Apical hypertrophic cardiomyopathy with apical endomyocardial fibrosis and calcification
Two case reports
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Abstract
Rationale: Apical hypertrophic cardiomyopathy (AHCM) is a rare form of hypertrophic cardiomyopathy which affects predominantly the apex of the left ventricle. Generally, left ventricular enlargement is not present in AHCM; additionally, endomyocardial fibrosis, and calcification are also rare.
Patient concerns: A 61-year-old female (Case 1) and a 60-year-old female (Case 2) both presented with the symptoms of atypical chest pain, dyspnoea, exercise intolerance, palpitations.
Diagnosis: Magnetic resonance and single-photon emission computed tomography (SPECT) revealed apical hypertrophic cardiomyopathy. Furthermore, 2D-transthoracic echocardiogram showed left atrium and ventricular enlargement, as well as endomyocardial fibrosis and calcification. Based on these findings, the patients were diagnosed with AHCM.
Interventions: Both the patients were treated with ACEI, metoprolol, and aspirin. Additionally, both these patient underwent genetic test.
Outcomes: The results of the genetic test of the 2 cases for hypertrophic cardiomyopathy (HCM) were negative. However, the gene mutation for dilated cardiomyopathy (TMPO) was detected in one of the cases. No change in condition during follow-up.
Lessons: In past reports, Apical hypertrophic cardiomyopathy has been shown to have a benign prognosis. But in this case report, the imaging studies of the 2 patients suggest a poor prognosis. Furthermore, diagnosing cardiomyopathy should require multimodality imaging examinations to rule out differential diagnoses.
Abbreviations: AHCM = apical hypertrophic cardiomyopathy, D-HCM = dilated phase of the terminal stage of hypertrophic cardiomyopathy, EMF = endomyocardial fibrosis, HCM = hypertrophic cardiomyopathy, LV = left ventricular, LVO = left ventricular opacification, SPECT = single-photon emission computed tomography.
Keywords: apical hypertrophic cardiomyopathy, dilated-hypertrophy cardiomyopathy, echocardiography, endomyocardial fibrosis and calcification

1. Introduction
Apical hypertrophic cardiomyopathy (AHCM) is a rare form of hypertrophic cardiomyopathy (HCM), first introduced by Sakamoto et al in 1976,[1] who described a cardiac disorder manifested by negative T-waves on electrocardiography. Asian countries have a higher incidence rate than western countries, and more commonly seen in men.[2] Most patients present with symptoms in their 4th decade of life.[3] AHCM affects predominantly the apex of the left ventricle and is usually characterized by nonobstructive physiology. Generally, left ventricular enlargement is not present in AHCM; additionally, endomyocardial fibrosis and calcification are also rare. Nevertheless, the precise cause and its effects remain unclear.

In this report, we describe 2 cases, whose imaging examinations showed apical myocardial hypertrophy, and apical endomyocardial fibrosis and calcification. Furthermore, left atrium (LA) and left ventricular (LV) enlargement (Ejection fraction >55%) was detected on the transthoracic echocardiogram, which is different from previous reported AHCM cases.

2. Case report
2.1. Case 1
A 61-year-old Chinese female with a history of hypertension was hospitalized due to chest pain at rest and shortness of breath after
activity. She denied a history of diabetes mellitus or other diseases and surgical treatment. Blood counts and chemistry parameters were within the normal range. The eosinophil count was 60/mm³, and the blood pressure was 112/73 mmHg. The electrocardiogram showed sinus rhythm and T-wave inversion in leads I, II, III, aVF, V2 through V6 (Fig. 1). Further, echocardiography revealed normal systolic function (EF: 55%) and LV hypertrophy, measuring up to 18 mm, as well as apical endomyocardial fibrosis (EMF) and calcification. LV enlargement was detected: LV end-diastolic dimension: 65 mm; LV end-systolic dimension: 46 mm (Table 1). In addition, the left ventricular opacification (LVO) revealed echo shadowing due to calcified and thick endocardium. Cardiac magnetic resonance imaging (CMR) detected LV hypertrophy of up to 38 mm. Single-photon emission computed tomography (SPECT) showed reversible ischemia of the anterior wall, septum, the posterior wall of the LV, and reduced myocardial apical movement. Moreover, the LV diastole function was decreased. It is noteworthy that the gene test results for HCM were negative, but the gene mutation for dilated cardiomyopathy (TMPO) was detected in this case, TMPO gene maps to chromosome band 12q22 and genomic coordinates (GRCh38): 12: 98909717. No improvement was seen in the follow-up serial imaging in case 1.

