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Clinical Case
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Apical hypertrophic cardiomyopathy phenotype differential diagnosis

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Abstract

Multiple causes of myocardial thickening may mimic hypertrophic cardiomyopathy (HCM) phenotypes. We present the case of a previously undiagnosed severe hypertensive patient with an incidentally discovered morphological and electrical HCM phenotype. The potential overlap of HCM, hypertensive heart disease, and other HCM phenocopies may lead to ambiguity in the absence of an adequate multi-modal differential diagnosis. Accurate diagnosis is mandatory for prognosis-tailored treatment, especially regarding the risk of sudden cardiac death and the complex decision of internal cardioverter-defibrillator implantation.

Keywords: apical hypertrophic cardiomyopathy; cardiac magnetic resonance imaging; internal cardioverter defibrillator.

Introduction

Multiple causes of myocardial thickening may mimic hypertrophic cardiomyopathy (HCM) phenotypes. We present the case of a previously undiagnosed severe hypertensive patient with an incidentally discovered morphological and electrical HCM phenotype. The potential overlap of genetic forms of HCM and hypertensive heart disease (HHD) may lead to ambiguity in the absence of an adequate multi-modal differential diagnosis.

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Case report

A 49-year-old obese male with a history of smoking presented to the Emergency Department (ED) for a 3-day history of cough and mucopurulent sputum. The patient had no relevant medical history and no treatment, yet moderate exertion dyspnea had manifested throughout last year. Maternal sudden cardiac death (SCD) at a similar age was noted.

The clinical examination revealed an afebrile patient with grade II obesity (BMI ≈ 36 kg/sqm). Right mid and basal thoracic coarse inspiratory crackles were audible. Brachial supine blood pressure (BP) was 160/84 mmHg bilaterally. No cardiac murmurs or additional heart sounds were noted. No other systemic pathological features were present.

Chest X-ray (Figure 1) revealed right lower lobe consolidation and local air bronchogram, which were consistent with community-acquired bacterial

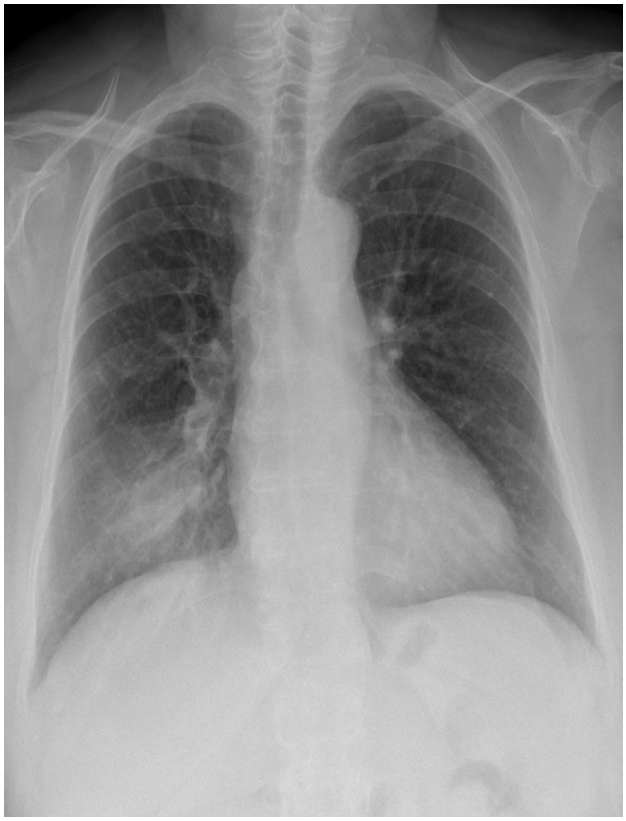

Figure 1. Postero-anterior chest x-ray showing right lower lobe pneumonia.

pneumonia (CAP) and considered to account for the aforementioned symptoms.

