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CASE REPORT

ADVANCED

CLINICAL CASE

Subclinical Hypertrophic Cardiomyopathy in Elite Athletes

Knowledge Gaps Persist

Fiona Chan, MBBS,[a,b] Tim Lockie, PhD,[b,c] Lorenzo Monserrat, PhD,[d] James C. Moon, MD,[b,e] Gabriella Captur, PhD[a,b,f]

ABSTRACT

Subclinical hypertrophic cardiomyopathy (HCM) is a phenotypic entity that has emerged from the increased use of cardiovascular magnetic resonance imaging in the evaluation and family screening of patients with HCM. We describe the case of a competitive athlete with a sarcomere gene mutation and family history of HCM who was found to exhibit the subclinical HCM phenotype on cardiovascular magnetic resonance imaging in the absence of left ventricular hypertrophy. We discuss the clinical uncertainties in her management. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2022;4:94–98) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 30-year-old competitive female athlete with a known family history of hypertrophic cardiomyopathy (HCM) was referred to our tertiary center with a history of intermittent palpitations associated with exertion. She reported no dizziness, syncope, dyspnea or chest pain.

Her mother had a diagnosis of HCM with a confirmed actin alpha cardiac muscle 1 (*ACTC1*) gene mutation (potentially pathogenic variant p.Val11Leu).

LEARNING OBJECTIVES

- To recognize the features of subclinical HCM.
- To review current guidelines regarding exercise in HCM.

Her maternal grandmother and maternal uncle had experienced sudden death; however, no antemortem cardiac phenotyping, autopsy, or genetic data were available (**Figure 1**).

On examination, blood pressure measured 91/60 mm Hg and resting heart rate 73 beats/min. Cardiovascular and respiratory systems were unremarkable.

PAST MEDICAL HISTORY

She reported well-controlled asthma managed with inhalers.

DIFFERENTIAL DIAGNOSIS

In this patient with a family history of HCM related to mutation of the *ACTC1* gene, the priority was to assess

From [a]The Royal Free Hospital, Centre for Inherited Heart Muscle Conditions, Cardiology Department, Pond Street, Hampstead, London, United Kingdom; [b]UCL Institute of Cardiovascular Science, University College London, Gower Street, London, United Kingdom; [c]The Royal Free Hospital, Cardiology Department, Pond Street, Hampstead, London, United Kingdom; [d]Cardiovascular Genetics, Health in Code, A Coruña, Spain; [e]Cardiac MRI Unit, Barts Heart Centre, West Smithfield, London, United Kingdom; and the [f]UCL MRC Unit for Lifelong Health and Ageing, University College London, Fitzrovia, London, United Kingdom.

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for HCM and/or cardiac structural abnormalities, and for associated arrhythmias.

INVESTIGATIONS

ELECTROCARDIOGRAM. A 12-lead electrocardiogram (ECG) showed normal sinus rhythm with normal PR interval, QRS duration and QTc (**Figure 2**). There was no left ventricular hypertrophy (LVH), but there was T-wave inversion in V_1 and III (which the International Criteria for ECG interpretation in Athletes disregards when considering pathological T-wave inversion) (1). There was QRS fragmentation in V_3, for which there is a paucity of data on clinical significance in both subclinical HCM and athlete's heart.

ECHOCARDIOGRAPHY. Transthoracic echocardiography showed normal left ventricular (LV) cavity size, wall thickness (maximally 9.1 mm at basal septum), systolic (LV ejection fraction 55% to 60%) and diastolic function (E/A = 2.07; E/e'=5.99). There was no intracavitary gradient and normal right ventricle (RV), valves, and atria.

HOLTER MONITORING. There was <1.5% ventricular ectopy burden on Holter monitor with no nonsustained ventricular tachycardia.

GENOTYPING. Given the known maternal mutation, the patient underwent targeted Sanger sequencing of the *ACTC1* gene fragment where the maternal variant was located (exon 2 and its flanking intronic regions): NP_005150.1:p.Val11Leu/NC_000015.9:g.35086979C>G. Results confirmed that our patient was a heterozygous carrier of the same variant identified in her mother. This variant has not been reported in public genetic databases, suggesting low frequency in the population. However, other variants affecting nearby residues have been clearly associated with HCM. Specifically, the neighboring variant p.Leu10Met has been identified in the center's database as showing significant overrepresentation in HCM patients with cosegregation in multiple families. The disease course with *ACTC1* gene mutations appears to have a good prognosis, with sudden death at a young age being exceptional.

Based on available data, the patient's identified variant was deemed to be potentially pathogenic. Targeted gene testing for other family members has been recommended to evaluate its segregation with the phenotype.

