Scientific letter

Ventricular hypertrophy and family history of cardiac amyloidosis: is it always what it seems?

Hipertrofia ventricular y antecedente familiar de amiloidosis cardiaca: ¿es siempre lo que parece?

To the Editor,

Left ventricular hypertrophy (LVH) is the main structural phenotypic manifestation of cardiac amyloidosis. However, the presence of specific LVH-associated characteristics in imaging studies should suggest differential diagnoses beyond amyloidosis in patients with LVH, even in carriers of pathogenic variants in the transthyretin (*TTR*) gene.

We present the case of a 60-year-old man with a history of hypertension, type 2 diabetes mellitus, and smoking. The patient had a family history of hereditary transthyretin amyloidosis (ATTRv), with several family members carrying a missense mutation (Val50Met) in the *TTR* gene. In addition, the patient's father had been diagnosed with hemochromatosis.

Family screening conducted in 2010 revealed that the patient was a carrier of the pathogenic familial variant in *TTR*. The initial workup with electromyography, echocardiography, cardiac magnetic resonance imaging (CMR), and myocardial perfusion imaging (MPI) found no indicators of cardiac amyloidosis.

Five years later, the patient developed atrial fibrillation. In response, ATTRv was again ruled out. At this time, the patient was asymptomatic and blood tests revealed slightly elevated levels of N-terminal pro-B type natriuretic peptide (NT-proBNP). Echocardiography (figure 1A-C) demonstrated normal systolic function and asymmetric basal septal hypertrophy, without an obstructive gradient. Global longitudinal strain was preserved and showed no pattern typical of amyloidosis. MPI identified no myocardial uptake (figure 1D, E). At this time, the presence of LVH suggested differential diagnosis between cardiac amyloidosis, hemochromatosis with cardiac involvement, hypertensive heart disease, and other causes. Accordingly, CMR was performed, which confirmed the asymmetric hypertrophy, identifying a maximum basal septal thickness of 18 mm. Tissue characterization showed a normal T_2 value. In addition, focal midventricular late enhancement was seen at the upper and lower right ventricular insertion points (figure 2A, B).

Although the imaging findings did not support a diagnosis of cardiac amyloidosis, we decided to conduct an endomyocardial

