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RESEARCH **ORIGINAL ARTICLE**

Apical Hypertrophic Cardiomyopathy in a Caucasian Male: A Case Report

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ABSTRACT

Apical hypertrophic cardiomyopathy (ApHCM) is a relatively uncommon variant of hypertrophic cardiomyopathy typically involving the left ventricular apex. We report a case of a 64-year-old Caucasian male who presented with chest pain and negative cardiac biomarkers and was later found to have a diagnosis of ApHCM. The variable presentation, the clinical course of the disease, and limited literature among the Caucasian population create a challenge in detecting ApHCM and result in a delayed or a missed diagnosis. However, by spotting its characteristic features on electrocardiography ("giant" negative precordial T-waves) and the "ace of spades" configuration on echocardiogram, as well as using cardiac catheterization and cardiac MRI, an ApHCM diagnosis can be confirmed. This particular case underscores the infrequent occurrence of ApHCM in Caucasians, along with its complex diagnostic and presentation characteristics

KEYWORDS - Apical Hypertrophic Cardiomyopathy, Left Ventricular Outflow Obstruction, Left Ventricular Hypertrophy, Yamaguchi Syndrome, Acute Coronary Syndrome, Missed Diagnosis, Electrocardiography Magnetic Resonance Imaging, Echocardiography, Cardiac Catheterization.

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CASE REPORT

A 64-year-old Caucasian male – presented to the emergency room with a complaint of new-onset chest pain that started an hour prior to his presentation. The chest pain was heavy in nature, associated with diaphoresis, and lasted about 15 minutes with no radiation. The patient denied experiencing syncope, dyspnea, nausea, or vomiting.

His medical background includes prediabetes and gout, for which he takes Allopurinol. The patient is an ex-smoker; he denies alcohol consumption. He was diagnosed with hypertension many years ago, which is now controlled with (Candesartan, bisoprolol fumarate, and indapamide). The patient also takes low-dose aspirin daily for primary prevention. The patient's family history was notable for myocardial infarction that led to the death of his father at the age of 75 years old. The patient's siblings and offspring have no known cardiac conditions.

In his case, the most important cardiac differential diagnosis that should be ruled out is acute coronary syndrome (ACS). Possible other causes include aortic dissection, gastric reflux disease, musculoskeletal pain, and pericarditis.

On arrival to the emergency room, the patient was doing relatively well and was seen by the cardiology fellow on call. The patient was conscious, alert, oriented, and not in pain. He was non-febrile and had a normal heart rate of 84 bpm and a normal blood pressure of 130/70 mmHg. His oxygen saturation was 97%. The bedside physical exam and lab findings were non-remarkable. The first high-sensitivity cardiac troponin (hs-cTn) assay, drawn shortly after arrival, was indeterminate (the normal reference range is less than 45.43 pg/ml). The second-high sensitivity cardiac troponin (hs-cTn) assay was also negative.

The 12-lead electrocardiogram (ECG) revealed a normal sinus rhythm of 84 bpm. Inverted T-waves were noticed in the anteroseptal leads, with inverted U-waves in the inferolateral leads. There were also signs of incomplete right bundle branch block (Figure 1).

In light of the previous history, the patient underwent left heart catheterization and selective native coronary angiogram. Coronary angiography demonstrated non-obstructive coronary artery disease. However, the left ventriculogram unveiled apical hypertrophy of the left ventricle that was indicative of the Japanese variant of apical hypertrophy, also known as Yamaguchi syndrome.

Two-dimensional transthoracic echocardiography (TTE) demonstrated a preserved ejection fraction (50-55%) and no significant valvular pathology. However, TTE also revealed concentric left ventricular hypertrophy and apical hypertrophy at the apex of the left ventricle, leading to a configuration that resembled an "ace of spades", consistent with the Japanese variant.

The left atrium, right atrium, and right ventricle were all of normal sizes. There was a trace of aortic and tricuspid regurgitation. There was grade I (mild) mitral regurgitation. There was no evidence of left ventricular outflow tract (LVOT) obstruction or increased LVOT pressure gradient by TTE. Finally, there was an E/A reversal on mitral inflow suggestive of diastolic dysfunction. A cardiac MRI with gadolinium enhancement revealed an enlarged left ventricle with reduced systolic function. There was an asymmetrical enlargement in the myocardium of the left ventricle, affecting mainly the apical and middle walls, reaching about 28 mm in maximum diameter at the anteroseptal and anterior lateral segments at the end-diastolic phase, significantly impeding the mid-ventricular cavity. Asymmetric hypokinesia of the left ventricular wall was also observed (Figure 2).