Laboratory tests showed 18,000/mmc leukocytosis (with a 90% neutrophil count). Normal transaminases, creatine kinase, renal function (eGFR = 76 ml/min/1.73 sqm), and normal plasma sodium and potassium levels were noted.

Routine ED ECG showed sinus rhythm, left atrial (LA) enlargement, and left ventricular (LV) electrical criteria of hypertrophy (LVH) with giant asymmetrical (14 mm) precordial T-wave inversion (Figure 2).

ED screening transthoracic echocardiogram (TTE) revealed significant LVH in the apical segments of the lateral and anterior walls (20 mm), while the basal septum measured 14 mm and the inferior basal wall measured 10 mm. There was preserved global LV systolic function (LVEF – 57%) without any wall motion abnormalities. No left ventricular outflow tract obstruction (LVOTO) was evident, and the maximum provoked peak gradient was 25 mmHg. Mild mitral regurgitation with no systolic anterior motion (SAM) and mild LA dilation were observed (35.2 ml/m2). There was no significant aortic valve stenosis. RV and RA had normal dimensions, wall thickness, and function, and there were no signs of pulmonary hypertension.

Consequently, the case was interpreted as a CAP in a possibly hypertensive patient who exhibited pronounced apical LVH. Empiric therapy with Amoxicillin-Clavulanate 875/125 mg b.i.d was initiated, and further evaluation was undertaken for arterial hypertension diagnosis (including screening of secondary causes) and differential diagnosis of LVH.

Automated blood pressure monitoring led to a clear diagnosis of arterial hypertension (HTN) (mean BP value of 194/97 mmHg) (Figure 3). Severe sleep apnea was diagnosed (AHI index – 38/hr). Treatment with Metoprolol succinate 100 mg q.d., Perindopril/Amlodipine 5/5 mg q.d. (with subsequent up-titration to 10/10 mg), and titrated continuous positive airway pressure (CPAP) were initiated. Other secondary causes of HTN were excluded.

Ambulatory 48h EKG monitoring was unremarkable and no non-sustained ventricular tachy-

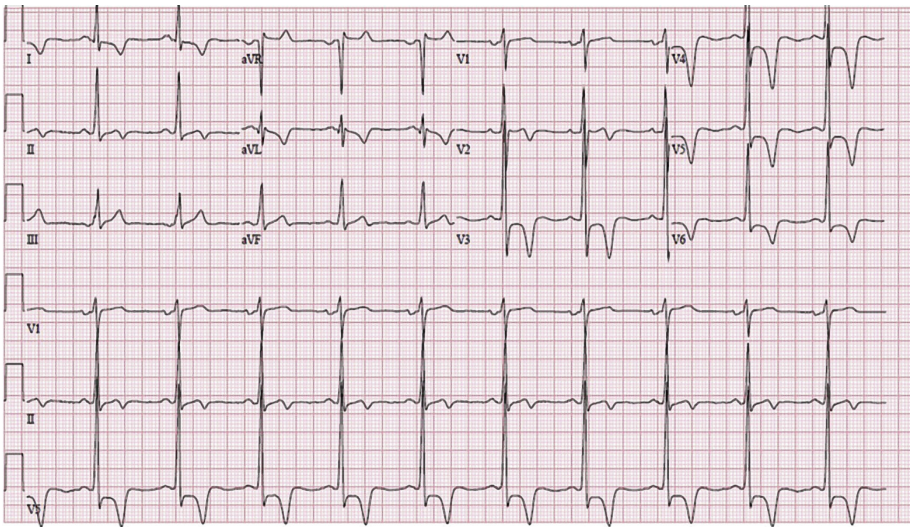

Figure 2. Routine emergency department ECG showing left ventricular hypertrophy, asymmetric giant inversion of the precordial T wave suggesting apical hypertrophy.

