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Editorial

Wisdom lies in applying critical clinical judgment that delves deeper than mere appearances. Apropos of a case of ventricular hypertrophy

La sabiduría está en aplicar un juicio clínico crítico que trascienda las simples apariencias. A propósito de un caso de hipertrofia ventricular

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Transthyretin cardiac amyloidosis (TTR-CA), once a rare and underdiagnosed disease. It was previously to affect only elderly people (particularly in its wild-type form) and to have no known treatment. However, in recent years, the disease has become a highly prevalent and can now be detected using highly accurate and routine diagnostic tools. Moreover, it has been found to affect not only elderly individuals, but also middle-aged people. The general management of the disease is distinct from that of other causes of heart failure and a specific therapy has been developed, which has radically altered its prognosis.[1,2]

Crucially, TTR-CA is a systemic illness, especially in its heritable form. Attention must therefore be paid to its extracardiac manifestations, not only neurological symptoms (polyneuropathy, carpal tunnel syndrome), but also gastrointestinal and ophthalmological manifestations, as well as and the associated dysautonomia (eg, orthostatic hypotension, erectile dysfunction).[1,2]

Cardiologists are increasingly likely to suspect TTR-CA due to the existence of red flags for the condition, and the first clues for its diagnosis are provided by echocardiography. However, the case reported by de Castro et al.,[3] selected by *Revista Española de Cardiología* among those presented to the 2023 League of Clinical Cases of the Spanish Society of Cardiology,[4] suggests that appearances or, rather, family history and genetics, may sometimes deceive. This case exemplifies a situation that can occur in clinical practice: the presence of ventricular hypertrophy together with a relevant family history and even a pathogenic TTR variant may lead us to believe that all features are connected and related to the same condition. Nonetheless, our clinical expertise and curiosity must always make us wonder if our approach is actually correct. Not all is as it seems, we must never neglect critical thinking, and we must apply our common sense as clinicians. In this case, even though the patient was a carrier, the absence of red flags for amyloidosis was striking. For example, the patient lacked extracardiac signs, hypotension and normotension, a typical electrocardiographic pattern, conduction disease, highly elevated levels of N-terminal pro-B type natriuretic peptide, a characteristic electrocardiographic strain, associated aortic stenosis, compatible late gadolinium enhancement, elevated native T_1 values, and increased extracellular volume. Accordingly, we must never prioritize appearances and findings obtained using certain techniques over a complete patient examination and never skip any step of the diagnostic algorithm.

Certainly, the sensitivity of cardiac scintigraphy with diphosphonate is not as high as initially reported. Many false negatives have already been seen, particularly in relation to more neurological variants (such as early-onset p.Val30Met, p.Ser97Tyr, and p.Phe84Leu), which is related to the type of amyloid fibers accumulating in the heart.[1,2] However, the case reported by de Castro et al.[3] is not explained by an initial false-negative result, but by the absence of cardiac deposits (confirmed by the authors using endomyocardial biopsy [EMB]). As in all genetic diseases, this finding is associated with the possibility of delayed expression or even incomplete penetrance.

EMB is indicated in patients without proven extracardiac signs or in whom the heart is the only affected organ.[1] In the case presented, the EMB was possibly not necessary, given that no evidence of TTR-CA was found in any of the other tests. However, the presence of a pathogenic variant acted as a confounding factor. Previous genetic analysis of variants related to hypertrophic cardiomyopathy (HCM) would perhaps have revealed the presence of the pathogenic variant in *MYH7* and the EMB would not have been necessary.

What is clear is that the detection of classic signs of cardiac amyloidosis with imaging techniques, such as grade 2 or 3 cardiac scintigraphy uptake with 3,3-diphosphono-1,2 propane dicarboxylic acid (DPD) or pyrophosphate (PYP), together with negative monoclonal gammopathy results, confers a sensitivity and positive predictive value of 100% for the diagnosis of TTR-CA. The use of scintigraphy has represented a paradigm shift that facilitates a noninvasive diagnosis beyond biopsy, a technique overused until recently.[1]

In HCM, studies show a prevalence of cardiac amyloidosis of 7%,[5] or even higher, if we include the results of the TTRACK study, which included 766 patients ≥ 50 years old with unexplained left

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ventricular hypertrophy ≥ 15 mm. The study revealed that up to 18% had TTR-CA and that 8% of the cases were hereditary (unpublished data presented at the Heart Failure 2023 Congress of the European Society of Cardiology). HCM is defined as any left ventricular hypertrophy ≥ 15 mm with an unexplained cause. This disease is much more frequent than cardiac amyloidosis. Genetic study, in the European setting and endorsed in the latest clinical guidelines, has a class I indication and must therefore be performed. Not only is it useful for the family study (for identifying carriers requiring follow-up and ruling out noncarriers of pathogenic variants), but numerous studies have linked genotypes to specific prognoses. The sarcomeric genes most commonly associated with HCM continue to be *MYBPC3* and *MYH7*, related to more than 85% of diagnoses. Family studies are vital for its early diagnosis and treatment, which can improve prognosis.[6]

Moreover, in the case in question,[3] the pathogenic variant found affects the converter region of the β-myosin heavy chain encoded by *MYH7* and increases the risk of early disease development, with a higher incidence of malignant ventricular arrhythmias and increased need for heart transplant. It is one of the variants clearly affecting the prognosis of patients and thereby influencing their management.[6]

Ultimately, the case presented by de Castro et al.[3] exemplifies the qualities that clinicians must possess to delve deeper and get to the root causes, required for complete comprehension of the true situation in all its complexity. Let's not get seduced by first impressions. Wisdom allows us to go beyond the obvious and develop clinical judgment skills that permit us to unravel the many possible diagnoses. We must always question our assumptions, search for solid evidence, and consider the context underlying the evidence.

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CONFLICTS OF INTEREST

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