin (TTRwt) cardiac amyloidosis in 3 patients with a previous diagnosis of a genetically determined cardiomyopathy.[1] We would like to highlight several aspects and potential difficulties in the diagnostic process of such complex cases.

In the past few years, awareness of inherited cardiac conditions has increased along with a greater use of genetic testing for the diagnosis of cases with a suggestive cardiac phenotype or for cascade testing. This has led to a more liberal approach regarding the age at which the genetic test is performed in an individual. As such, the number of diagnoses in older patients, particularly hypertrophic cardiomyopathy, has significantly increased as has the mean age at diagnosis.[2]

Individuals with inherited cardiomyopathies can obviously also develop acquired cardiovascular conditions with age, just like the general population. These include acquired cardiomyopathies, such as amyloid light-chain and TTRwt amyloidosis. We would like to congratulate the authors for illustrating this new reality and the challenges in the diagnosis and management of such cases.

All 3 cases presented in the article had an initial diagnosis of hypertrophic cardiomyopathy or dilated cardiomyopathy with a positive genotype at rather advanced ages (73, 74, and 76 years). The 2 male patients diagnosed with hypertrophic cardiomyopathy were both probands and the subsequent genetic cascade testing found no evidence of the same mutation in relatives, which would have been valuable for further assessment of the phenotypical expression. Both were diagnosed with cardiac amyloidosis 4 years after the initial diagnosis. The first patient was genotyped at diagnosis at the age of 73 years, having been found to have a left ventricular wall thickness of 20 mm, while the second patient had a long-standing diagnosis of left ventricular hypertrophy made 12 years previously and was genotyped only after developing more severe hypertrophy (15 mm known 12 years previously to 23 mm) with left ventricular outflow tract obstruction at the age of 74 years.

In a cohort of 150 patients older than 60 years diagnosed with hypertrophic cardiomyopathy who underwent ^{99}mTc-PYP (pyrophosphate) imaging, the scan was positive in 8%.[3] Nevertheless, it has been shown that this does not necessarily indicate cardiac amyloid deposition, as false positive cases have been reported in patients with hypertrophic cardiomyopathy with subsequent negative endomyocardial biopsies.[4,5] It has been speculated that focal cell necrosis related to ischemia secondary to perfusion defects and small vessel disease could lead to a false positive bone scintigraphy in hypertrophic cardiomyopathy.[4] Furthermore, false positive results can also be seen in patients with myocardial ischemia due to coronary artery disease, which could arguably be the case of the first patient.[6]

Therefore, clinicians should exercise caution when faced with an overlap in elderly patients with hypertrophic cardiomyopathy, particularly when they have associated coronary artery disease, in the absence of microscopic evidence of cardiac amyloid deposition. Cardiovascular magnetic resonance and or echocardiography findings suggestive of amyloidosis could prove unreliable in overlap cases, particularly in long-standing diseases. Hence, if clinical suspicion exists, histologic evidence appears to be necessary, and endomyocardial biopsy should ideally be pursued for a definitive diagnosis. Depending on availability, salivary gland biopsy or histologic study could be used after carpal tunnel surgery.

An irrefutable diagnosis is important as the indication for specific treatment with transthyretin stabilizer and the appropriate dosage depends on the presence of cardiac involvement. To our knowledge, none of the patients received treatment with transthyretin stabilizer, but perhaps this information was omitted in the article.

We highly value the discussion around these difficult cases which arise because of increasing awareness of the complexity of cardiomyopathies, and hope that future case series will shed further light on this association.

FUNDING

None.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tool was used in the preparation of this article.

AUTHORS' CONTRIBUTION

Both authors contributed equally.

CONFLICTS OF INTEREST

None.

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Available online 4 December 2023

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https://doi.org/10.1016/j.rec.2023.09.012

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https://doi.org/10.1016/j.recesp.2023.11.012

Diagnosing transthyretin amyloidosis in patients with known genetic cardiomyopathies – opportunities and open questions. Response

Amiloidosis por transtirretina diagnosticada en pacientes con una miocardiopatía previa - oportunidades y preguntas abiertas. Respuesta

To the Editor,

We would like to thank Casian et al. for their interest in our article,[1] and we will try to address some of the issues raised.

Although the family study in the first 2 cases did not identify more carriers, the *TNNC1* p.Ala8Val and *MYL3* p.Met173Val variants have been reported in other families with hypertrophic cardiomyopathy and functional studies have been reported that support their pathogenicity.[2,3]

False positives of cardiac scintigraphy occur mostly in other types of amyloid cardiomyopathy, but also in recent myocardial infarction or hydroxychloroquine cardiotoxicity. Blood pool could be interpreted as a false positive, and consequently single photon emission computed tomography is recommended to confirm uptake.[4] We acknowledge that false positive cases have been reported in hypertrophic cardiomyopathy,[5] but unlike ours, those did not show the red flags or imaging findings expected in cardiac transthyretin amyloidosis, such as apical sparing in speckle-tracking or high T_1/extracellular volume.[4] Our first case had a chronic coronary syndrome but not recent myocardial infarction, and transthyretin amyloidosis deposits were confirmed in endomyocardial biopsy.[1] Currently, a noninvasive diagnosis of cardiac transthyretin amyloidosis is accepted when the clinical picture is compatible and there is grade $\geq$ 2 uptake in cardiac scintigraphy in the absence of monoclonal gammopathy.[4]

Finally, tafamidis 61 mg was initiated in the first and second cases. In the third case, it was not initiated because the patient refused to attempt histological confirmation.

FUNDING

No funding was received for this study.

SEE RELATED CONTENT:
https://doi.org/10.1016/j.rec.2023.11.012

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence tools were used in this study.

AUTHORS' CONTRIBUTIONS

E. Martín-Álvarez, R. Barriales-Villa and J.M. Larrañaga-Moreira designed and wrote the manuscript. M.G. Crespo-Leiro critically reviewed the manuscript.

CONFLICTS OF INTEREST

J.M. Larrañaga-Moreira, M.G. Crespo Leiro, and R. Barriales-Villa report they received funding from Pfizer to attend conferences. M.G. Crespo-Leiro received funding from Pfizer at her institution to participate in a clinical trial. R. Barriales-Villa has performed consultancy work for Pfizer, Alnylam, and Akcea.

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Available online 16 January 2024

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