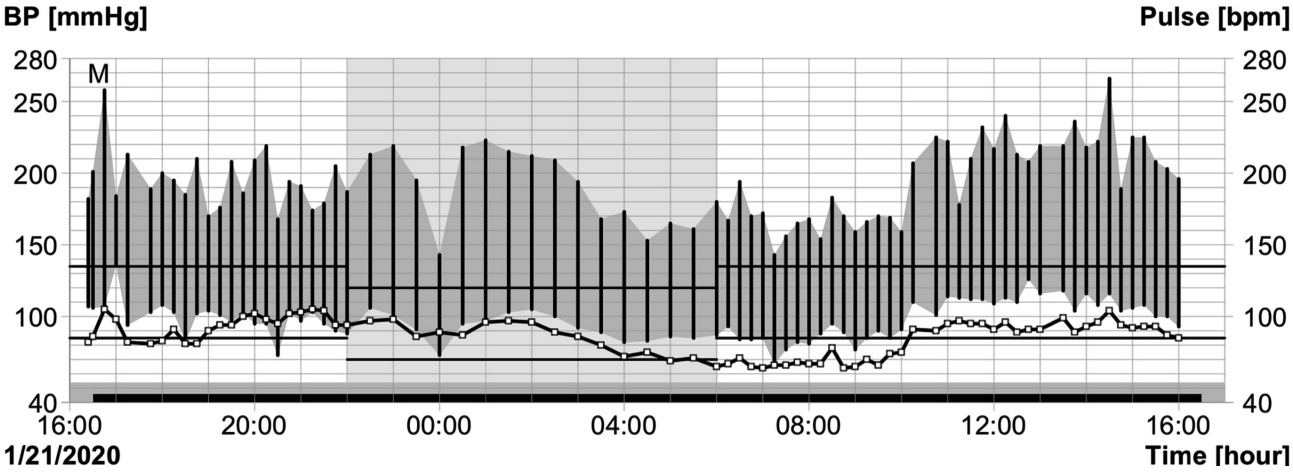

Figure 3. Automated blood pressure monitoring revealing severe hypertension with a reverse-dipper pattern.

cardia (NSVT) or supraventricular tachycardia were diagnosed.

The matter of LVH causality warranted further investigations. Cardiac magnetic resonance imaging (CMR) confirmed the echocardiographic findings. Predominantly apical anterior and lateral wall LVH was revealed without myocardial edema and no late gadolinium enhancement (LGE) areas (Figure 4). An apical thrombus was excluded. LV systolic function was borderline abnormal (LVEF – 50%) with mild longitudinal systolic dysfunction, and the indexed LV mass was within the normal range (84 g/m). No SAM or LVOTO were visible; however, a mid-anteroseptal myocardial crypt was evident (Figure 4C). T1 mapping revealed borderline increased values (native – 1019 msec and post-contrast – 352 msec) but without a significant increase of the extracellular volume (ECV) – 26% in the hypertrophied myocardium (Figure 4H). STIR and T2 mapping did not show evidence of myocardial edema (Figure 4D).

Predominantly apical left ventricular hypertrophy can be observed in diastolic cine frames