CARDIOVASCULAR MAGNETIC RESONANCE. Cardiac magnetic resonance (CMR) imaging at 1.5-T showed normal LV size and maximal diastolic wall thickness (9.5 mm) but increased septal systolic wall thickness at 12.5 mm (normal, 11.2 ± 2.1 mm) (2). There was hyperdynamic function (mitral annular plane systolic excursion, 20 mm; LV ejection fraction, 72%). The LV contained 3 inferior myocardial crypts (1 crypt considered normal) (**Figure 3,** Video 1) and prominent septomarginal trabeculum (2 mm). The anterior mitral valve leaflet was elongated at 24 mm (normal, 19.7 ± 3.1 mm). The maximal apical fractal dimension was marginally increased at 1.25 (normal, 1.199 ± 0.05) (**Figure 3**) (2). Native T1 was normal (1,040 ms; normal, 950 to 1,060 ms). There was trace RV insertion point late gadolinium enhancement.

Given her carriage of this *ACTC1* variant and the constellation of structural and functional abnormalities noted on CMR, subclinical HCM was diagnosed.

ABBREVIATIONS AND ACRONYMS

ACTC1 = actin alpha cardiac muscle 1

CMR = cardiac magnetic resonance

EF = ejection fraction

HCM = hypertrophic cardiomyopathy

LGE = late gadolinium enhancement

LV = left ventricle

LVH = left ventricular hypertrophy

RV = right ventricle

MANAGEMENT

As she does not currently meet familial HCM criteria and the subclinical HCM phenotype is not recognized as a phenotype-positive entity in guidelines, no restriction on her athletic activities has been imposed.

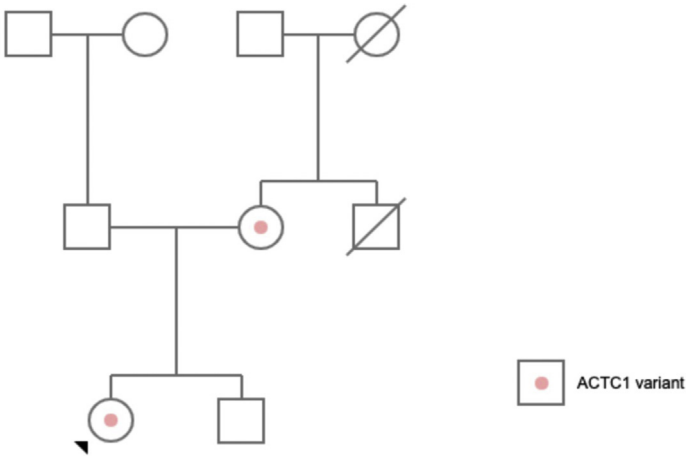
DISCUSSION

"Subclinical HCM" is a recently recognized term that has emerged from increasing use of CMR in the assessment of cardiomyopathy. Features of subclinical HCM include multiple myocardial crypts, anterior mitral valve leaflet elongation, and abnormal trabeculae, which reflect the underlying sarcomere mutation (3,4). We suggest defining subclinical HCM as patients who have a sarcomere gene mutation without LVH as a separate entity from those who are genotype-positive, phenotype-negative; these patients have a phenotype – that of subclinical HCM.

Our patient is an athlete, which raises the possibility of overlap with exercise-induced cardiac remodeling (EICR). Generally speaking, subclinical HCM phenotype differs from EICR observed in athletes. Features of EICR include balanced biventricular dilatation, mild-to-moderate increases in LV wall thickness, and biatrial dilatation (5). None of these EICR features were observed in our patient.

Our patient has RV insertion point late gadolinium enhancement (LGE) on her CMR. Although this pattern of fibrosis has been observed in healthy endurance athletes and has been associated with low risk of adverse events in patients with confirmed HCM, the significance of LGE in subclinical HCM is unknown (6,7); therefore, no restrictions have been placed on our patient regarding exercise. This is in contrast to the wealth of evidence showing that

