



Case Report

Asymptomatic Apical Hypertrophic Cardiomyopathy: Case Report and Review of Literature

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Received: 20-06-2023 / Revised: 17-07-2023 / Accepted: 20-08-2023

Conflicts of Interest: Nil

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DOI: <https://doi.org/10.32553/ijmsdr.v7i5.990>

Abstract:

Apical hypertrophic cardiomyopathy (AHCM) is a known entity since its first introduction by Sakamoto and Yamaguchi. However, unlike classical hypertrophic cardiomyopathy (HCM), it is less explored in terms of its associated diagnosis and long-term outcomes. Given the increased availability and utilization of ultra-sophisticated cardiac imaging modalities, AHCM will be increasingly recognized as a distinct, clinically significant variant of classical HCM. It is associated with a wide spectrum of presentation ranging from asymptomatic course with incidental findings on imaging to rarely being associated with ventricular arrhythmias, syncope and sudden cardiac death (SCD). Contrast echocardiography is the most effective and diagnostic study when performed in the right setting with high suspicion on clinical and typical electrocardiogram (ECG) findings. Cardiac magnetic resonance imaging (CMR) has an equal diagnostic yield as a contrast echocardiogram. We are presenting a unique case report of a 57-year old gentleman with asymptomatic AHCM which was distinctly delineated after utilizing contrast tuned imaging (CnTI) echocardiography sans administration of intravenous contrast agents. This is a first case report of AHCM portrayed by this ingenious technology.

Keywords: Apical Hypertrophic Cardiomyopathy, LV Contrast Echocardiography, Contrast Tuned Imaging, 4Dimensional XStrain Echocardiography.

Introduction

AHCM typically has an autosomal dominant inheritance pattern but can also be sporadic. Contemporary literature indicates the association of AHCM with genetic mutations in ACTC1, TPM1, MYBPC3 and MYH7 [1]. Detected first in Japan in 1976 [2], AHCM is characterised by "giant" negative precordial T-waves on ECG and by "spadelike"

configuration of its left ventricular (LV) cavity in end diastole on LV angiography [3].

AHCM accounts for up to 25% of HCM in Asian populations and 1% to 10% in non-Asians [4]. A more malignant course is found in western population [5].

There are numerous imaging modalities to distinctly identify and illustrate this rare entity

of AHCD: echocardiography, cardiovascular magnetic resonance, cardiac computerized tomography, nuclear scintigraphy, left

ventricular angiography and left ventricular contrast study employing intravenous contrast agents (Figure 1).