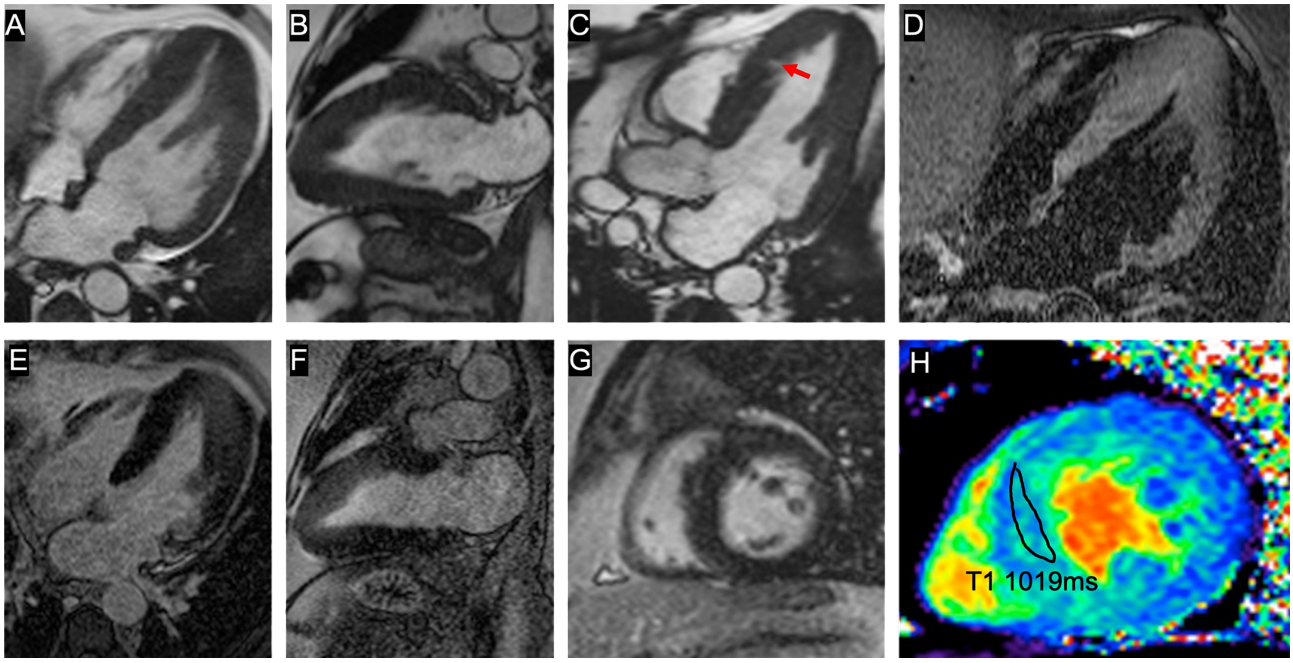

Figure 4. Contrast-enhanced cardiovascular magnetic resonance (CMR). Predominantly apical left ventricular hypertrophy can be observed in cine diastolic frames acquired in 4-chambers (A), 2-chambers (B) and 3-chambers long axis views. Apical insertion of the papillary muscles can be seen (A), as well as the antero-septal myocardial crypt (C, red arrow). Four-chambers T2-weighted image (D) shows no evidence of myocardial edema. Late gadolinium enhancement (LGE) acquired in 4-chambers, 2 chambers and short axis views (E, F and G, respectively) show no evidence of focal myocardial fibrosis. Native T1 value was measured as 1019 ms in the interventricular septum.

acquired in 4-chambers (Figure 4A), 2-chambers (Figure 4B) and 3-chambers long axis views. Apical insertion of the papillary muscles can be seen (Figure 4A) as well as the antero-septal myocardial crypt (Figure 4C, red arrow). Four-chambers T2-weighted image (Figure 4D) shows no evidence of myocardial oedema. Late Gadolinium enhancement (LGE) acquired in 4-chambers, 2 chambers amd short axis views (Figure 4E, F and G, respectively) showed no evidence of focal myocardial fibrosis. Native T1 value was 1019 ms in the interventricular septum.

An intermediate risk of SCD at 5 years was calculated (5.38%) based upon LA dilation and familial SCD history by using the ESC-validated algorithm.

The patient was reevaluated after six months and adequate BP and BMI control were achieved (mean BP – 130/80 mmHg). ECG and TTE were stationary and the patient was clinically asymptomatic.
A final decision of primary prophylaxis internal cardioverter-defibrillator implant was made, and the patient was scheduled for genetic testing.

Discussion

Apical hypertrophy

The hypertrophic cardiac phenotype may be induced by several diseases. HCM is established in adults by an objective measurement of the maximal end-diastolic wall thickness of ≥15 mm (if no HCM first-degree relatives are known) in the absence of other causes of LV hypertrophy [1, 2]. HTN-induced hypertrophy leads to a well-known pressure-adaptive morphology known as HHD. Whether our patient exhibited a form of HHD or primitive hypertrophic cardiomyopathy is the first subject of the current discussion.