FIGURE 1 Genetic Pedigree

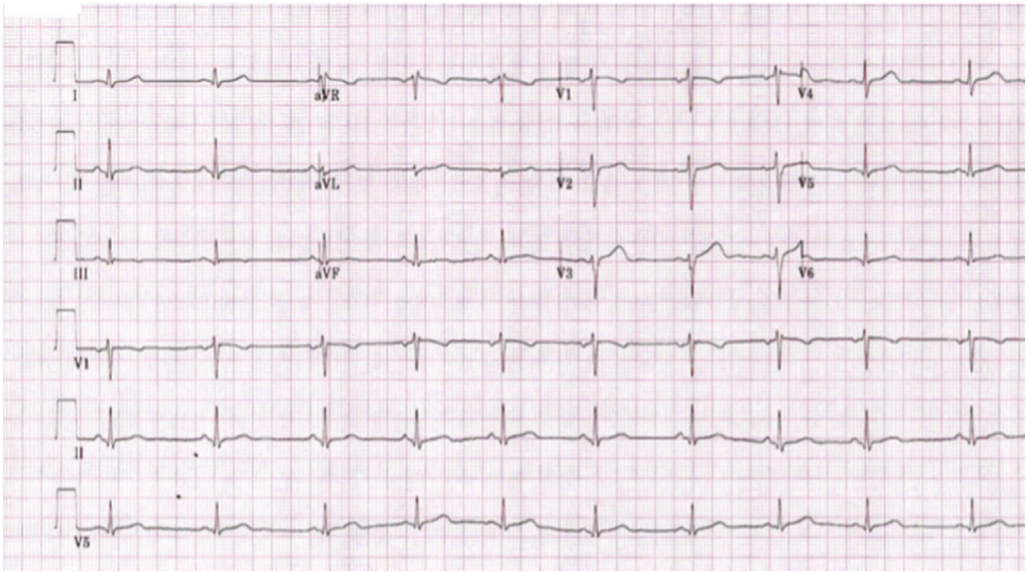


Patient indicated by arrowhead. ACTC1 = actin alpha cardiac muscle 1.

diffuse, extensive LGE in overt HCM is considered a high-risk marker for sudden cardiac death events, and a prophylactic implantable cardioverter-defibrillator may be recommended (8,9).

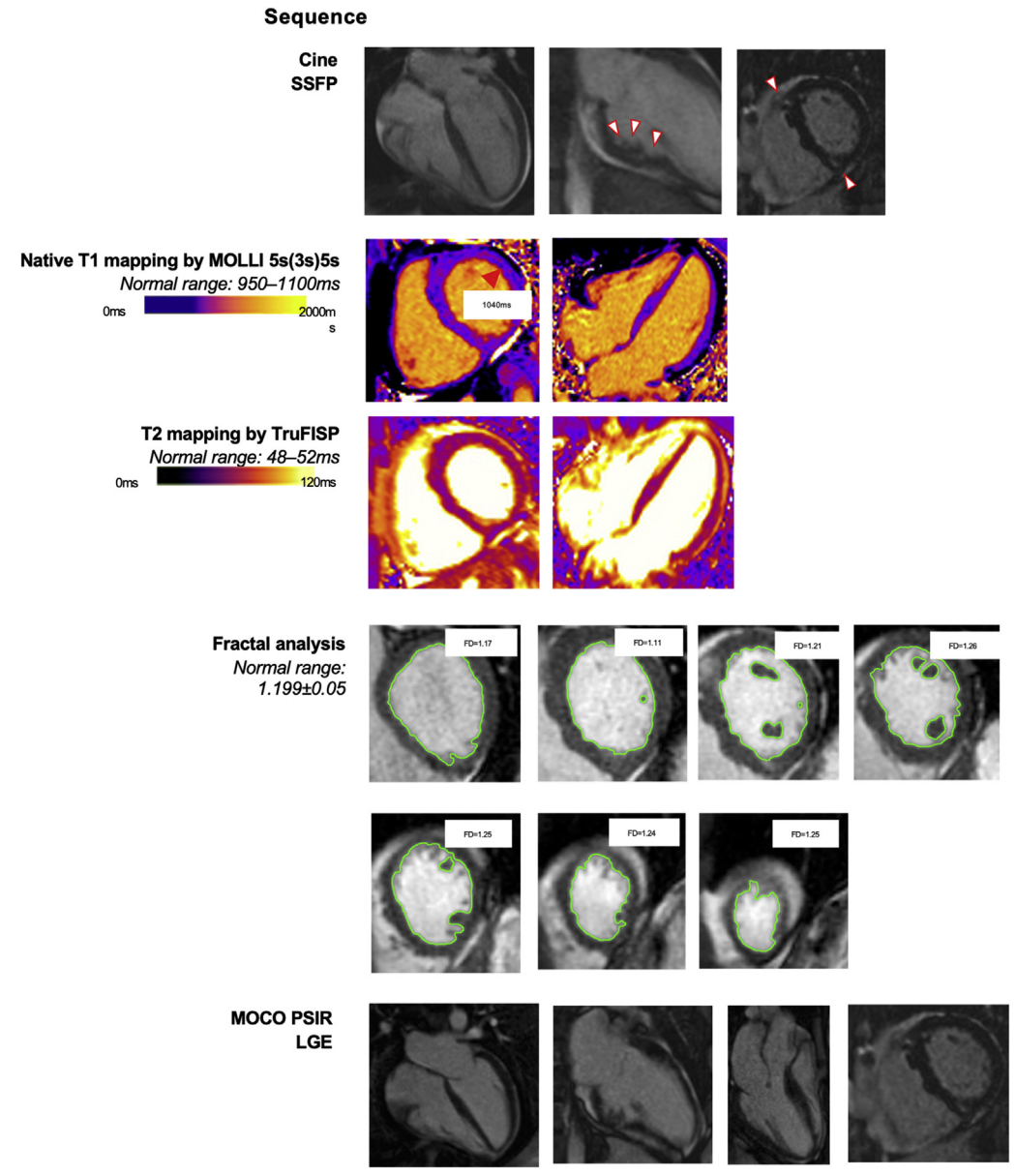
Can she continue to exercise at a competitive level? Both the American Heart Association and European Society of Cardiology guidelines have class II recommendations regarding the participation in competitive sports for patients who have HCM gene mutation without LVH: "participation in all competitive sports may be considered…" (10); "…participation in competitive athletics is reasonable" unless there are

