

# Diagnosis of hypertrophic cardiomyopathy accompanied with secondary hypertension - case report

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## Diagnosis of hypertrophic cardiomyopathy accompanied with secondary hypertension - case report

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### Abstract

Hypertrophic cardiomyopathy (HCM) is a prevalent genetic cardiac condition, known to be the most common. However, there have been limited reports on the diagnosis of HCM accompanied by secondary hypertension and the subsequent systematic therapy. In this case report, we present the case of a 65-year-old male patient who presented with recurring chest discomfort during physical activity, along with refractory hypertension. Cardiac Magnetic Resonance Imaging and transthoracic echocardiogram revealed the presence of HCM in this individual. Further investigation revealed hypokalemia, elevated aldosterone levels, decreased plasma renin activity, and an aldosterone-to-renin ratio above 30. These findings strongly indicated primary aldosteronism (PA) as an additional condition affecting this patient.

Through the utilization of Whole Exome Sequencing, we successfully identified a suspected pathogenic gene TTN as the underlying cause of the patient's condition. The presence of hypertrophic cardiomyopathy (HCM) accompanied by secondary hypertension due to primary aldosteronism (PA) resulted in significant enlargement of the left ventricle, particularly the ventricular septum. While certain genetic mutations may suggest a potential link to cardiomyopathy development, they cannot definitively establish a direct association between HCM and PA.

**Key word** : Hypertrophic cardiomyopathy, TTN gene, Primary aldosteronism

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### Introduction

Hypertrophic cardiomyopathy (HCM) is a prevalent genetic cardiac condition, affecting approximately 1 in every 200-500 individuals in the general population. It is characterized by left ventricular outflow tract obstruction, observed in up to two-thirds of patients, which can contribute to progressive heart failure

symptoms. Primary aldosteronism (PA) represents the most common form of secondary hypertension and is associated with increased cardiovascular risks. Interestingly, reports suggest that HCM accompanied by hypertension becomes more frequent as individuals age. This combination often results in significant hypertrophy of the ventricular septum and walls. In this case study, we present a patient with a long history of hypertension who experienced accelerated left ventricular hypertrophy during middle to late stages of life. This led to reduced systolic function and hemodynamic changes. Existing literature highlights both an increased occurrence and poor prognosis for this particular complication [1].

To our knowledge, cases involving HCM accompanied by secondary hypertension caused by PA leading to significant hypertrophy of the left ventricle, particularly the ventricular septum, have been rarely reported. We provide this case report following the CARE reporting checklist guidelines.

## Case presentation

A 65-year-old male patient was admitted with a chief complaint of recurrent chest distress that had been ongoing for over 10 years, but became aggravated in the past month. The patient's medical history revealed a previous diagnosis of Hypertrophic Cardiomyopathy (HCM) based on findings from a transthoracic echocardiogram (TTE). However, the patient did not receive regular treatment for this condition. In the past month, the patient experienced more frequent and severe symptoms during physical activity, specifically while walking. These episodes lasted between 10 minutes to half an hour and were relieved after rest. Concerned about his cardiovascular health, he measured his systolic blood pressure at 152mmHg. Further investigations through an Electrocardiogram (ECG) revealed sinus bradycardia, first-degree atrioventricular block, left ventricle hypertrophy, and ST-T changes. Additionally, a thoracic CT scan showed cardiac enlargement and nodules present on both adrenal glands.

**Past History:** The patient has a 30-year history of hypertension, with the highest recorded blood pressure reaching 190/110mmHg. They have been on regular treatment consisting of amlodipine, metoprolol, irbesartan, and hydrochlorothiazide to manage their blood pressure. Recent monitoring shows readings ranging between 140-150/80-90mmHg. The patient also presents with hyperuricacidemia and hyperlipidemia. There is a family history of hypertension. During the physical examination, the patient's blood pressure was measured at 153/88mmHg. No jugular vein distension or rales were observed in the lungs. The heart rhythm was regular, but an enlargement of the heart border was noted along with an ejective murmur detected in both first and second aortic valve regions as well as the apex region. No edema was present. Laboratory tests revealed hypokalemia (potassium levels ranging from 3.01-3.52mmol/L; normal range: 3.3-5.3mmol/L). Aldosterone (ALD) levels ranged from 456.21-762.179pg/mL, plasma renin activity (PRA) ranged from 0.154-166ng/mL/hour, and aldosterone-to-renin ratio (ARR) ranged from 69.12-141.126.