The patient was proposed the diagnosis of pure AHCM and apical secondary EMF. She was treated with ACEI, metoprolol, and aspirin, and after 1 week of treatment, she was discharged from hospital. Follow-up includes serial electrocardiography and echocardiography every 6 months.

2.2. Case 2
A 60-year-old Chinese female was hospitalized for cardiomyopathy. She had a history of hyperlipidemia, cholecystitis, cystitis, but denied a history of chronic diseases, such as hypertension, diabetes, and infectious diseases (e.g., tuberculosis).

She had an operation history of appendicitis, variceal exfoliation, and cerebral infarction but with no sequelae. Blood counts and chemistry parameters were normal; the eosinophil
count was 80/mm$^3$, and the blood pressure was 105/63 mmHg. Echocardiography also revealed normal systolic function (EF: 61%), LV hypertrophy (20 mm), and apical endomyocardial fibrosis, accompanied with calcification. LV enlargement was found: LV end-diastolic dimension: 57 mm; LV end-systolic dimension: 38 mm (Table 1), as well as moderate diastolic dysfunction. LVO was similar to that of case 1 of the present study. CTA showed no signiﬁcant coronary artery stenosis.

This patient was also proposed the diagnosis of pure AHCM and apical secondary EMF. The patient was treated with ACEI, metoprolol, and aspirin. After 9 days treatment, she was discharged from hospital with remission and was planned for serial electrocardiography and echocardiography every 6 months.

3. Discussion

AHCM is a morphologic variant of hypertrophic cardiomyopathy.[1,4] Recently, apical EMF and calcification have been reported[5–9] but their precise cause and effects remain unclear. The patients in this study had LV enlargement and EF > 55%. To the best of our knowledge, this type of presentation has not been previously reported in the literature.

3.1. Morphology

There are 3 types of AHCM according to MF Jan et al classification.[10]

(A) Pure AHCM, which is typically limited to the thickening of LV apical segments.

(B) Mixed AHCM, which generally increased thickening of the LV wherein the apical segments are necessarily involved along with thickening of contiguous, nonapical LV regions (midventricle, basal septum, or both).

(C) The last subtype is noncontiguous AHCM with predominant thickening in the midventricular distribution.

From the imaging point of view, these 2 patients only LV apical myocardial segment hypertrophy, and we consider restrictive cardiomyopathy (RCM) does not occur above changes, they can be classified as Pure AHCM.

LVO showed echo shadowing behind calcified and thick endocardium (Fig. 2C). Given the patient’s ultrasound findings, we recommended further cardiac imaging to evaluate for the patient’s cardiac morphology. The main advantage of CMR over echocardiographic examination is complete coverage of LV morphology, including the apex.[10] It revealed that the LV apical myocardium was signiﬁcantly thickened; the apex displayed a high-density mass shadow. SPECT can detect local ischemia mostly in the LV, creating a typical picture of a “solar polar” map pattern, and showed increased resting apical tracer uptake and a spade-like configuration of the LV that was observed in the vertical and horizontal axes.[10] In these 2 cases, a diagnosis of AHCM was considered based on the results of all aforementioned examinations.

EMF is divided into primary and secondary. Secondary EMF commonly occurs in patients with underlying ischemic heart disease, primary myocardial disease and is related to myocardium thickening and abnormal movement,[11,12] which lead to compression on the small coronary arteries during ventricular filling. This results in inadequacy of the microvascular perfusion, causing decreased microvascular perfusion pressure and inducing myocardial ischemia; eventually, death of the myofibroblasts is caused, and replacement fibrosis appears a mechanism of repair.[11] These hemodynamic events induce ischemia and the potential subsequent pathophysiological cascade of infarction, fibrosis, and dystrophic calcification.[13,14]