FIGURE 2 Electrocardiogram Was Negative for Left Ventricular Hypertrophy



According to 4 criteria, the electrocardiogram was negative for left ventricular hypertrophy: 1) Sokolow-Lyon: SV1+ RV5/6 <3.5 mV; 2) Cornell for females: SV3 + RaVL <2.0 mV; 3) Lewis: RI+SIII – (SI+R III) <1.7 mV; and 4) Gubner: RI + SIII <2.0 mV. Studies suggest that Cornell, Lewis, and Gubner criteria show the greatest sensitivity and specificity for left ventricular hypertrophy diagnosis of hypertrophic cardiomyopathy (14). In the case of our patient who is an athlete, the electrocardiogram is considered normal.

FIGURE 3 **Cardiac Magnetic Resonance Images**



There are 3 inferior myocardial crypts and right ventricular insertion point late gadolinium enhancement (LGE). Myocardial crypts are thought to be congenital, representing abnormal fetal cardiac morphogenesis due to in utero expression of the underlying sarcomere gene mutation (15). There is prominent septomarginal trabeculum. Native myocardial T1 is within normal range. There is increased maximal apical fractal dimension (reported normal range for fractal analysis is for maximal apical fractal dimension). MOLLI = modified Look-Locker imaging; SSFP = steady-state free precession; MOCO = motion corrected; PSIR phase-sensitive inversion recovery.

"high risk features," as there is no evidence at present that genotype-positive patients without LVH are at risk of sudden cardiac death above that of the general population (11). The guidelines categorize patients with subclinical HCM into the "phenotype negative" group, as only patients with confirmed LVH are considered to be "phenotype positive." This definition should be re-explored. It is possible that years before

the development of overt LVH, a subtle but detectable "phenotype" had already been established (ie, that of subclinical HCM), meaning that these sarcomere gene mutation carriers are not actually "phenotype-negative." This point is not well addressed in current guidelines.

This case highlights the crucial role of advanced cardiac imaging. In this case, CMR was necessary to recognize the subtle characteristics of subclinical HCM that were not identified with conventional imaging, thereby informing management recommendations. The case also highlights the role of cardiovascular genetics, a subspecialty evolving as our understanding of heritable cardiac disorders grows. Cascade testing in family members can identify individuals with variants before overt disease expression, raising questions around frequency of surveillance, lifestyle modification, and the identification of unreported variants, such as in our case. Variant interpretation is subject to reassessment. In such cases, a specialist in genetic counselling is beneficial. Conversely, the disadvantages of genetic testing should be acknowledged. Our patient could be labelled as having heart disease, which may have undesirable implications on her ability to obtain health insurance, and may have considerable psychosocial impact stemming from a gene-positive result without a clear clinical diagnosis.

FOLLOW-UP

The patient remains stable and continues to compete. Based on current natural history studies, her likelihood of developing clinical HCM is considered to be low, assuming her *ACTC1* variant has the same penetrance as established sarcomere variants reported in the literature (12,13). She is reviewed yearly with ECG and imaging by echocardiography, which is replaced by CMR every 3 years to track phenotype evolution. At last review, maximal wall thickness was <13 mm and ECG showed no voltage criteria for LVH.

CONCLUSIONS

The management and risk stratification of patients with subclinical HCM is being steadily elucidated. Subclinical HCM needs formal recognition in HCM guidelines and further studies are necessary to understand its natural history to better inform patient care.

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ADDRESS FOR CORRESPONDENCE: Dr Gabriella Captur, UCL MRC Unit for Lifelong Health and Ageing, University College London, London WC1E 7HB, United Kingdom. E-mail: gabriella.captur@ucl.ac.uk. Twitter: @gabycaptur.

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APPENDIX For a supplemental video, please see the online version of this paper.