Case report

Overlapping phenotype of cardiomyopathy in patient with double mutation

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Abstract: Left ventricular noncompaction (LVNC) and hypertrophic cardiomyopathy (HCM) commonly occur as separate disorders with distinct clinical and pathoanatomical features. However, these cardiomyopathies may have a similar genetic origin with mutations encoding sarcomeric proteins. The described case demonstrates an example, in which phenotypic expression of both cardiomyopathies occurs in the same patient having double mutation.

Keywords: left ventricular noncompaction, apical hypertrophic cardiomyopathy, next-generation sequencing.

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1. Introduction

Left ventricular noncompaction (LVNC) (ORPHA:54260) and hypertrophic cardiomyopathy (HCM) (ORPHA:217569) commonly occur as separate disorders with distinct clinical and pathoanatomical features [1, 2]. Here we report one patient with features of both LVNC and apical HCM carrying two different potentially causative variants in myosin light chain 3 (MYL3) and myosin heavy chain 6 (MYH6) genes. Additionally, we emphasize the importance of multimodality imaging for the comprehensive assessment of cardiac morphology, function and the anatomy of coronary arteries.

2. Case report

A 39-year-old male was consulted by a cardiologist on an outpatient basis due to isolated apical HCM, which was diagnosed by transthoracic echocardiography (TTE) 3 years ago. At the time of consultation, the patient was asymptomatic with unremarkable personal history and positive family history of unspecified congenital heart disease in his sister and sudden cardiac death of his aunt. His physical examination was without any pathological findings. Electrocardiogram showed sinus rhythm, 80 bpm, LV hypertrophy, and negative T-waves in leads I, aVL, V4-6. Blood biochemistry was normal. TTE was performed and demonstrated isolated apical HCM with apical micro-aneurysm. Interestingly, blood flow was registered in the projection of hypertrophied apical segments raising the question about the correctness of the previous diagnosis. 1.5 T Siemens Avanto (Erlangen, Germany) cardiovascular magnetic resonance (CMR) was scheduled for clarification of heart morphology and function, as well for additional risk stratification of the patient. CMR revealed an overlapping phenotypical pattern of LV myocardium with hypertrophy of compacted apical segments (maximum wall thicknesses up to 13 mm, Figure 1, panels E and F) and hyper-trabecularization of midventricular segments with a ratio of

non-compacted to compacted myocardium up to 2.4 (Figure 1, panels C and D, see Supplementary files I-V). Additionally, LV apical micro-aneurysm (Figure 1, panels A and B) was detected with transmural late gadolinium enhancement in its wall representing fibrotic changes (Figure 2, panel A). To exclude any coronary artery anomalies or atherosclerotic changes computed tomography (CT) angiography was performed. CT angiography revealed normal coronary arteries and morphological LV changes consistent with CMR findings (Figure 2, panel B). 24-hour ECG monitoring showed sinus rhythm with only four sporadic ventricular premature beats. The patient underwent genetic consultation and testing. The latter revealed a heterozygous missense type MYL3 gene variant NM_000258.2c.382G>T, NP_000249.1:p.(Gly128Cys), rs199474704 and a heterozygous missense type MYH6 gene variant NM_002471.3:c.169G>A, NP_002462.2:p.(Gly57Ser), rs199474704.

