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IMAGE

Transthyretin Amyloidosis Mimicking Obstructive Hypertrophic Cardiomyopathy: A Great Imitator

Anurut Huntrakul, MD [a], Prasit Phowthongkum, MD [b], Patita Sitticharoenchai, MD [a], Maythinee Chantadisai, MD [c], Sarinya Puwanant, MD [a], Smonporn Boonyaratavej, MD [a], Pairoj Chattranukulchai, MD [a*]

[a]Division of Cardiovascular Medicine, Department of Medicine, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Bangkok, Thailand
[b]Division of Medical Genetics and Genomics, Department of Medicine, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Bangkok, Thailand
[c]Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Bangkok, Thailand

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A 56-year-old man was referred to our tertiary hospital for septal myectomy due to medically refractory obstructive hypertrophic cardiomyopathy (HCM). He presented with progressive exertional dyspnoea and reported that a number of episodes of exertional syncope had occurred over the previous year. He denied a significant past medical history or family history of cardiomyopathy. Physical examination revealed a grade 3 systolic ejection murmur along the left upper sternal border. A 12-lead electrocardiogram (ECG) demonstrated marked left ventricular (LV) hypertrophy by voltage criteria and inverted T waves in the inferolateral leads (panel A). A transthoracic echocardiogram showed severe concentric LV hypertrophy (anterior septum 30 mm, posterior 24 mm), with borderline impairment of LV systolic function (panel B). A resting LV outflow obstruction with a peak pressure gradient of 56 mmHg between the LV septum and the hypertrophied anterior papillary muscle was clearly seen (panel C; Supplementary Video 1). Two-dimensional speckle-tracking echocardiography revealed an abnormal global longitudinal strain (−10.3%) with a relatively apical-sparing pattern (ratio of 1.24, so-called ''cherry on top''; panel D), which raised the suspicion of cardiac amyloidosis.

Additional cardiovascular magnetic resonance imaging demonstrated diffuse delayed enhancement of thickened LV (panels E and F), right atrium (panels G and H, arrows), and interatrial septum (panels G and H, asterisks; Supplementary Video 2). The markedly hypertrophic LV was difficult to null. Abnormal pharmacokinetic washout of gadolinium contrast was also seen. All cardiovascular magnetic resonance findings were highly suggestive of cardiac amyloidosis as an aetiology of thickened LV rather than sarcomeric HCM. Serum protein electrophoresis, serum immunofixation, and serum-free light-chain assay were normal, essentially excluding amyloid light-chain amyloidosis. The patient had no history or biomarkers of chronic inflammatory disorders suggestive of amyloid A amyloidosis. A subsequent Tc-99 m pyrophosphate scan revealed grade 3 homogeneous radiotracer uptake at the LV myocardial region including the right atrium wall (panel I, arrows). The heart to contralateral lung ratio was 1.88, consistent with transthyretin (TTR) cardiac amyloidosis, which was the suggested nonbiopsy diagnosis by technetium-labelled bone scintigraphy tracer [1].

Next-generation sequencing of multiple genes revealed a known heterozygous pathogenic variant (p.Val50Met) in *TTR*, causing TTR-related cardiac amyloidosis. There was no pathogenic variant in sarcomeric genes associated with HCM.

A combined heart and liver transplantation was discussed with the patient and his family, but owing to a lack of efficient social support, the patient was, unfortunately, not eligible for the organ transplantation. Thus, diflunisal, a proposed TTR tetramer-stabilising drug, was prescribed and the patient has been closely followed up in the specialised clinic Figure 1.

*Corresponding author at: Division of Cardiovascular Medicine, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand, Email: pairoj.md@gmail.com