Figure 1. Electrocardiogram on admission exhibited deep T wave inversions in anteroseptal leads, inverted U-waves in the inferolateral leads and signs of incomplete right bundle branch block

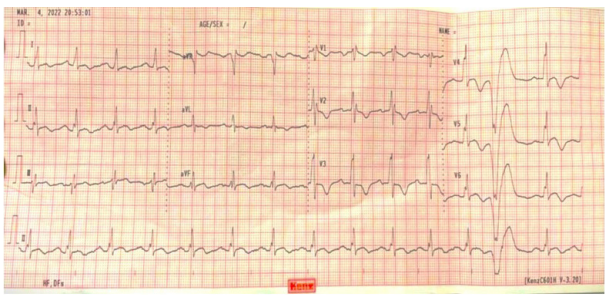
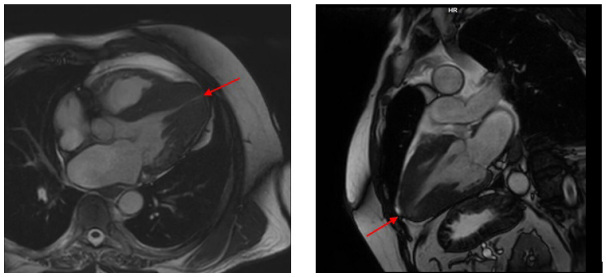
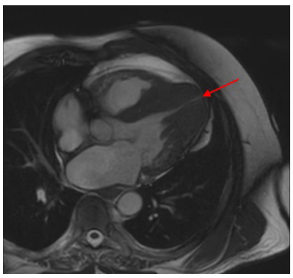
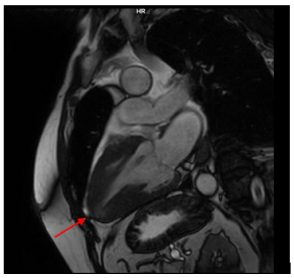


Figure 2. .Cardiac magnetic resonance exhibited was asymmetrical enlargement in the myocardium of the left ventricle affecting mainly the apical and middle walls







GENETIC TESTING

The Patient underwent comprehensive whole exome sequencing, which revealed c.371G>T (p. Cys124Phe). This gene variant is located in exon 8 of the GDF1 (growth differentiation factor 1) gene. This specific gene synthesizes a secreted cytokine known as TGF-beta (Transforming growth factor-beta). This secreted ligand plays a critical role in the development of various organs in the body like the heart, nervous system & bones (NCBI Gene ID: 2657). Genetic mutations in the GDF1 gene are linked to multiple congenital heart defects (CHTD6, OMIM 613854). This genetic variant has been reported in The Genome Aggregation Database (gnomAD) with the highest allele frequency of 0.0002535. However, no homozygosity has been reported (Variant ID: 19-18869345-C-A).

The variant's in-silico predictions were classified as potentially harmful through PolyPhen-2 (HumDiv/Mendelian disease diagnostics). Furthermore, SIFT (Sorting Intolerant from Tolerant) deemed this variant deleterious. In ClinVar, a database that provides information regarding different types of genetic variants and their interpretation, the clinical significance of this variant has been reported as "likely pathognomonic" (VCV000392938.2), but no clinical condition was reported. According to ACMG guideline for interpretation, this variant is classified as a variant of uncertain significance (VUS).

Table 1. Genetic testing where a variant significance (VUS) was identified

Gene	Variant	Genotype
GDF 1 (growth differentiation factor 1)	19:18869345 C>A c.371G>T p.Cys124Phe	Heterozygous
Classification	**Inheritance**	
VUS (variant of uncertain significance)	Autosomal recessive Autosomal dominant	

DISCUSSION

Our case is about a 64-year-old patient who was diagnosed with ApHCM, an uncommon form of non-obstructive hypertrophic cardiomyopathy (HCM) that typically affects the left ventricle's apex and infrequently the right ventricle or even both. (Figure 4)[1]