Primary EMF is related to malnutrition, allergy, dietary factors, infective agents. Abnormal eosinophils were involved in the pathogenesis led to EMF. Loefler’s endocarditis deﬁned as eosinophilia > 1500/mm$^3$ for longer than 6 months, without any secondary cause and with evidence of organ involvement, which occurs in tropical and subtropical regions, particularly in some countries of Africa, as well as in India and Brazil.[14,15] Usually, the diagnosis of Loefler’s endocarditis is to be considered after clariﬁcation of the patient’s travel history, previous medical history, and blood chemistry. The blood counts and chemistry parameters of the 2 studied patients were examined and found to be normal. In addition, they reported no history of travel to the epidemic area, and no evidence existed of parasitic infection, tuberculosis, and rheumatic fever. Since there was no evidence of primary EMF, based on the above, it was possible to consider 2 patients with secondary EMF.

3.2. Myocardial mechanics

The reduced distensibility of the calcified LV myocardium could lead to heart failure.[16] Earlier myocardial mechanical analyses showed that the apical myocardium was inversely related to the motion of the myocardium in other segments, and the global strain in the longitudinal and circumferential directions and the radial area were lower than those in normal people.[17,18] As can be seen in Figure 2F, the strain in the other segments was
relatively enhanced, which suggests that the systolic function of the apex in our 2 patients was impaired.

3.3. Gene analyses

Arad et al found that the yield of genetic testing of AHCM was relatively low (25.5%),\(^1\) indicating that only 25% of the patients were genotype-positive. Two most common genotypes (MYBPC3-HCM and MYH7-HCM) were most commonly associated with AHCM,\(^7,17\) which is different from the findings in previous reports that this disorder is associated with mutations in ACTC1 and MYH.\(^20\)

The genetic testing results of our 2 patients’ patients for AHCM were negative, but in 1 case found gene mutations were found for DCM-TMPO (12q23.1).\(^21,22\) Considering the disease-causing genes of inherited cardiomyopathy overlap,\(^23\) that is, 1 gene mutation can cause different types of cardiomyopathy, in some exceedingly peculiar case, 1 patient could have mixed phenotype of hypertrophic, dilated, restrictive, even apical thinning.\(^24\) We postulate that one of the patients was affected by gene regulation, she had both phenotypes of hypertrophic and dilated cardiomyopathy. Nevertheless, the relationships between the genotype and phenotype need to be further studied.

It has been reported that a small part of the terminal stage of HCM is accompanied by remodeling of the ventricle, when expansion of the left heart chamber and a loss of the systolic function occur, which is the dilated phase of the terminal stage of hypertrophic cardiomyopathy (D-HCM). D-HCM is a special and rare evolutionary outcome.\(^25,26\) Eriksson et al found a significant increase in LV diastolic and systolic dimensions and

Figure 2. Morphology: the echocardiography of the 2 patients (A and B) showed apical myocardial hypertrophy, endomyocardial fibrosis and calcification, and left ventricular enlargement. LVO (C) revealed a thick ridge of tissue surrounding the calcium, and the echo shadowing behind the calcium and thick endocardium. Magnetic resonance (D) showed significant hypertrophy of the myocardial apex. SPECT (E) revealed increased resting apical tracer uptake and a spade-like configuration of the left ventricular chamber that was observed in the vertical and horizontal axes. The left ventricular strain was significantly reduced (F). LVO=left ventricular opacification, SPECT=single-photon emission computed tomography.
the left atrial diameter during 10 decades of follow-up,[27] but such reports are scarce.

With the occurrence of apical EMF, impaired LV diastolic function and LV dilatation, case 1 and case 2 patients may have “poor” prognosis.

3.4. Treatment and prognosis

Treatment of AHCM includes medical and surgical treatment. The use of a β-blocker or calcium channel blockers is recommended in patients with preserved EF in maximal tolerated doses; typical heart failure medication should be used in patients with depressed EF. Surgical treatment for patients with trans-apical myectomy is performed by incising the apex of the LV, which results in increasing of end-diastolic volume.[28] The overall cardiovascular mortality rate of AHCM patients is low, compared with other forms of HCM has a favorable long-term prognosis.[10,28]

3.5. Limitations

Due to research limitations, no complete genetic family studies and myocardial biopsy were performed of the 2 patients.

Author contributions

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