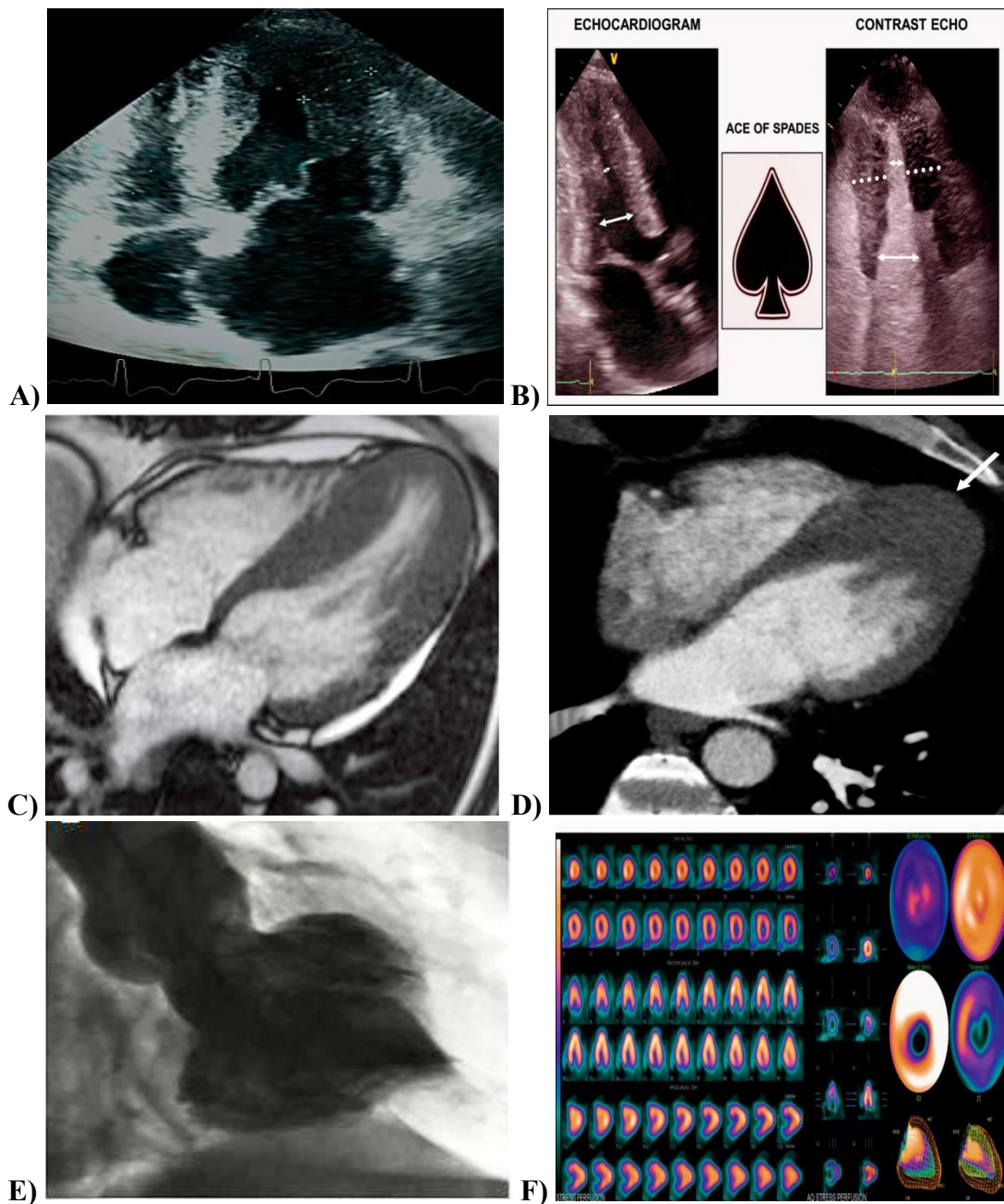


Figure 1: Imaging modalities for AHCM, A) Standard echocardiography in apical 4CH view, B) An echocardiogram and a contrast echocardiogram showing predominant apical hypertrophy and a narrowing of the left ventricular cavity at the apex, resulting in a so-called ace of spades morphology. In the echocardiogram, the left ventricular cavity is displayed in black; in the contrast echocardiogram, the left ventricular cavity is white. Arrows indicate the cavity diameter at the apex and the base, and dotted lines illustrate the significant left ventricular wall thickening at the apex, C) Cardiac MRI - 4CH View, D) Cardiac CT- 4CH View reveals striking hypertrophy of apical segments (arrow), E) LV angiography showing the characteristic diastolic “ace- of spade” sign, F), SPECT (single photon emission computed tomography) in a patient of AHCM showing mild ischemia at the true apex

Transthoracic Echocardiography (TTE) is a versatile, easy to use tool, relatively cheap and available at the bedside. Hence, it is a preferred modality for imaging in AHCM. TTE can reveal apical hypertrophy and identify additional prognostic features that could influence outcome such as the presence of diastolic dysfunction, mid ventricular obstruction, cavity obliteration or apical aneurysms [6-8]. Notwithstanding, imaging the apex always remains a challenge because of frequent foreshortening of LV apex and difficulty in detecting apical akinesis or sequestration caused by the massive hypertrophy [9]. Such phenotypes of AHCM could be missed by echocardiography; thus, those with deep T-wave inversion and noncontributory echocardiography findings should undergo additional imaging [10].

AHCM may not be detected by standard 2-Dimensional echocardiography, because of indiscrete visualization of the apical endocardial border [11]. When apical hypertrophic cardiomyopathy is suspected but not clearly documented contrast studies should be contemplated. If AHCM is present, the characteristic spadelike appearance of the LV cavity, with severe apical myocardial wall thickening, is vividly identified on contrast-enhanced images [12]. A number of earlier studies have reported intravenous microbubble contrast agents improving diagnostic sensitivity of echocardiography [13-15].

Cardiac magnetic resonance (CMR) the most outstanding and unparalleled modality for AHCM characterisation, may create additional risks, time delays, and costs [16]. In particular a major drawback of CMR is that it has got genotoxic effects as demonstrated by the significantly higher level of DNA double-strand breaks measured in human lymphocytes after exposure even with a 1.5 T machine [17]. This cancerogenic effect is compounded by the possible gadolinium induced nephrogenic systemic fibrosis [18]. Contrast echocardiography on the other hand is totally

safe, easily repeatable, showing the same diagnostic potential as CMR, to evaluate LV wall thickness and function and is extremely cost-effective [16]. Hence, it is a preferable test for assessing AHCM and in general LV function and LV wall thickness in patients with poor visualization of LV apex.

Contrast tuned Imaging echocardiography

Contrast Tuned Imaging (CnTI) is an advanced technology for Contrast-Enhanced ultrasound (CEUS) Imaging. Based on low mechanical index and real-time scanning, CnTI represents the best way to use second-generation contrast media [19].

CnTI can be used for diagnosis and follow-up, as well as during interventional procedures. Its sophisticated architecture based on linear pulser technology, is capable of managing various typologies of pulsing techniques in order to optimize the beam forming management for a wide range of clinical applications.

Contrast-enhanced ultrasound (CEUS) has the advantages of the absence of ionizing radiation, widespread availability, even at the bedside, and the possibility to characterize a lesion as soon as it is detected on conventional 2-Dimensional echocardiography, commonly used as the first technique for exploration of the left ventricular opacification and other areas [20].

In CnTI second generation contrast agents are utilized for left ventricular opacification. However, in the current case report we have employed CnTI echocardiography for left ventricular opacification sans intravenous contrast agent, to recognize and substantiate the presence of AHCM. To our knowledge, this is a first report on CnTI echocardiography without deploying contrast agents.

Case Report

A 56 year old male with a history of uncontrolled moderate hypertension, presented

to us with transient pricking type sensation in the left mammary region. The chest pain seemed to be atypical, and there was no sweating / shortness of breath / radiation to jaws or arms. Patient denied any family history of coronary artery disease, smoking or tobacco chewing. On clinical examination, the patient was healthy looking with a pulse rate of 67/min, BP of 150/106 mmHg, right upper

extremity in the sitting position, respiratory rate was 15/min and SPO2 was 98% at room air. Systemic examination, particularly of cardiovascular system was unremarkable. The first and second heart sounds were normally heard without any clicks, murmurs or gallops sounds. Resting ECG was typical of AHCM with global “Giant” T wave inversions (Figure 2).

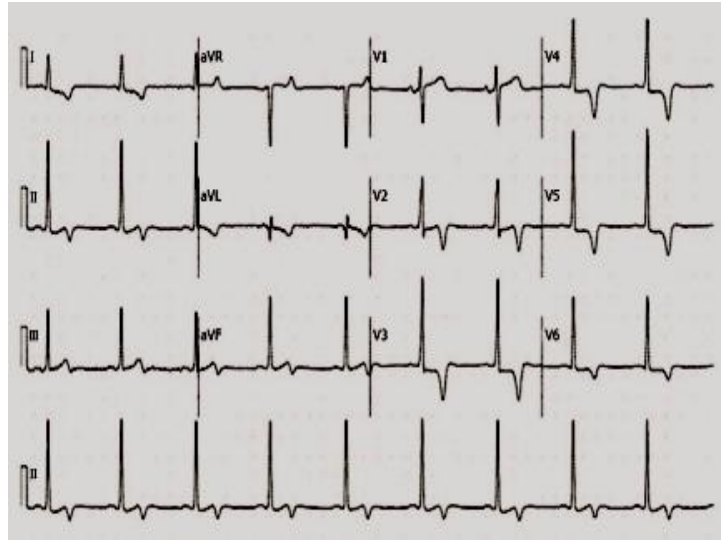


Figure 2: Resting ECG- identifies typical findings of AHCM with global “Giant” T wave inversion.