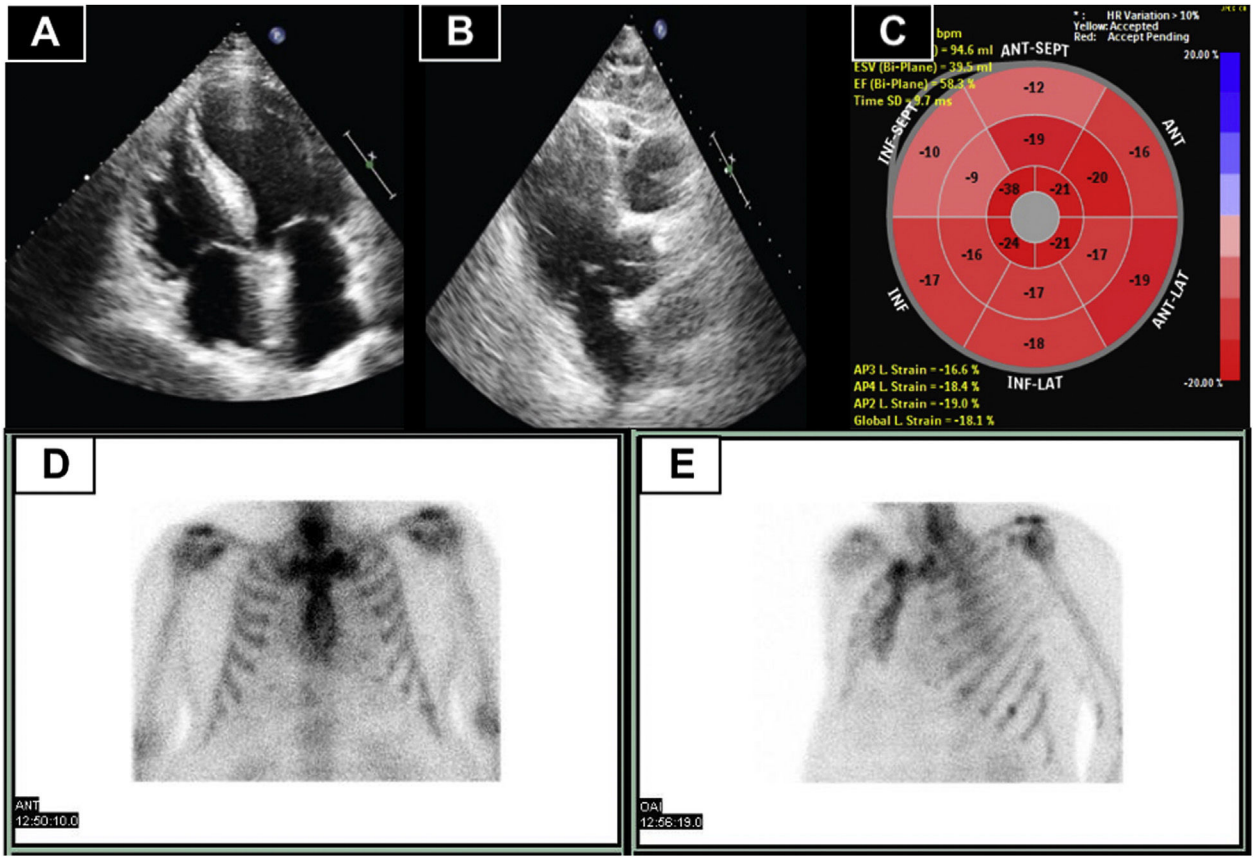

Figure 1. A and B: transthoracic echocardiography showing basal septal thickening. C: global longitudinal strain pattern of the left ventricle, with reduced values, particularly in the basal and mid-anteroseptum and inferoseptum. D and E: myocardial perfusion imaging showing absence of cardiac uptake (Perugini score, 0). ANT, anterior; ANT-LAT, anterolateral; ANT-SEPT, anteroseptal; INF, inferior; INF-LAT, inferolateral; INF-SEPT, inferoseptal.

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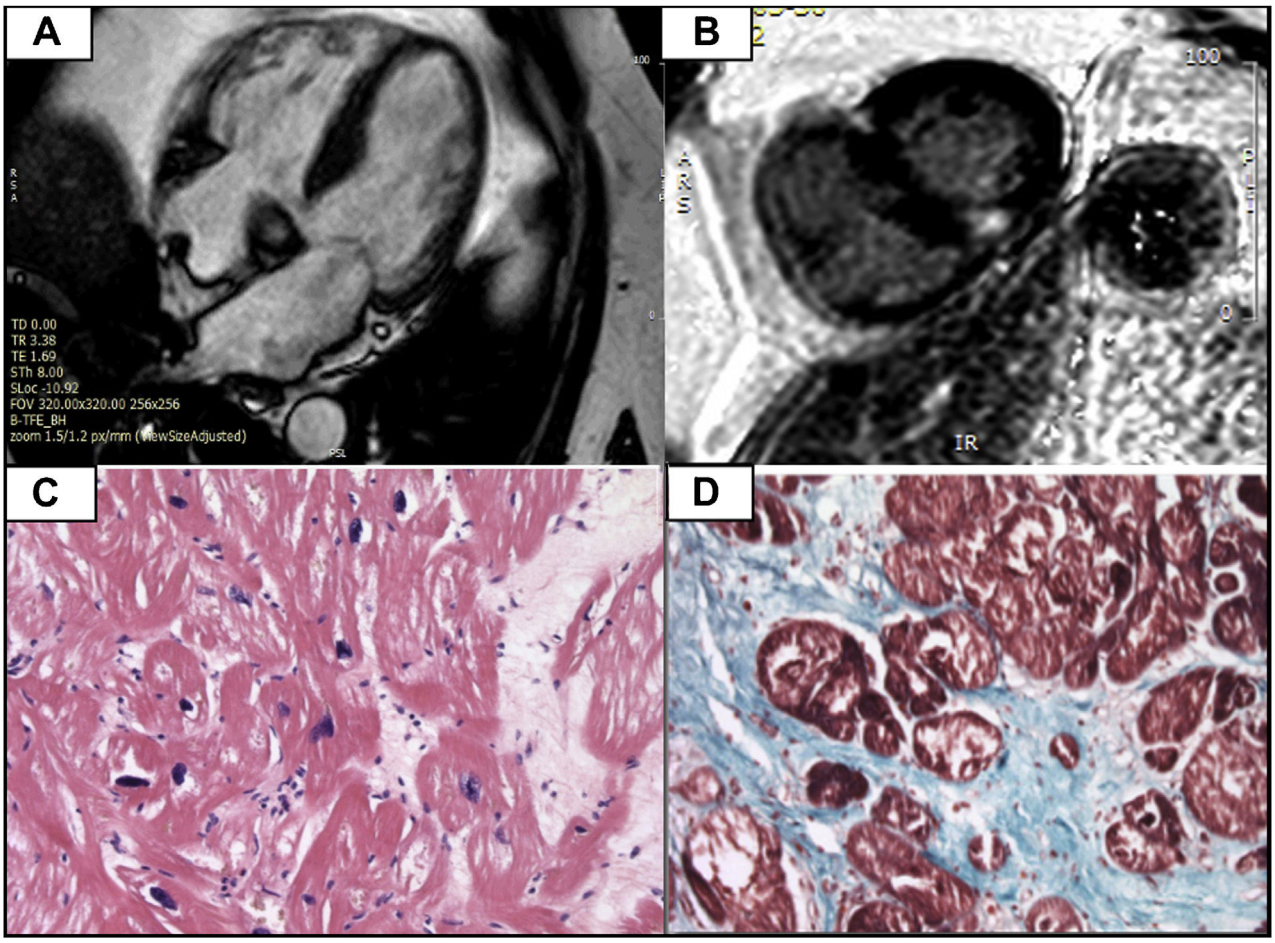