A clear predominant apical hypertrophy pattern was shown by CMR. Involvement of segments proximal to the papillary muscle insertion (which did not regress after BP control) suggests a form of "distal dominant" [3] or "mixed" [4] type of apical HCM (ApHCM). It is not characteristic of HHD where hypertrophy is usually concentric and does not display an apical-to-basal gradient. Theoretically, whether the patient manifested both genetic ApHCM and a degree of "basal" HHD is to be judged by the potential basal hypertrophy regression after BP control. Furthermore, we consider it not clinically relevant as ApHCM dictates prognosis and not the "accompanying" HHD.

Apart from HHD, the differential diagnosis of HCM should involve HCM phenocopies. However, phenocopies seldomly present as ApHCM.
Anderson-Fabry's disease is usually characterized by concentric hypertrophy with typical inferolateral wall LGE but can infrequently manifest as ApHCM [5]. Due to intracellular glycosphingolipid storage, mainly the hypertrophied segments exhibit decreased native T1 values (which can manifest diffusely) [6, 7]. However, the "T1 pseudonormalization" may be encountered in advanced cases due to progressive inflammation-induced myocardial fibrosis. Isolated cases of apical sarcoidosis have been mentioned [8]. However, cardiac sarcoidosis is characterized by (multi)focal inflammation leading to subendocardial, mid-wall, and subepicardial edema and scars (increased T1/T2/ECV) [6].

Even if not applicable for our patient, the athlete's heart may present as ApHCM [9, 10]. Native T1 mapping is usually lower in athletes than sedentary HCM patients. As LVH increases in athletes, ECV continues to decrease (because of cellular hypertrophy), whereas, in HCM, ECV increases by cellular disarray and extracellular matrix expansion [10].

Myocardial crypts

Myocardial crypts are slit-like structures that penetrate the compacted myocardium, such as the one depicted in Figure 4C. Even though more prevalent in HHD and HCM, they do not possess specificity for diseased myocardium [11]. Interestingly, myocardial crypts are more frequently encountered in negative-phenotype patients with proven gene-causing mutations that were referred for CMR due to family history [11]. Whether crypts should guide genetic testing in patients with familial history of HCM and otherwise normal CMR is to be studied further.

Patient prognosis

ApHCM in Asian cohorts seems to have a more favorable clinical outcome than non-ApHCM. Kim *et al.* enrolled 350 Asian subjects diagnosed with HCM who underwent CMR and TTE, 85 of which were classified as "pure" ApHCM [12]. Non-ApHCM patients were more likely to have a family history of SCD, and NSVT was more frequently detected during 24h ECG monitoring. ApHCM patients had less frequent LVOTO and more frequent apical aneurysms. "Pure" ApHCM had less presence and amount of myocardial fibrosis, lower LV mass, and a milder LV diastolic dysfunction. All these findings conclude that this unique phenotype of HCM is associated with a more benign course of disease in Asians (rare occurrence of adverse cardiac events and lower mortality), which is concordant in many studies on this population [13, 14].

However, in 2020, Steinberg *et al.* performed a retrospective analysis on a French-Canadian cohort of 301 subjects, which showed a significantly increased risk of ventricular arrhythmia for ApHCM compared to non-ApHCM [15]. Interesting-

ly, there was no difference in the family history of SCD between the two groups. The presence of an apical aneurysm and a phenotype of ApHCM were identified as independent predictors of the occurrence of sustained VT and ApHCM phenotype; alongside significant LGE, these were independent risk factors for the primary endpoint (documented sustained ventricular arrhythmia, appropriate Implantable Cardioverter Defibrillator (ICD) therapy, arrhythmogenic syncope, cardiac arrest, or all-cause mortality) in multivariate analysis. Familial history of SCD also independently predicted sustained monomorphic VT. Genetic testing was also performed in this study, showing decreased diagnostic yield in ApHCM compared to non-ApHCM.