Xray chest PA was normal without any cardiomegaly or apical bulge (Figure 3). The pathological investigation were all within normal limits. However, no genetic studies were performed.

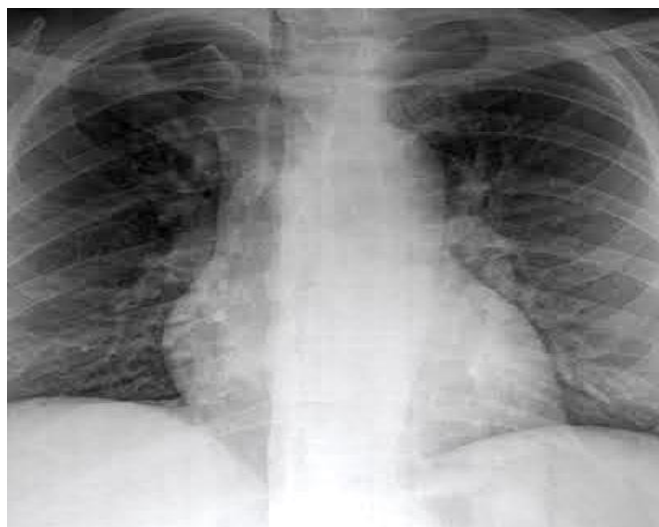


Figure 3: X-ray chest PA view was normal without any cardiomegaly or apical bulge.

Transthoracic Echocardiography (TTE)

Standard TTE was performed by the author in the left lateral decubitus position. 2Dimensional echocardiography was conducted in the parasternal long axis view (LX), parasternal short axis view (SX), apical 4-chamber view (4CH), apical 2-chamber view (2CH) and apical 5-Chamber view (5CH).

2Dimensional echocardiography

The standard 2Dimensional echocardiogram was apparently normal. There was no obvious hypertrophy of LV and neither there was any left ventricular outflow obstruction. The LVEF was 67 % by biplane simpson's method (Figure 4).