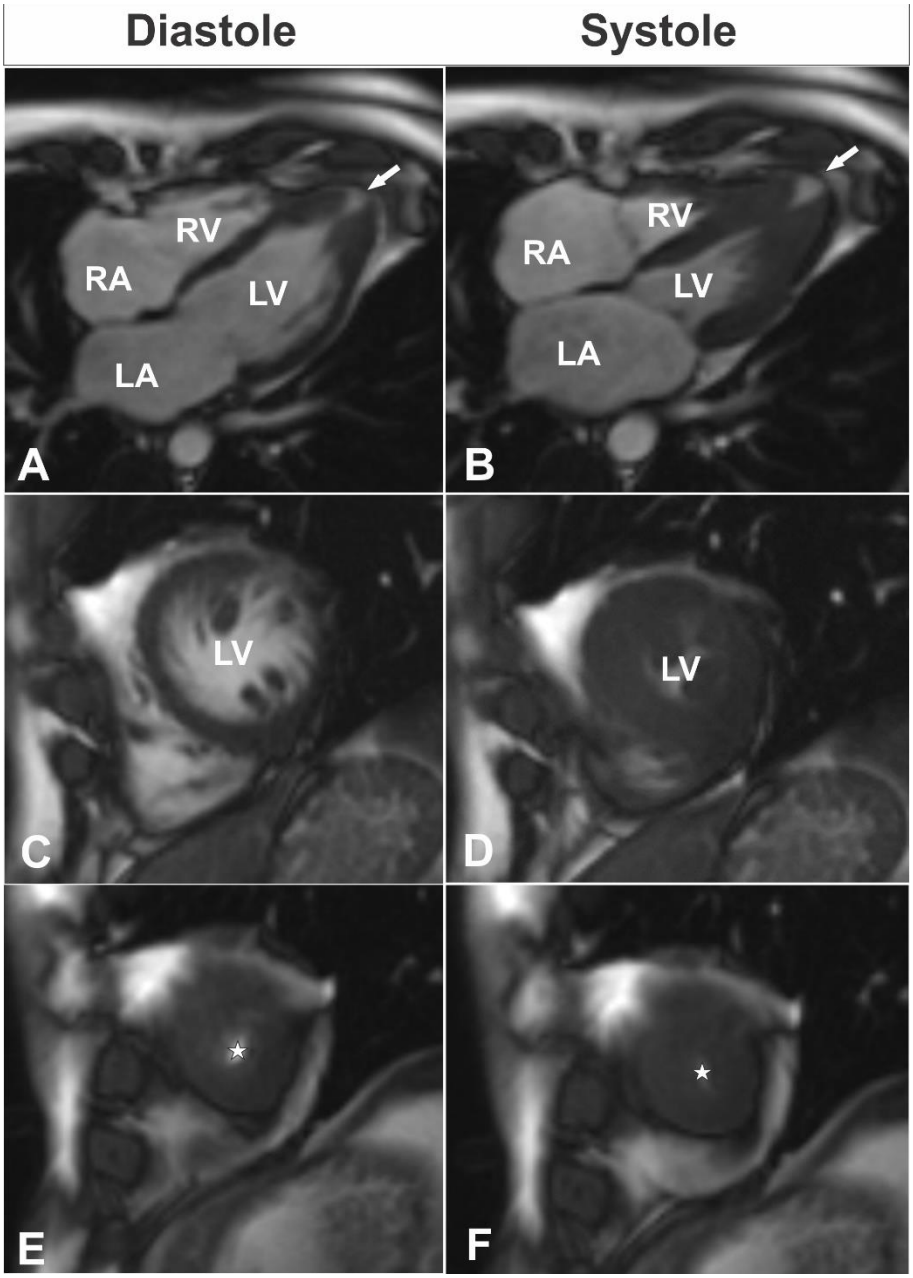

Figure 1. Magnetic resonance cine heart views in diastole (left-sided column) and systole (right-sided column). A and B: four-chamber cine views; C and D: midventricular short-axis cine views; E and F: apical short-axis cine views (* denotes blood pool). LA – left atrium, LV – left ventricle, RA – right atrium, RV- right ventricle,

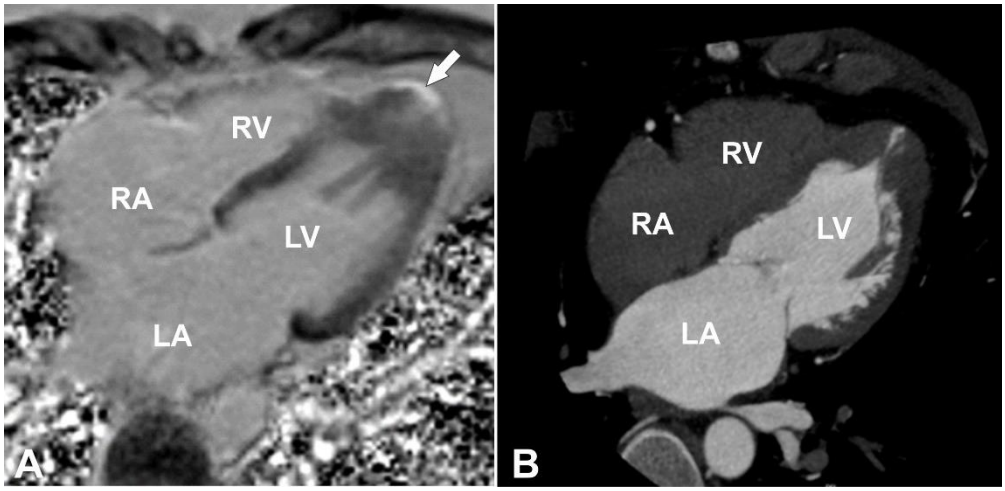

Figure 2. A, magnetic resonance four-chamber heart view obtained with inversion recovery sequence 10 minutes after injection of gadolinium-based contrast agent (late gadolinium enhancement image) with apical transmural fibrotic changes denoted with white arrow. B, four-chamber computed tomography heart view representing the morphologic findings of the heart seen on magnetic resonance images. LA – left atrium, LV – left ventricle, RA – right atrium, RV – right ventricle.