This leads to an apparent contradiction between the prognosis of ApHCM in Asian and French-Canadian cohorts. Different genetic substrates may explain this within the two populations, leading to the same clinical phenotype but having a clearly different prognosis. Genetic testing was unfortunately not performed in the former cohort.

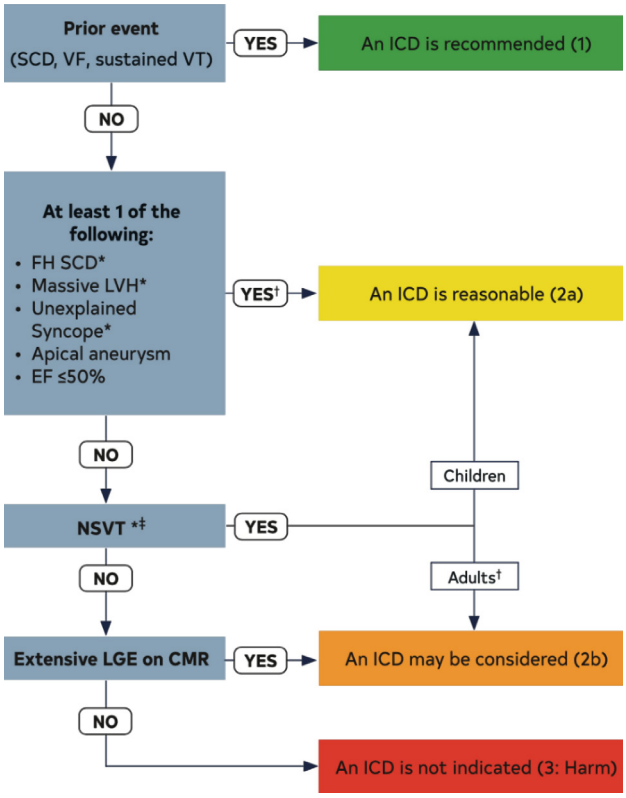

Figure 5. Summary of sudden cardiac death (SCD) risk factors that should be accounted for when deciding if an ICD should be implanted in HCM patients [1].

Primary prophylaxis ICD

The decision to implant an ICD is complex, and ICD-related anxiety and potential lead-system complications and [16] inappropriate therapies should always be taken into consideration. Modern ICD programming in HCM patients still leads to a 2.1%/year incidence of inappropriate shocks [16].

The most recent available guidelines derive from the 2020 American Heart Association/American College of Cardiology Guidelines for Hypertrophic Cardiomyopathy (Figure 5). The updates of the preexisting SCD predicting factors (compared to the 2014 ESC guidelines) underline the growing field of knowledge in HCM-related SCD understanding [1, 2].

The higher sensitivity of predicting SCD in HCM patients according to the ACC/AHA guidelines stems from the newly incorporated risk factors, such as extensive LGE, systolic dysfunction with ejection fraction <50%, and LV apical aneurysms [17]. These factors account for approximately one-fourth of the appropriate ICD therapies and are excluded from the ESC algorithm. This is why the former should be currently used for ICD implant decisions. It should be noted that the importance of LA dimensions and maximal LVOT gradient has been down-graded, but these are still mentioned in the AHA guidelines [1].

Diagnosis of HCM at a young age (<40 years old, which is probably due to a more aggressive disease), atrial fibrillation (which may be a surrogate of disease progression), and extensive LGE predict ventricular arrhythmias in HCM [16]. Even though there are multiple high-risk mutations reported, there are no currently available formal indications for genotype-driven ICD implants [18].

Considering our patient's history of maternal SCD (which seemed to have been arrhythmic) and borderline CMR LV systolic function, ICD implantation for primary prophylaxis was considered justifiable.

Conclusion

Hypertrophic cardiomyopathy may be regarded as an umbrella phenotype shielding very different pathologies. Proper grasp and understanding of the disease and its individual prognosis may prove challenging in real-life clinical scenarios and should rely on multi-modal evaluation (with emphasis on accurate CMR interpretation) for treatment decisions.

Conflict of interest

The author confirms that there are no conflicts of interest.

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