A computed tomography scan showed nodules on both adrenal glands measuring between 10mm to 17mm in diameter. Transthoracic echocardiogram (TTE) indicated hypertrophic left ventricle (LV wall thickness measuring 15mm; basal segment of ventricular septum measuring 22mm), positive SAM sign (Fig1. Systolic Anterior Motion), Vmax (left ventricular outflow tract velocity measurement) of LVOT measured 2.47m/s and Peak Pressure Gradient of LVOT was 24mmHg, and an ejection fraction (EF) of 68%. Cardiac magnetic resonance imaging (MRI) revealed a left atrium measurement of 47mm, right atrium measurement of 45mm, left ventricular end-diastolic diameter (LVED) measuring 91mm, right ventricular end-diastolic diameter (RVED) measuring 77 mm. The thicknesses of the LV walls ranged from 11-23mm with improper movement noted (Fig 2.). Cardiac output (CO) was calculated as 130.52 L/min. Coronary artery computed tomography scan and Holter monitoring both yielded negative results. A comprehensive timeline summarizing the patient's historical information and treatment course is provided in Table 1.

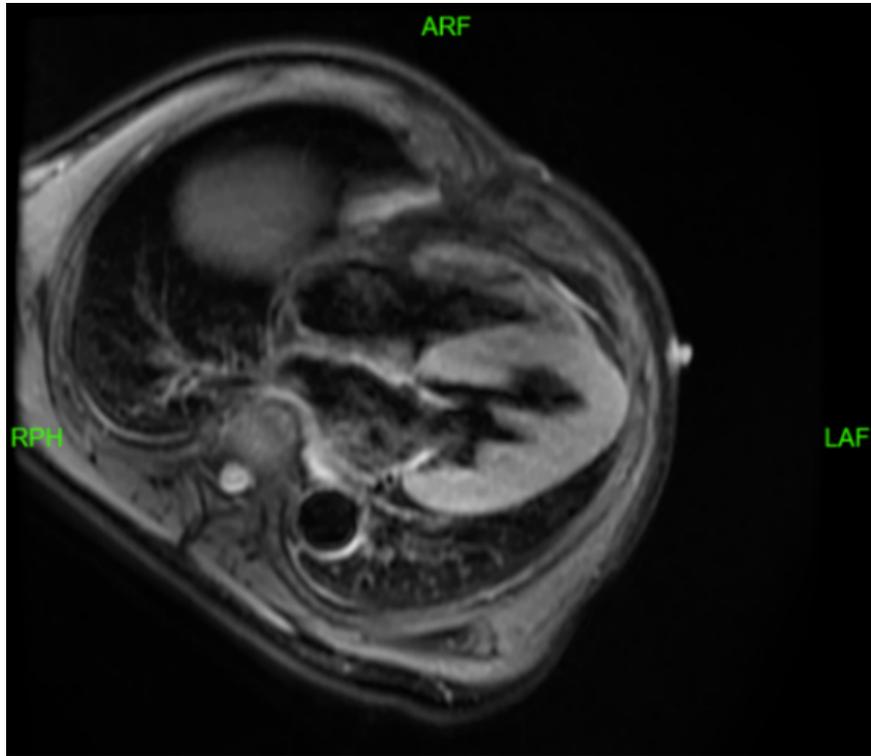


Fig1. TTE(SAM sign) Fig2. Cardiac MRI (four chamber, T2WI+Black Blood)

Table1. Timeline

Time	Events
30 years ago	Hypertension with 4-types of medical therapy
10 years ago	Chest distress, TTE revealed HCM and no regular therapy
1 months ago	Aggressive symptoms while activities with refractory hypertension
Day 0	Admitted to our cardiology department
Day 1	Lab test showed hypokalemia and refractory hypertension
Day 2	TTE indicated HCM
Day 3	Coronary CT scan showed negative
Day 4	Lab test showed ARR above 30
Day 5	Adrenal gland CT scan showed bilateral nodes and antisterone applied
Day6 - 8	No other abnormal results of adrenal gland found
Day 9	Cardiac MRI showed HCM

TTE, transthoracic echocardiogram; HCM, hypertrophic cardiomyopathy; ARR, aldosterone-to-renin ratio; CT, computed tomography; MRI, magnetic resonance imaging.

## Discussion

Initially, we hypothesized that the myocardial hypertrophy observed in this case was primarily attributed to secondary hypertension caused by primary aldosteronism (PA). However, the left ventricular wall thickness, ranging from 15 to 22mm, exceeded what is typically seen in hypertensive hypertrophy (usually around 13-14mm). Conversely, an average left ventricular wall thickness of 21mm is commonly observed in cases of Hypertrophic Cardiomyopathy (HCM) [2]. Additionally, HCM alone cannot fully explain the presence of left atrial hypertrophy. Therefore, we propose that the changes observed in this particular case are likely a complication resulting from both HCM and PA.