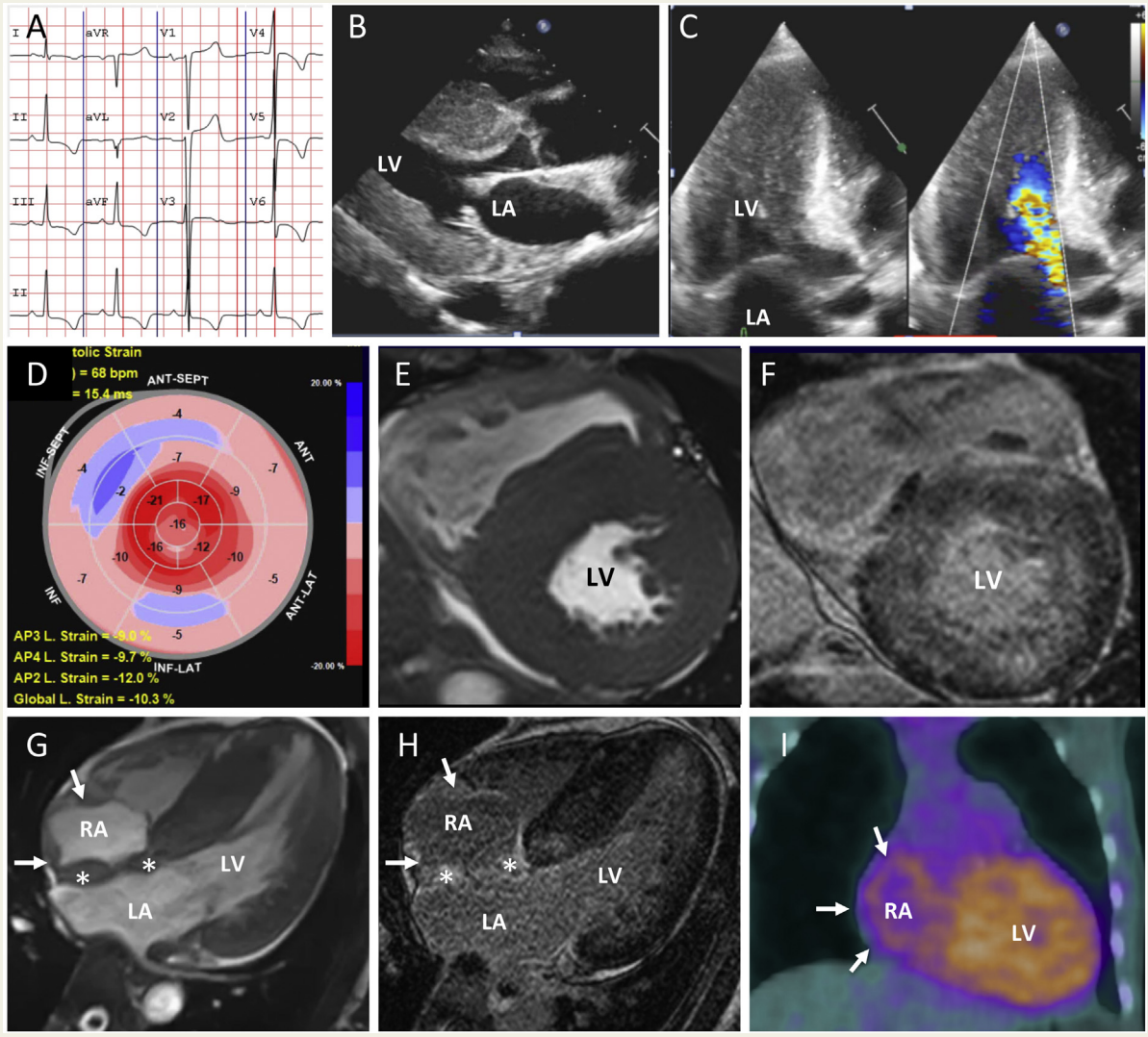

Figure 1 Abbreviations: LV, left ventricle; LA, left atrium; RA, right atrium.

Transthyretin cardiac amyloidosis has been widely underdiagnosed in patients with heart failure with preserved ejection fraction, or misdiagnosed as HCM. There were two distinct features in our patient that misled the clinicians towards obstructive HCM and myectomy. The first feature was the high ECG voltage, which met the criteria for left ventricular hypertrophy. In fact, a low voltage on ECG is found in less than one-third of patients with TTR cardiac amyloidosis and in even fewer individuals with the p.Val50Met (TTR-V30 M) mutation [2]. Globally, this is the most common variant associated with cardiac amyloidosis. Interestingly, genetic studies of sarcomeric genes and TTR identified three patients with TTR-V30 M from 45 patients diagnosed with HCM [3]. The second feature was the significant LV outflow tract gradient, a common finding in sarcomeric HCM; however, it has rarely been reported in patients with cardiac amyloidosis [4].

This case highlights the clinical challenges in distinguishing between two distinct diseases with different treatment strategies, and emphasises the important role of multimodal imaging and genetic testing in the diagnosis of atypical cases of TTR cardiac amyloidosis, with crucial prognostic significance and therapeutic implications. The combined results of grade 3 myocardial radiotracer uptake on Tc-99 m pyrophosphate scanning and the absence of a monoclonal protein profile provided a specificity and positive predictive value for TTR cardiac amyloidosis of 100% [1], which obviated the need for endomyocardial biopsy in this patient.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2018.11.021.

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