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(CASE REPORT)

# Hypertrophic cardiomyopathy in a patient with myxedema: Clinical case

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## Abstract

Hypothyroidism is a common endocrine disorder that primarily affects females and has both direct and indirect effects on the cardiovascular system. Hypothyroid cardiomyopathy is a rare manifestation of this disease and can present as dilated cardiomyopathy (DCM) or, less commonly, as hypertrophic cardiomyopathy (HCM), with or without asymmetric septal hypertrophy. The deficiency of thyroid hormones leads to changes in the energy metabolism of cardiomyocytes and provokes electrical instability of the myocardium. This clinical case raises questions about the assessment of the risk of sudden cardiac death (SCD) in these patients and the need for an appropriate therapeutic strategy to improve prognosis.

**Keywords:** Hypothyroidism; Myocardial Hypertrophy; Mucopolysaccharides; Sudden Cardiac Death

## 1. Introduction

Cardiomyopathies, according to the latest guidelines from the European Society of Cardiology (ESC), are defined as disorders of myocardial function and structure in the absence of etiological causes such as ischemic coronary artery disease, arterial hypertension, valvular pathology, or congenital heart defects [1]. A patient with cardiomyopathy may have concomitant conditions, but they are not the primary cause of myocardial dysfunction [2]. Hypertrophic cardiomyopathy (HCM) is defined as the presence of an increased wall thickness of the left and/or right ventricle greater than 15 mm, which cannot be explained by increased preload or afterload. When diagnosing severe myocardial hypertrophy, various laboratory and imaging tests are necessary to determine the etiology and assess the patient's risk [1]. Hypothyroidism affects approximately 4.6% of the general population (with manifest forms at 0.3% and subclinical forms at 4.3%), with the prevalence of the disease increasing with age. Over 40 years ago, it was demonstrated that myxedema affects the cardiovascular system, being associated with reduced cardiac output, arterial hypertension, sinus bradycardia, pericardial effusion, and prolonged QT interval [3]. Hypothyroid cardiomyopathy is a rare manifestation of the disease and can present as either dilated or hypertrophic cardiomyopathy, with or without asymmetric septal hypertrophy [4].

## 2. Description of the Clinical Case

This is a 66-year-old woman who was admitted urgently to the hospital following a collapse. The medical history was taken from her relatives due to pronounced bradypsychia and quantitative changes in the patient's consciousness. According to them, over the past three years, the woman gradually became apathetic and gained weight. In the last 1–2 months, she had been bedridden due to extreme weakness and an inability to stand upright. Due to a mild depressive disorder in her younger years, her relatives attributed the symptoms to her mental state and did not seek medical help. On the day of hospitalization, the patient briefly became unresponsive while sitting up to eat, prompting her relatives to seek emergency medical assistance.

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Upon admission to the hospital, the patient was in a somnolent state, responding sluggishly and inappropriately to questions. Her face was swollen with peri-orbital edema, a thickened tongue, peripheral firm edema, and dry skin. Cardiovascular status revealed an arrhythmic heart rate with faint heart sounds and no added murmurs. The heart rate (HR) was 115 beats per minute, and the blood pressure (BP) was 110/70 mmHg. There were no objective signs of pulmonary congestion.

Clinical and laboratory tests showed a mildly expressed anemic syndrome with hemoglobin at 114 g/l, while white blood cells and platelets were within normal limits. Serum creatinine, urea, transaminases, and electrolytes were all within normal ranges. Markers of myocardial injury were mildly elevated: creatine kinase-MB fraction (CK-MB) at 51.2 U/l, and hsTroponin at 579.4 pg/ml. Follow-up of myocardial necrosis markers before discharge showed a reduction in values: CK-MB at 31.2 U/l and hsTroponin at 279.4 pg/ml. Thyroid-stimulating hormone (TSH) levels were above 100 mU/ml. The lipid profile showed elevated LDL levels of 5.06 mmol/l and triglycerides at 2.54 mmol/l. The electrocardiogram (ECG) showed atrial fibrillation (AF), left anterior fascicular block (LAFB), right bundle branch block (RBBB), low-voltage complexes, and a heart rate of 135 beats per minute (Figure 1).