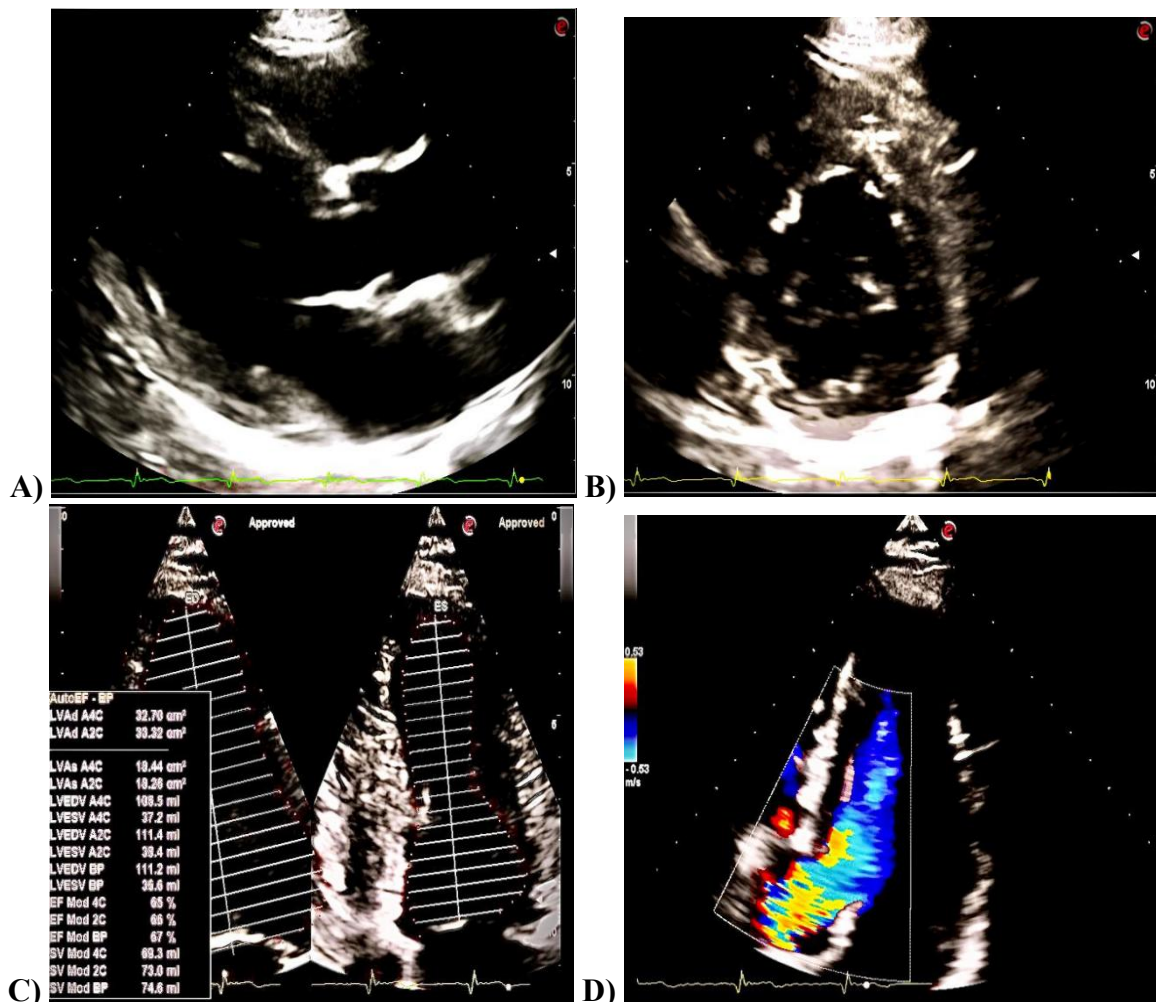


Figure 4: The standard echocardiogram was apparently normal. No hypertrophy of left ventricular muscular capacity was discerned and neither there was any left ventricular outflow obstruction. A) Parasternal long axis view (LX), B) Parasternal short axis view (SX), C) Biplane simpson's method for determination of EF%, D) Apical 5-ch view - color flow imaging

Considering the ECG presence of classical “Giant” T wave inversions, the apex of LV was scanned to rule out AHCM. A nondescript thickening of the LV apex and the upper anterolateral wall was detected, suggestive of AHCM (Figure 5).

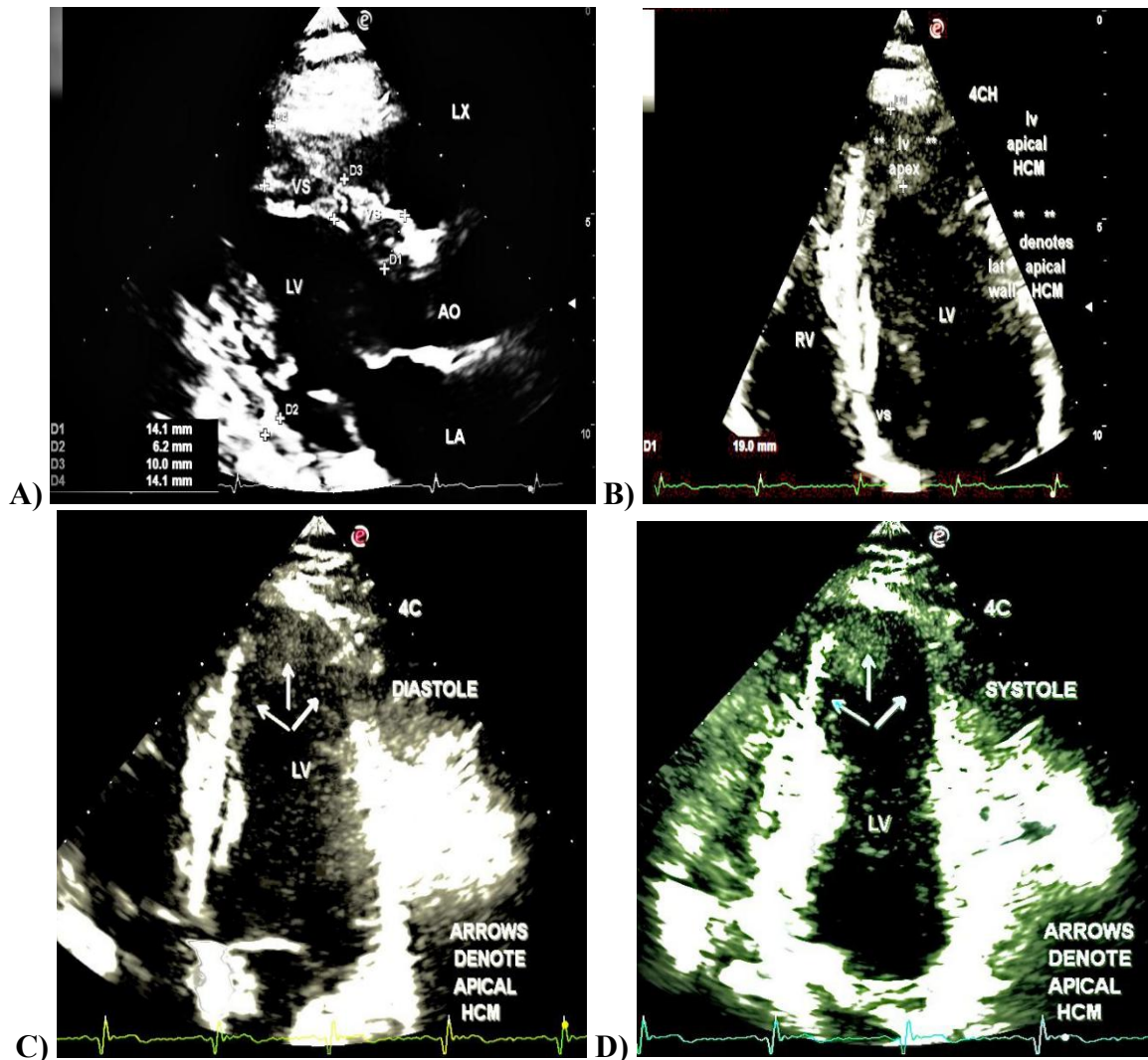


Figure 5: On focused echocardiography of the LV, a nondescript thickening of apex and the upper anterolateral wall was detected which may be suggestive of apical hypertrophic cardiomyopathy. A) In the LX view apical anterior septum is thickened (14 mm), B) In the apical 4CH view there is presence of marked thickening of lv apex (19 mm), apical anterior septum and apical lateral wall, C) In another apical 4CH view in diastole similar thickening is visualised at the lv apex, apical anterior septum and apical lateral wall, D) In the systolic frame the lv cavity has significantly reduced in size alongwith indistinguishable motion of lv apex.

In the LX view there was presence of thickening of apical anterior septum (14 mm). Moreover in the apical 4CH view in diastole, marked hypertrophy was detected at the LV apex, apical anterior septum and apical lateral wall. Maximum LV apical thickening was 20 mm and LV apical and posterior wall ratio was 3.3:1. Furthermore, in systole the LV cavity was significantly reduced in size alongwith hypokinetic motion of LV apex.