Table 2. Genetic testing where a variant significance (VUS) was identified

	Classic HCM	ApHCM
Demographics	-Represents 46% of all HCM cases -Mean age at diagnoses is 46 years old	-Represents 8% of all HCM cases. -Mean age at diagnoses is 41.1 years old.
EKG	-Voltage criteria indicative of LVH. -Nonspecific alterations in ST-segment and T-waves. -The presence of Deep and narrow Q-waves in the lateral and inferior leads.	-Characteristic giant negative T-waves. -Relatively common atrial fibrillation with non-sustained ventricular tachycardia (NSVT).
Echocardiography	-Left ventricular hypertrophy and outflow tract obstruction. -Diastolic dysfuntion and Mitral valve leaflet abnormalities.	-Apical hypertrophy resulting in a spade-like appearance. -Midventricular obstruction and cavity obliteration (MVOCO), and is some cases apical aneurysms.
Genetics	-Autosomal dominant mutations identified in 34% - 40% of cases.	-Autosomal dominant mutations indentified in 13% - 25% of cases
Mortality	1.3% mortality rate	-0.5% - 4% mortality rate

When Dr. H. Yamaguchi originally described ApHCM in 1976, it was believed only to affect Japanese people as it accounted for 15–25% of HCM in the Asian population, compared to 1-10% of HCM in non-Asians. [2] Prognosis, prevalence, and progression of the disease over time are all influenced by ethnic variance. For instance, Westerns can have a more malignant presentation of the disease with a worse prognosis. Males predominate in apical HCM, compared to females, with a ratio of around (2:1). The disease presentation's age is 41.4 + 14.5 years on average. [2] There are very limited population studies or case studies regarding ApHCM among Caucasian patients.

Compared to classic HCM, ApHCM is more likely to be sporadic in nature, with only a few reporting a positive family history. [2] Further, ApHCM is more likely to be genotype-negative, with only 25% having identifiable gene mutation, compared to 35-50% in classic HCM. [2] As with classic HCM, genetic mutations in ApHCM are mainly sarcomeric autosomal dominant mutations with variable penetrance. [2] Despite its low diagnostic yield, current HCM guidelines continue to emphasize genetic testing in all HCM patients, including ApHCM variant. [3]

Classic EKG findings in ApHCM include prominent "giant" T-wave inversion in precordial leads and voltage criteria for left ventricular hypertrophic (LVH). [2] Classic TTE and CMR findings in ApHCM include LVH predominantly in LV apex with apical wall thickness ≥15 mm, with a ratio of apical to posterior maximal wall thickness ≥1.5 times. [2] In ApHCM, there is typically no LVOT obstruction from systolic anterior motion (SAM) of the anterior mitral valve leaflet, and therefore, no associated mitral regurgitation. However, ApHCM can present with or without Midventricular cavity obstruction/obliteration. Apical aneurysms are more prevalent and occur in 15% of patients with ApHCM, compared to 2% of classic HCM. [2] Apical myocardial fibrosis (late gadolinium enhancement on CMR) is common (45%) and typically occurs in apical and Subendocardial patterns. [2] The major advantage of CMR lies in its ability to capture the complete morphology of the left ventricle with visualization of the entire apex. [6] Consequently, CMR is valuable for diagnosing, pinpointing the location, and quantifying the extent of apical hypertrophy or cardiac aneurysms [6]. Finally, a left ventriculogram can show the characteristic "Ace-of-spades" LV cavity morphology in two-thirds of cases and aid in visualizing apical aneurysms. [6]

During the initial evaluation, clinical screening by ECG and TTE should be performed on first-degree relatives of patients whose genetic screening is positive but does not exhibit phenotype. Then, depending on their age, this should be followed by serial ECG and TTE imaging. [6] In terms of symptoms, ApHCM) displays a broad array of clinical indications. These include chest discomfort, shortness of breath, irregular heartbeats, fainting, and heart failure. [5] With regards to chest pain often resembles that caused by ACS, leading to challenges in diagnosing it accurately or potentially causing delays in diagnosis. [5]

CONCLUSION

ApHCM is now recognized to be more prevalent than previously thought in none-Asian populations. Classic features of ApHCM include "giant" T wave inversion in precordial leads, spade-like morphology of LV cavity on TTE, and LVH that predominantly affects the apex with apical wall thickness ≥15 mm – with or without apical aneurysms. Unlike classic HCM, apical HCM is not typically associated with LVOT obstruction from SAM of the mitral valve anterior leaflet. In ApHCM, there is typically no LVOT obstruction from systolic anterior motion (SAM) of the anterior mitral valve leaflet and, therefore, no associated mitral regurgitation. ApHCM tends to be sporadic, with pathogenic genes identified in less than one-fourth of patients.

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