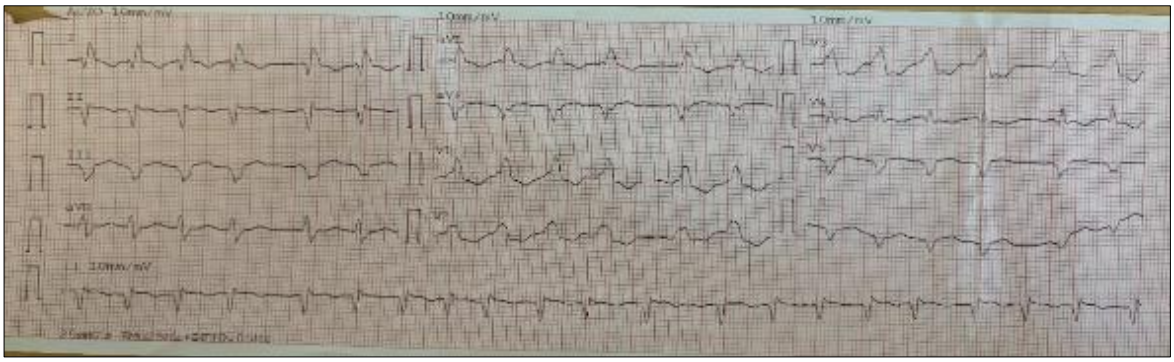

**Figure 1** ECG at the time of patient admission

Chest X-ray showed an enlarged cardiac silhouette with a cardiothoracic ratio of 0.6 and pleural effusion in the right cardiophrenic angle. Two-dimensional echocardiography revealed severe concentric hypertrophy with a septal thickness of 18 mm and posterior wall thickness of the left ventricle (LV) of 21 mm. The left atrium (LA) had a diameter of 43 mm, measured from the parasternal long-axis view (PLAX). The left ventricle (LV) had a moderately reduced ejection fraction (EF) of 46% with volumes of 54/28 ml. The valve apparatus showed no significant changes, and the diastolic mitral blood flow demonstrated pseudonormalization with an E/E' ratio of 15, which indicates diastolic dysfunction with elevated left ventricular end-diastolic pressure (LVEDP) (Figure 2).

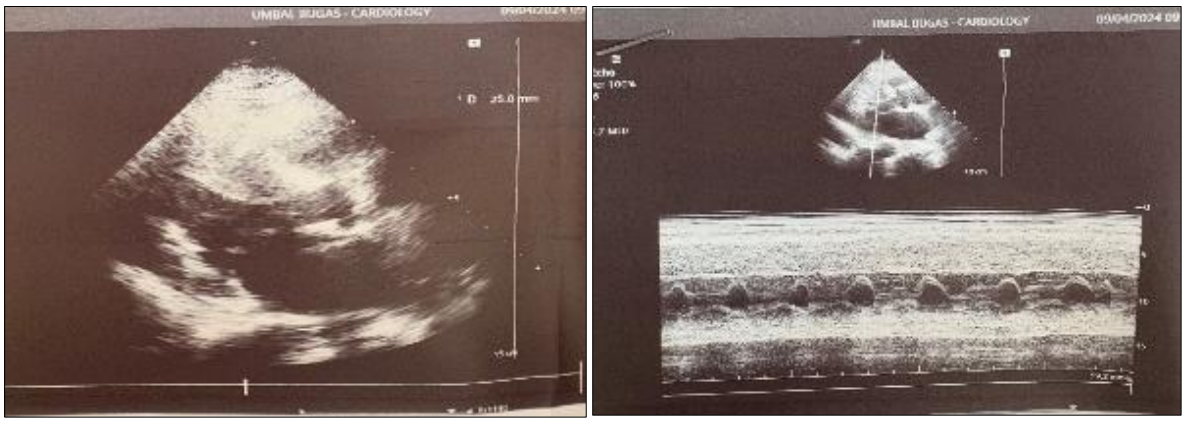


**Figure 2** 2D parasternal long-axis and M-mode image showing severe symmetrical hypertrophy and absence of SAM (systolic anterior motion) phenomenon

Holter ECG monitoring did not reveal any pauses in the heart rhythm, with the heart rate (HR) varying between 135 and 95 beats per minute in the presence of persistent atrial fibrillation. The patient was started on anticoagulant therapy due to a high embolic risk, with a $CHA_2DS_2$-VASc score of 2. After consultation with an endocrinologist, treatment with

AcuThyrox 3 ml daily was initiated for 3 days, after which the dose was increased to 5 ml daily until the follow-up visit 20 days later.

After stabilization of the condition, the patient was discharged for home treatment with the following prescribed therapy: AcuThyrox according to the scheme, apixaban 60 mg daily, bisoprolol 5 mg daily, and atorvastatin 40 mg daily. At the follow-up visit after 20 days, the patient showed visible improvement. She was alert, with reduced edema of the face and body, and responded appropriately to the questions asked. The hypothyroidism treatment was adjusted – Levothyroxine 75 mcg daily was started for one week, with titration of the dose to 100 mcg for the next two months. The cardiovascular status showed atrial fibrillation (AF) with a normal ventricular response, blood pressure (BP) of 130/80 mmHg, and heart rate (HR) of 92 beats per minute. Echocardiography showed no significant changes compared to the baseline from 20 days earlier, with a slight reduction in the thickness of the left ventricular (LV) walls – the septum was reduced to 16 mm, and the posterior wall of the LV (PWLV) measured 20 mm.