To further validate our assumption, we conducted a comprehensive analysis of the patient's whole exome sequencing data. We focused on identifying pathogenic variations by cross-referencing with the OMIM database. Our assessment revealed suspected variants in TTN, SLC36A2, and TWNK genes.

Familial hypertrophic cardiomyopathy (HCM) is known to be associated with various gene mutations, including MYH7, MYBPC3, TNNT2, GLA, and TTR. However, the presence of TTN, SLC36A2, and TWNK mutations in this particular case appears to be rare and has not been widely reported [2][3]. TTN encodes a large protein found abundantly in striated muscle and myocardial cells. Mutations in this gene have been linked to familial hypertrophic cardiomyopathy 9. Additionally, patients with the autoimmune disease scleroderma often produce autoantibodies targeting titin.

SLC36A2 is primarily expressed in renal cells but has no documented reports linking it to the pathogenesis of HCM. TWNK mutations are responsible for infantile onset spinocerebellar ataxia (IOSCA), progressive external ophthalmoplegia (PEO), as well as several mitochondrial depletion syndromes. Considering the patient's clinical history and examination findings mentioned earlier, we identified a suspected pathogenic variation within the TTN gene as being potentially relevant to this case study.

These findings provide additional support for our hypothesis regarding the involvement of multiple genetic factors in this case, contributing to both hypertrophic cardiomyopathy (HCM) and primary aldosteronism (PA). The identification of these specific gene variants adds valuable insights into understanding the underlying mechanisms and potential genetic basis for this rare clinical presentation.

In addition to our investigation into the genetic factors associated with HCM in this case, we also sought to explore whether there might be a shared genetic mutation underlying both HCM and primary aldosteronism (PA). Our review of relevant literature and summaries on PA yielded some interesting findings: The exact

pathogenesis of PA is not yet fully understood. However, it is believed that somatic mutations occurring in ion channels and pumps within adrenal cells play a role in initiating the development of PA [4]. Studies focusing on three types of Familial Hyperaldosteronism have identified mutations in genes such as CYP11B1, CYP11B2, CLCN2, GIRK4, and CACNA1D [5][6][7]. These gene mutations may provide insights into potential pathways involved in the pathogenesis of PA.

By considering these facts and examining possible connections between HCM and PA at a genetic level, we aim to shed light on any potential shared mechanisms or common underlying genetic variations that could contribute to both conditions.

(HCM) and primary aldosteronism (PA) has been associated with a poor prognosis [1]. Compared to primary hypertension, PA has been shown to cause more damage to end-organs and is linked to increased cardiovascular morbidity. This includes conditions such as heart failure, non-fatal myocardial infarction, and atrial fibrillation [8][9]. Additionally, HCM itself can lead to progressive heart failure symptoms due to obstructive physiology and diastolic dysfunction. Therefore, maintaining positive control over blood pressure levels in patients with HCM becomes crucial. By achieving a target blood pressure of 120/80mmHg in these patients, it may help decrease both preload and afterload on the left ventricle. This approach holds potential for positively impacting the prognosis of this particular complication.

By recognizing these factors and implementing appropriate management strategies for both HCM and PA, we aim to improve patient outcomes and mitigate the risk of adverse cardiovascular events associated with this challenging combination.

Based on the guidelines for hypertrophic cardiomyopathy (HCM) and primary aldosteronism (PA), we have devised a treatment plan as follows: Sacubitril/valsartan 100mg twice daily: This medication combination has been shown to be effective in managing heart failure symptoms and improving outcomes in patients with HCM [4]. Nifedipine 30mg once daily: Nifedipine is a calcium channel blocker that helps relax blood vessels, reducing blood pressure and alleviating symptoms associated with PA [10]. Bisoprolol 5mg once daily: Bisoprolol is a beta-blocker that can help control heart rate and reduce cardiac workload, which may be beneficial for patients with both HCM and PA [4].

Additionally, it is worth noting that mavacamten, an investigational therapy for HCM, has shown promising results in reducing obstruction of blood flow, improving symptoms, overall well-being, and enhancing the ability to engage in daily activities [10]. However, there is currently no evidence regarding its use specifically in PA patients.

At the time of completing this report, our management approach has successfully controlled blood pressure within the range of 120-130/70-80mmHg. Further follow-up will be necessary to monitor any changes in myocardial health. By combining appropriate pharmacological interventions tailored to address both HCM and PA conditions, we aim to optimize patient care while considering their individual needs and potential benefits from emerging therapies such as mavacamten.

## Footnote

**Reporting Checklist:** The authors have completed the CARE reporting checklist

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form. The authors have no other conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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