Left ventricular diastolic function

[Pulse wave doppler (PWD) study at the tip of mitral valve identified tall E and small A waves and on tissue doppler imaging (TDI) there was presence of small e' waves and E/E' ratio was 17:1, indicating a moderate grade LV diastolic restrictive dysfunction (Figure 6).

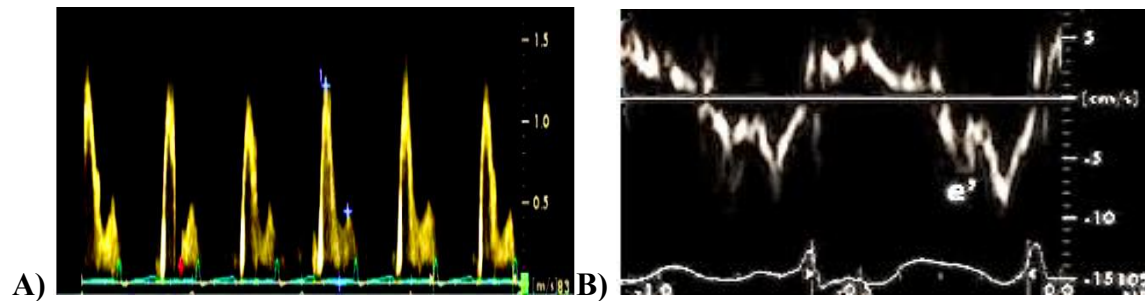


Figure 6: LV diastolic dysfunction in AHCM, A) pulse wave Doppler at the tip of mitral valve detects large E and small A waves, B) tissue doppler imaging shows small E' wave and E/ E' ratio was 17:1, indicating a moderate grade diastolic restrictive dysfunction.

Contrast tuned Imaging (CnTI) echocardiography

LV Contrast Tuned Imaging was accomplished by 4Dimensional XStrain Echocardiography (Figure 7).

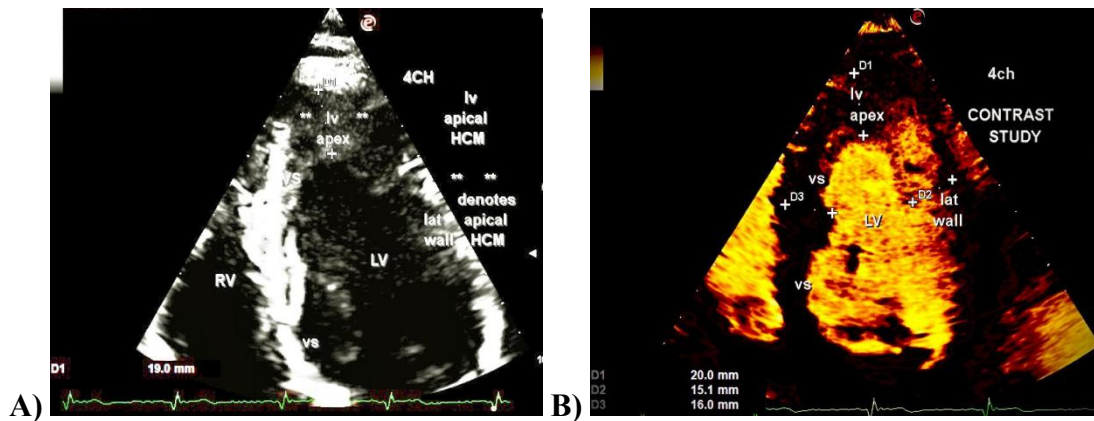


Figure 7: LV Contrast Tuned Imaging Echocardiography, A) Standard apical 4CH view showing hazy images of hypertrophic LV apex, apical anterior septum and apical anterior wall, B) on contrast tuned imaging in diastole there is a distinctive AHCM discerned with notable hypertrophy of LV apex, apical ventricular septum and apical lateral wall. The LV cavity size is normal. The thickness of LV apex, apical anterior septum and apical lateral wall was 20.0 mm, 15.1 mm and 16.0 mm respectively.

The standard apical 4CH view exhibited hazy and indistinct thickening of the LV apex. Meanwhile, on contrast tuned imaging in diastole, there was distinctive AHCM discerned with notable hypertrophy of the LV apex, apical ventricular septum and apical lateral wall. The LV cavity size was normal. We want to highlight that no intravenous contrast agent was utilized during CnTI imaging.

4Dimensional XStrain speckle tracking echocardiography

4Dimensional XStrain speckle tracking echocardiography was analysed offline, and “Bull’s” eye and polar mapping of LV global and LV apical strain analysis was conducted in apical 2CH, LAX, 4CH views (Figure 8). Moreover, global strain analysis was simultaneously performed. There was severely decreased values of LV strain in apical segments (varying from -2% to -4%), and correspondingly the global strain values were conspicuously reduced (global strain 2CH being - 10.11 %, global strain LAX being - 11.02 %, global strain 4CH being - 8.46 %, global strain being - 9.86 % respectively).