Figure 2. A: cardiac magnetic resonance imaging showing asymmetric septal hypertrophy at the basal level. B: presence of late gadolinium enhancement at the right ventricular insertion points (typical of sarcomeric hypertrophic cardiomyopathy, although not specific for it). C: absence of amyloid deposits with hematoxylin and eosin and Congo red. D: fibrosis shown using Masson's trichrome stain.

biopsy, given the possibility of false-negative MPI results due to the Val50Met mutation. The results showed fibrosis, without amyloid infiltration (figure 2C, D).

Due to the global longitudinal strain pattern on the echocardiogram and the late enhancement on the CMR, as well as the absence of amyloid in the endomyocardial biopsy, a new genetic study was conducted with a next-generation sequencing panel for hypertrophic cardiomyopathy (HCM). The genetic analysis revealed the presence of a pathogenic heterozygous missense variant (p.Gly771Ala) in the gene for beta-myosin heavy chain (*MYH7*), in addition to the previously identified mutation in the *TTR* gene. Accordingly, the patient was diagnosed with nonobstructive sarcomeric HCM, as well as being a carrier of a mutation in *TTR* that, thus far, had no cardiac involvement.

During follow-up, the patient developed sinus node dysfunction requiring pacemaker implantation. Because this condition might have been the first manifestation of ATTRv, caused by amyloid infiltration of the conduction system, another MPI was performed, 10 years after the first scan. Perugini grade 1 cardiac uptake was detected, and a diagnosis of noninvasive ATTRv could not be established.

Two years later, repeat MPI showed uptake progression, which was now Perugini grade 2. This, together with the *TTR* mutation, led to a dual diagnosis in this patient: sarcomeric HCM and ATTRv. The patient gave his informed consent for publication of the case.

Transthyretin cardiac amyloidosis (ATTR) can be diagnosed invasively or noninvasively.[1] Currently, Perugini grade 2/3 uptake on MPI together with screening for plasma cell dyscrasia allows noninvasive and highly specific diagnosis of patients with ATTR.[2] Once ATTR is diagnosed, a genetic study must be performed due to its therapeutic and familial implications.[1]

MPI is a highly sensitive and specific technique for ATTR diagnosis. Nonetheless, there is always the possibility of false positives, such as the light-chain amyloidosis (AL) forms, and false negatives.[1]

Classically, the pattern of concentric hypertrophy associated with amyloidosis has been associated with the infiltrative nature of the disease. Nonetheless, the largest study of patients with ATTR who underwent CMR showed that the most common pattern is that of a sigmoid septum.[2] For CMR-mediated tissue characterization, general or transmural subendocardial late gadolinium enhancement is considered diagnostic for the condition, together with alteration of the gadolinium kinetics.[1] In addition, it is usually accompanied by an elevated native T_1 value and very high extracellular volumes.[3]

The accurate diagnosis of patients with LVH relies on a combination of a clinical history including red flags, family history, electrocardiography, imaging studies, histology, and a genetic study.

DECLARATION

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AUTHORS' CONTRIBUTIONS

Drafting and design of the article and figures: D. de Castro. Revision, article editing, and figures: E. González-López. Article revision: B. Angulo-Lara, D. Pujol-Pocull, and C. Collado-Macián.

CONFLICTS OF INTEREST

None.

