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Article type: Clinical image

Received: November 26, 2019.

Accepted: January 3, 2020.

Published online: January 14, 2020.

ISSN: 1897-9483
From hypertrophic cardiomyopathy to transthyretin amyloidosis: an unusual case and a challenging diagnosis

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Conflict of interest: none declared

Short title: Differential diagnosis of transthyretin amyloidosis

Word count: 503
Transthyretin amyloidosis (ATTR) is a protein-misfolding disease, in which amyloid fibrils preferably infiltrate the myocardium [1]. On echocardiography, ATTR may present as a phenocopy of hypertrophic cardiomyopathy (HCM). Several methods may facilitate the diagnosis, such as echocardiography, scintigraphy, biomarkers, or genetic analysis [1]. We report a case that highlights the role of cardiac biomarkers, extracardiac symptoms and genetic analysis in a differential diagnosis of cardiac amyloidosis (CA).

A 47-year-old man with heart failure (NYHA class II) and suspicion of HCM or amyloidosis was referred to our hospital for a differential diagnosis. Doppler echocardiography revealed asymmetric left ventricular (LV) septal hypertrophy (2.2 cm at diastole) (Figure 1A) with preserved LV ejection fraction (61%), and LV outflow tract gradient of 22 mm Hg at rest and 36 mm Hg after provocation. The ratio of early to late diastolic transmitral flow velocity (E/A) was 1.6, indicating a nonrestrictive filling pattern. The global longitudinal strain (GLS) was preserved in the apical segments, and there was no “apical sparing” pattern typical for ATTR. The mean GLS was -18.3%, but there was a marked abnormal gradient of deformation between the basic and apical segments (min, -4%; max, -32%) (Figure 1B). For comparison, Figure 1C shows the totally abnormal GLS pattern of a patient with more advanced ATTR [2].

Patient had normal high-sensitive troponin T (hs-TnI- 9.3 ng/ml) and N-terminal pro-B-type natriuretic peptide (NT-proBNP- 98.5 pg/ml) levels (double negative results of biomarkers). Possible explanation for such results might be early phase of disease. One year later, measurement of NT-proBNP revealed positive result (374 pg/ml). Next, he experienced new-onset numbness in the hand (primarily the left one), indicating carpal tunnel syndrom with neural compression. This led us to change the tentative diagnosis from HCM to CA [1,2]. We performed $^{99m}$Tc-DPD scintigraphy, which showed a radiotracer uptake in the heart, typical for ATTR [1,2].
Genetic analysis revealed the ATTR variant c.325G>A p.(Glu109Lys). The variant E109K TTR is absent in ClinVar, however two other substitutions in the position of 109 in the TTR gene are assessed there either as pathogenic (E109Q) or uncertain significance (E109D). This finding supports the ATTR diagnosis.

The GLS polar map did not provide any conclusive findings. However, scintigraphy yielded strong evidence for ATTR, and the final diagnosis was confirmed by genetic analysis. The patient presented with normal hs-TnI and NT-proBNP levels despite several echocardiographic features typical for HCM with mild obstruction. Therefore, we postulate that the normal levels of hs-TnI and NT-proBNP may help distinguish HCM and ATTR (in early stage of disease). In study [3] in HCM subgroup with negative troponin, we have no data about minimal value of NT-proBNP but values of median and lower quartile are very high “1166.7 (775.5-1818.5) pg/ml” and probably troponin/NT-proBNP negative patients has not present. In methodology section, authors [3] did not mention about exclusion of HCM phenocopies. Authors [3] did not use any specific tests, examinations for differential diagnosis for ATTR. It is possible that some HCM patients (the lowest abnormal or hypothetically normal?) NT-proBNP level had undiagnosed ATTR.

References


Figure 1 A, Echocardiography: asymmetric left ventricular hypertrophy (septal) characteristic for hypertrophic cardiomyopathy; B, Echocardiography: a near-normal pattern of the global longitudinal strain (GLS) without typical features for transthyretin amyloidosis (ATTR), seen in our current patient; C, an abnormal pattern of the GLS typically seen in patients with more advanced ATTR