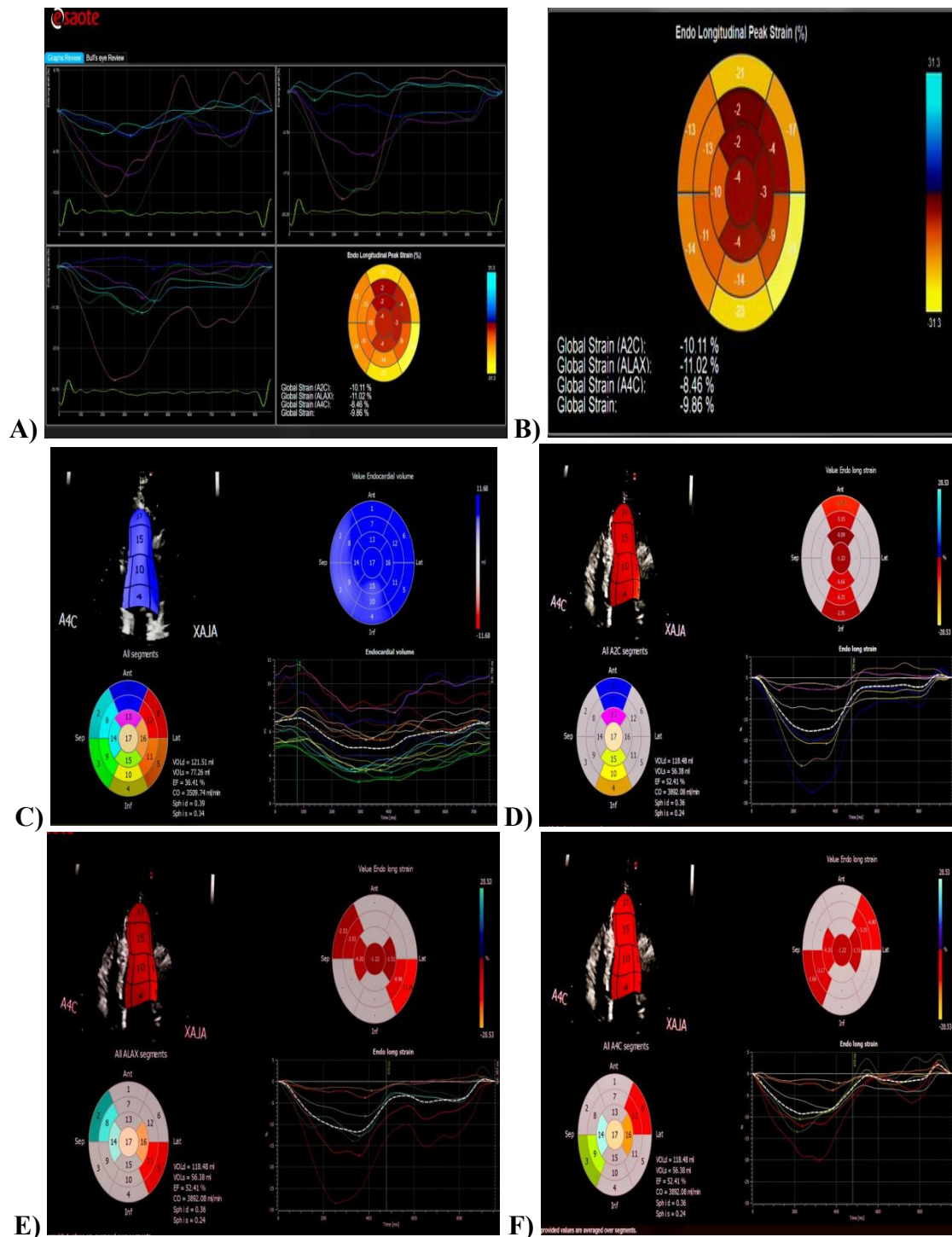


Figure 8: 4Dimensionsl XStrain Echocardiography, A) “Bull’s” eye mapping of LV global apical 2CH, LAX, 4CH and Global Strain, B) Polar mapping of LV strain in our patient of AHCM, C) 4Dimensional XStrain derived end- diastolic volume, end systolic volume, cardiac output and EF % , D) apical 2CH strain values, E) apical LAX strain values, F) apical 4CH strain range values.

It would be noteworthy to state that according to American society of echocardiography normal global longitudinal strain values are $\geq -20\% \pm 2\%$ in normal healthy adults.

Discussion and review of literature

AHCM is an atypical phenotype of non-obstructive HCM with an increased prevalence in Japanese population [21]. Typically, it is considered a benign condition and is incidentally detected by echocardiography. AHCM was first described in Japan by Sakamoto *et al.* in 1976 [2]. Yamaguchi *et al.* went on to describe the syndrome and its ventriculographic features in 1979 [3]. Kitaoka *et al.* [21] found the apical HCM in 15% of Japanese and 3% of American patients of HCM. It is rare in the West (1 to 11%) [22], but more common in oriental people and

accounts for 13% - 41% of all variants of HCM among Asian individuals [23]. In a study of 200 patients in Japan, Sakamoto observed that the prognosis of AHCM was generally benign [24].

Apical hypertrophic cardiomyopathy - morphological types

Choi *et al.* morphologically divided AHCM into 3 types: pure focal, pure diffuse and mixed, of which pure focal is most common [7]. Our patient is presenting with pure focal type of AHCM.

Pathophysiology of apical hypertrophic cardiomyopathy

The morphologic and functional changes associated with AHCM result in complex changes in cardiac physiology (Figure 9).