Daniel de Castro,[a,b,*] Basilio Angulo-Lara,[a,b] David Pujol-Pocull,[a,b] Carlos Collado-Macián,[a,b] and Esther González-López[a,b]

[a]*Servicio de Cardiología, Hospital Universitario Puerta de Hierro, IDIPHISA, Majadahonda, Madrid, Spain*
[b]*Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain*

[*] Corresponding author.
E-mail address: danidcc93@gmail.com (D. de Castro).
𝕏 @decastro9

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REFERENCES

1. Garcia-Pavia P, Rapezzi C, Adler Y, 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;42:1554–1568.
2. Patel RK, Fontana M, Ruberg FL. Cardiac Amyloidosis: Multimodal Imaging of Disease Activity and Response to Treatment. *Circ Cardiovasc Imaging.* 2021;14:e009025.
3. Vidula MK, Bravo PE. Multimodality imaging for the diagnosis of infiltrative cardiomyopathies. *Heart.* 2022;108:98–104.

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Middle-aged woman with congestive symptoms: more than just pulmonary arterial hypertension

Mujer de mediana edad con síntomas congestivos, algo más que hipertensión arterial pulmonar

To the Editor,

We present the case of a 46-year-old woman who attended the emergency department with New York Heart Association (NYHA) class II-III dyspnea, dry cough, orthopnea, and generalized edema. Physical examination revealed bibasilar crackles and pitting edema in the lower limbs. Electrocardiography demonstrated sinus rhythm at 95 bpm and incomplete right bundle branch block. Chest radiography showed congestive signs, blood tests detected elevated natriuretic peptide levels, and focused cardiac ultrasound identified right heart dilatation. Computed tomography (CT) angiography of the pulmonary arteries ruled out a pulmonary thromboembolism and the patient was admitted to the cardiology department.

During hospitalization, the patient improved in response to diuretic therapy. A comprehensive echocardiogram showed right heart dilatation and signs of pulmonary arterial hypertension (PAH) (figure 1A). Right heart catheterization revealed a mean pulmonary artery pressure of 25 mmHg. The remaining parameters were normal and a vasoreactivity test was negative. Because pulmonary disease was ruled out using chest CT and spirometry, the PAH was classified as primary idiopathic PAH. The patient was discharged on sildenafil 20 mg/12 h and furosemide 40 mg/8 h.

Two months later, she was admitted with asthenia, anorexia, weight loss of 15 kg, and early satiety; notable findings included hemoglobin of 9 mg/dL, but no gastrointestinal bleeding. No cardiac decompensations had occurred since the previous hospitalization and the patient was free from edema and dyspnea at admission. A neoplastic condition was suspected. Abdominal CT demonstrated an increase in the thickness of the third duodenal portion and multiple mesenteric and retroperitoneal adenopathies, findings suggestive of lymphoma (figure 2A). Upper gastrointestinal endoscopy, colonoscopy, and positron emission tomography (PET)-CT were performed. Endoscopy showed a thickened, edematous, and friable duodenojejunal mucosa, with multiple lymphangiectasias and petechiae and ecchymosis in the biopsied tissue. The PET-CT revealed inflammatory or infectious findings of unclear significance (figure 2B). Intestinal biopsy demonstrated infiltration of the lamina propria by foamy histiocytes, which were stained by periodic acid-Schiff (PAS) stain, a finding compatible with Whipple disease (WD). Fecal polymerase chain reaction (PCR) was positive for *Tropheryma whipplei* (TW). Cerebrospinal fluid (CSF) analysis ruled out a central nervous system infection. Echocardiography performed to rule out cardiac diseases secondary to WD showed mobile vegetation, attached to the septal leaflet of the tricuspid valve, and severe tricuspid regurgitation, not present in the previous analysis, compatible with tricuspid endocarditis due to WD (figure 1B). Treatment was begun with ceftriaxone i.v. 2 g/24 h for 4 weeks and doxycycline 100 mg/12 h and hydroxychloroquine 200 mg/8 h for 1 year; the furosemide dosage was reduced to 40 mg/24 h and sildenafil was maintained at 20 mg/12 h.

Ambulatory care was selected with echocardiographic follow-up every 3 months (figure 1C). The dyspnea resolved and the patient experienced no cardiac decompensations. Her pulmonary pressure normalized, sildenafil was withdrawn, the furosemide was maintained at 40 mg/24 h, and the echocardiographic evidence of PAH abated. Her pro-brain natriuretic peptide (proBNP) level was 261 pg/mL. Echocardiography at 1 year of follow-up showed a tricuspid valve with a small hyperechogenic vegetation on the septal leaflet and persistence of the severe tricuspid regurgitation (figure 1D). The patient is currently asymptomatic and remains under follow-up. The patient's legal guardian signed informed consent for publication of the case.

WD is a rare disease caused by infection with TW that has an estimated prevalence of 0.1 to 1 cases/million.[1] Diagnosis is based on the presence of PAS-positive macrophages in histological samples of duodenal biopsies and on serological tests showing TW DNA in different tissues.[2]