The above-described genetic alterations were discussed in the dedicated cardiomyopathy team and having into account the presence of double gene alterations and LV apical micro-aneurysm with transmural fibrotic changes, considering the patient's wishes the decision to implant a cardioverter-defibrillator for primary prevention of sudden cardiac death was taken. Treatment with beta-blockers was prescribed and the patient was referred for regular cardiological follow-up. The patient's daughter was scheduled for screening.

4. Discussion

The MYL3 gene (MIM#160790) encodes myosin light chain 3 protein belonging to the myosin family [3]. Myosins are essential in the maintenance of structural integrity and shape of the cell. Moreover, the interaction with actins plays a major role in myocyte contractility [4]. The alteration of MYL3 protein (either hereditary or secondary due to the activation of caspase) results in disruption of sarcomeres and eventually in contractile dysfunction due to the disorganized actin-myosin bonds in cardiomyocytes [5]. Pathogenic variants of the MYL3 gene have been associated with familial hypertrophic cardiomyopathy, type 8 (MIM#608751) inherited in an autosomal dominant or autosomal recessive manner. To date, 41 different pathogenic variants have been identified in the individuals affected with HCM [6]. The alteration NM_000258.2c.382G>T, NP_000249.1:p.(Gly128Cys), rs199474704 has been reported in a patient with end-stage HCM. The variant leads to an amino acid change in the conservative position (EF-hand domain/EF-hand domain pair domain of the protein) and the biochemical difference between glycine and cysteine is high (Grantham score 159). In silico analysis results: SIFT – deleterious (score 0.01), PolyPhen2 – probably damaging (score 0.927), Mutation taster – disease-causing (score 0.99). The variant is listed in The Human Mutation Database (CM117919), the frequency in the 1000 genomes project is 0.0, ExAC project - 0.0. Functional analyses have not been performed. Based on these observations the alteration was classified as possibly pathogenic according to the ACMG criteria and segregation analysis in the family was recommended.

Another heterozygous missense type MYH6 gene variant NM_002471.3:c.169G>A, NP_002462.2:p.(Gly57Ser) was also identified to the patient. MYH6 gene (MIM#160710)

encodes alpha heavy chain myosin functioning as a fast ATPase in cardiac muscle and participating in the contraction of myocytes [7]. The alteration of alpha-MHC protein may lead to the switch of expression to the MYH7 gene located upstream of the MYH6 gene thus accelerating the development of HCM [8]. Pathogenic variants of MYH6 gene have been associated with the atrial septal defect, type 3 (MIM#614089), dilated cardiomyopathy, type 1EE (MIM#613252), hypertrophic cardiomyopathy, type 14 (MIM#613251), and sick sinus syndrome, type 3 (MIM#614090) [9]. The alteration in MYH6 gene NM_002471.3:c.169G>A, NP_002462.2:p.(Gly57Ser) rs199474704 has not been described in scientific literature previously. The variant causes an amino acid change in semiconservative position (myosin, N-terminal, SH3-like/ P-loop containing nucleoside triphosphate hydrolase domain of the protein) but the biochemical difference between glycine and serine is moderate (Grantham score 56). In silico analysis results: SIFT – deleterious (score 0.024), PolyPhen2 – benign (score 0.256), Mutation taster – disease-causing (score 0.99). The frequency of the variant in the 1000 genomes project is 0.0, ExAC project - 0.0. Functional analyses have not been performed. The genetic change was classified as a variant of unknown significance (VUS) according to the ACMG criteria. Still, the segregation analysis is likely to uncover the true nature of the variant.

Nevertheless, the possession of two very rare alterations in cardiomyopathy genes might be associated with faster development of the disorder and with the diverse manifestation of structural rearrangements (both HCM and LVNC are present in our patient).

5. Conclusions

In summary, our case suggests that the phenotypical expression of both LVNC and HCM can occur in the same patient having two different genetic alterations (one of them likely pathogenic and the second VUS so far). This case also highlights the need for comprehensive multimodality imaging for the simultaneous assessment of morphological and functional changes of the heart. In the clinical practice, more awareness should be paid regarding the existence of the overlapping cardiomyopathy phenotypes, at the same encouraging the broader use of cardiovascular magnetic resonance in these patients.

Supplementary Materials: Video S1: magnetic resonance four chamber cine heart view. Video S2: magnetic resonance two chamber cine heart view. Video S3: magnetic resonance three chamber cine heart view. Video S4: magnetic resonance midventricular short axis cine heart view. Video S5: magnetic resonance apical short axis cine heart view.

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