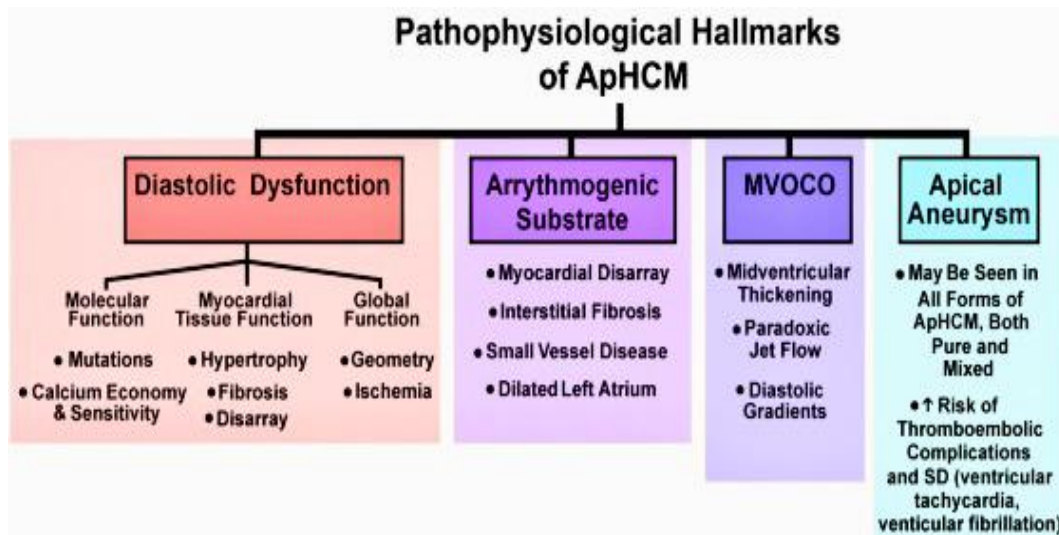


Figure 9: Major factors involved in the clinical manifestations of apical hypertrophic cardiomyopathy (ApHCM). Note that increased risk of sudden death is associated with the development of an apical aneurysm independent of the arrhythmogenic substrate. MVOCO = midventricular obstruction with cavity obliteration; SD = sudden death.

LV outflow tract obstruction and mitral regurgitation are conspicuously absent [1]. Nonetheless, two noticeable phenomena are found in patients with AHCM: midventricular obstruction with cavity obliteration (MVOCO) and apical aneurysm formation. MVOCO occurs due to the "hypertrophied" muscular

walls. Diastolic dysfunction (Figure 10) leads to increased filling pressures and left atrial enlargement (diastolic heart failure) causing dyspnea, exercise intolerance, and pulmonary edema [1]. In our case, the PWD of the mitral valve and TDI of LV were indicative of moderate grade diastolic dysfunction.

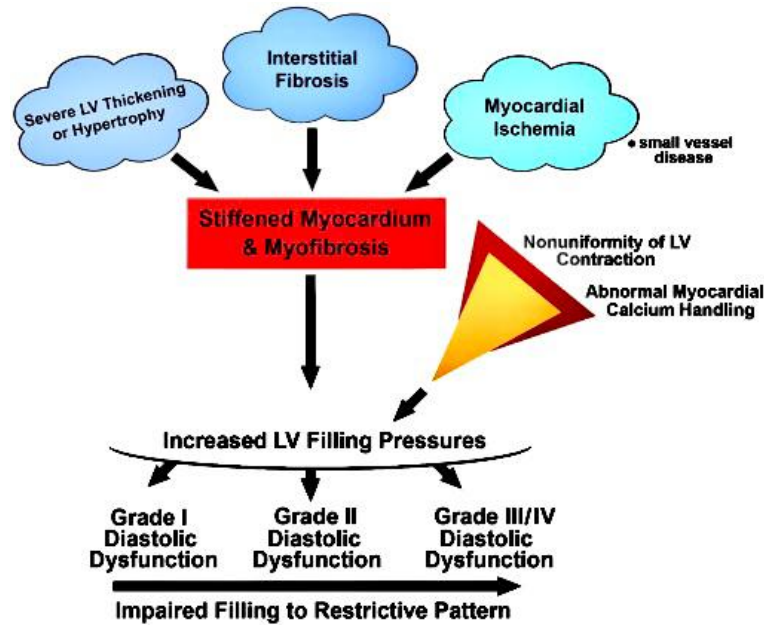


Figure 10: Diastolic dysfunction is a cardinal feature of apical hypertrophic cardiomyopathy (ApHCM). Heart failure symptoms in ApHCM are closely linked to marked diastolic dysfunction due to increased myocardial stiffness. LV = left ventricular.

The most feared complication of AHCM is arrhythmogenic sudden cardiac death (SCD) caused by sustained ventricular tachycardia and/or ventricular fibrillation. Consequently, an implantable cardioverter-defibrillator may be a compelling strategy for SCD prevention in high risk AHCM patients [1].

Symptomatology

Clinical expression of apical HCM is highly variable. Apical HCM may manifest early in adulthood [25] and most series reported a mean age of 41 years [4]. About 54% of patients with apical HCM are symptomatic and the most common symptoms are chest pain, followed by palpitations, dyspnea and syncope. Atypical chest pain is the most frequent symptom and typical angina may also occur due to diminished vasodilatory reserve. Atrial fibrillation (12%), apical myocardial infarction (10%), ventricular arrhythmia and apical thrombosis with embolization may occur in up to 33% of cases [26]. Occasionally, sudden cardiac death (SCD) may be the first manifestation of AHCM [5]. Our patient only

experienced infrequent episodes of atypical chest pain and was largely asymptomatic.

Electrocardiography (ECG)

The most common ECG findings are negative T waves in the precordial leads, found in 93% of patients (a depth >10 mm in 47%) and a documented left ventricular hypertrophy on imaging is seen in 65% of patients with HCM. Giant T wave negativity (defined as depth or voltage >1 mV or 1.2 mV in any of the leads) in the left precordial leads is the hallmark feature of AHCM [27]. Correspondingly, "Giant" T wave inversions were also encountered in our patient.

In AHCM, larger degree of T wave inversions are seen and its depth does not correlate with severity of apical hypertrophy [29]. Presence of giant T wave inversions in Japanese HCM patients has been recognized as a predictor of favourable outcome and it is more common in sporadic cases of AHCM [29].

Transthoracic Echocardiography (TTE)

The preferred initial imaging test is TTE and it is the most frequently utilized diagnostic modality [30].

AHCM is exemplified as concentric, circumferential hypertrophy of the entire apex due to apical left ventricular thickening of the anterior and posterior walls, resulting in a spade-like morphology of the left ventricular cavity during end diastole in LV long axis view of MRI and RAO projection of LV angiography [31]. Likewise, we detected AHCM in our index patient.

Echocardiographic diagnostic criteria of hypertrophic cardiomyopathy (HCM)

Standard 2D echocardiography is the first-line imaging modality for the identification of HCM. The current diagnostic criteria for HCM are an increase in LV wall thickness ≥ 15 mm in at least one myocardial segment or ≥ 13 mm for patients with a first-degree relative with confirmed HCM, in the absence of abnormal loading conditions/other causes of LVH (e.g., hypertension, valvular heart disease) [32, 33]. The measurement of LV wall thickness in parasternal short-axis views at end-diastole is the most accurate.

Meanwhile, asymmetric hypertrophy (a septal-to-posterior wall thickness ratio ≥ 1.3 in normotensive patients or ≥ 1.5 in hypertensive patients) may be suggestive of HCM, albeit it is not specific for HCM.

Echocardiographic diagnostic criteria of apical hypertrophic cardiomyopathy (AHCM)

For AHCM echocardiographic diagnostic criteria [32, 33] are the following: 1) asymmetrical left ventricular hypertrophy confined to the left ventricular apex below the papillary muscle level; 2) apical wall thickness ≥ 15 mm; 3) a ratio of maximal apical to posterior wall thickness ≥ 1.5 . In our case, the maximum diastolic thickness of LV apex was 20 mm and ratio of maximal apical to posterior wall thickness was 3.3:1.

LV Contrast study

Current generation contrast agents are microbubbles consisting of a shell and encapsulated gas. The echo reflecting and ultrasound properties of the contrast agents are decided by the size, shell and encapsulated gas of the microbubbles within the different contrast agents. Microbubble ultrasound scattering is proportional to the sixth power of the radius, so the largest bubble capable of passing through the pulmonary microcirculation will have the best backscatter properties [34-37].

The harmonic properties of microbubbles means that they reflect sound not only at the quintessential frequency of the ultrasound source but also at higher harmonics [38]. Characteristics of the three commercially available contrast agents are listed in Table 1.

Table 1: Current commercially available ultrasound contrast agents

Agent	Manufacutre	Shell	Gas
Optison [®]	GE Healthcare	Albumin	Perfluoropropane
Definity [®] / Luminity [®]	Lantheus Medical Imaging	Lipid	Perfluoropropane
SonoVue [®] / Lumason [®]	Bracco Diagnostics	Amphiphilic phospholipids	Sulfur hexafluoride

Contrast imaging employs the non-linear scattering properties of ultrasound contrast agents to expedite their recognition within the myocardial cavities [39-40].

Contrast tuned imaging echocardiography (CnTI)

CnTI is advanced technology for Contrast Enhanced Ultrasound (CEUS) imaging [18]. Based on low mechanical index and real-time scanning, CNTI is an ideal way to employ second-generation contrast media. CnTI is characterized by:

- High Sensitivity - it detects and visualizes all the lowest intensity signals.
- High Homogeneity - it offers the same representation for signals coming from same vessels or same tissues.
- High Spatial Resolution - it offers the possibility to identify very small structures (both hyperechoic and hypoechoic).
- High Temporal Resolution - it allows the user to follow both the arterial and the portal phase by Real-time detailed analysis.

Contrast Enhanced Ultrasound (CEUS).

Ultrasound contrast agents are liquid suspensions of biocompatible gas-filled microspheres. When injected into a patient's vein during an ultrasound exam, they flow around the circulatory system, producing enhanced ultrasound reflectivity. CEUS uses special biocompatible ultrasound contrast agents to improve the quality and reliability of ultrasound scans, thereby helping physicians more accurately diagnose medical conditions and monitor therapy. In our index patient CnTI echocardiography was performed and the exquisite images of AHCM were illustrated.

Decorrelated Contrast Tuned Imaging technology (DCTI)

In addition to the traditional Flash mode for rupturing of contrast agent bubbles, CnTI offers a unique DCTI function [18], which automatically captures the breaking frame and decorrelates the signal, thus eliminating all artifacts by increasing sensitivity in the late phase. DCTI is designed to maximize contrast

information, even during the late phase. By using specific decorrelation software and combining the technique with a low and high mechanical index, DCTI is able to detect even the weakest information from low concentrations of contrast agent that are still in circulation more than 5 minutes after the bolus injection.

DCTI Technology is characterized by:

- High-Power transmission to destroy the microbubbles, registering the signal coming from them, and saving the first frame after their destruction.
- Diagnostic information optimization by applying a decorrelation algorithm and combining low and high mechanical index technologies.

DCTI Technology increases the ability to distinguish between a signal coming from static tissue and contrast agent bubbles inside the vessels. DCTI is designed to:

- Maximise contrast information.
- Remove artifacts in the late phase.
- Detect information even from low concentrations Just 5 minutes after the bolus injection.

Conclusion

The diagnosis of apical hypertrophic cardiomyopathy is important because most of these patients are relatively young. Classic findings include giant T inversions on ECG and characteristic spade shaped apical hypertrophy of the myocardium.

Given the increased availability and utilization of ultra-advanced cardiac imaging modalities, AHCM will be increasingly be recognized as a distinct, clinically significant variant of classical HCM. Contrast echocardiogram is the most effective and diagnostic study when performed in the right setting with high suspicion on clinical examination findings and typical ECG findings.

Apical HCM is generally associated with good prognosis in both Asian and Caucasian population and a long-term mortality is 0.1% per year. The approach to management of apical HCM depends on symptoms and risk of SCD. There is lesser incidence of sudden cardiac death in apical variant, compared to patients with normal variant HCM.

In asymptomatic patients, no specific therapy has been outlined, but counseling is certainly recommended for symptomatic monitoring to notice any syncope or presyncopal events on follow up. The medical regimen in symptomatic patients primarily consists of beta-blockers, which have been shown to decrease symptoms as well as overall mortality [41].

Acknowledgement

Our deepest gratitude to Mr. Faiz Illahi Siddiqui, for his impeccable typing skills and his unwavering attitude and commitment towards his assignments.

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