At the 2-month follow-up, the patient was contacted via the provided phone number for a scheduled check-up, but the relatives reported that she had passed away in her sleep one week prior.

## 3. Discussion

As early as 1980, Santos et al. described a series of 19 patients with myxedema in whom reversible asymmetric left ventricular (LV) hypertrophy was identified, which was practically macroscopically indistinguishable from hypertrophic cardiomyopathy [5]. Since then, relatively few similar cases have been reported. Myocardial involvement in this condition may result from several pathogenic mechanisms. The lack of thyroid hormones leads to decreased energy production in cardiomyocytes, and the presence of increased demands can result in cellular damage [6]. Additionally, thyroid hormones play a role in the body's antioxidant defense, and their deficiency is associated with oxidative stress and low levels of glutathione in the myocardium, which also leads to cardiomyocyte damage. The energy metabolism of the cell is also affected due to impaired function of both SERCA 2-a (sarcoplasmic/endoplasmic reticulum Ca2+-ATPase) and α-myosin heavy chains in the hypothyroid heart, which may lead to the manifestation of both systolic and diastolic dysfunction. It is not known whether these changes in the myocardium are reversible, but it is assumed that persistent cellular dysfunction may develop over time with prolonged hypothyroid states. We believe that the elevated myocardial necrosis markers found upon the patient's admission were the result of impaired cardiomyocyte energetics, rather than an acute coronary event.

Histological findings from studies in experimental animals with hypothyroidism show the accumulation of mucopolysaccharides in the intercellular space, with normal alignment of myofibrils, and an absence of signs of inflammation, fibrosis, or amyloid deposits [7]. The deposition of mucopolysaccharides in tissues is relatively rare, typically resulting from a genetic defect, as in the case of mucopolysaccharidoses [8]. Acquired diffuse deposition of these compounds has been described in some systemic collagenoses and metabolic disorders, where myocardial involvement may also occur. Thyroid hormones are involved in the breakdown of mucopolysaccharides into soluble substances, which are excreted in the urine [9]. As a result, in hypothyroid states, these substances accumulate in tissues, primarily in the skin, and to a lesser extent in parenchymal organs, including the myocardium and the central nervous system.

In the presented clinical case, the hypothyroid state developed gradually over the past 3 years and led to the manifestation of a severe myxedema clinical picture. The prolonged persistence of impaired thyroid function may explain the extreme myocardial hypertrophy, which resulted in left ventricular (LV) diastolic dysfunction and left atrial (LA) dilation, followed by an episode of atrial fibrillation (AF). Due to the hemodynamic deterioration in the last month, it can be assumed that the tachyarrhythmia further contributed to the reduction in stroke volume and a decline in the patient's physical capacity. It may also be hypothesized that there was dynamic left ventricular outflow tract (LVOT) obstruction due to significant hypertrophy, although no gradient was recorded at rest during hospitalization.

Renin precursors are synthesized in the liver as a result of stimulation by 3-iodothyronine (T3), which may explain the reduced production in hypothyroidism [7]. Increased vascular tone, on the one hand, and low renin levels, on the other, lead to diastolic hypertension and low pulse pressure. The onset of tachyarrhythmia and the sudden drop in stroke volume can explain the severe orthostasis, which likely led to the collapse and inability to be verticalized in this clinical case.

At the follow-up visit, clinical improvement in the patient's condition was noted, although we believe that a longer period of time is necessary for the reversal of LV hypertrophy. The most likely cause of the fatal outcome is suspected to be a rhythm disorder or a massive ischemic or hemorrhagic cerebrovascular event. Given the $CHA_2DS_2$-VASc score of

2 points, dilated LA, and low physical activity, anticoagulant therapy with apixaban was initiated. Considering the adequate anticoagulant therapy over nearly 2 months, the likelihood of an embolic event was relatively low, and the patient did not have prior symptoms of transient ischemic attacks (TIA).

Massive cerebral hemorrhage cannot be ruled out as a likely cause of the fatal outcome. About 20% of patients with subarachnoid hemorrhage experience sudden death and do not reach a hospital facility [10]. Since there is no prior medical history, it can be hypothesized that massive cerebral hemorrhage, in the context of anticoagulant therapy, was the cause of the sudden death.

A probable ventricular tachyarrhythmia is also a possible cause of the patient's sudden death. In hypothyroidism, there is an increase in the QT interval due to the prolongation of the action potential. This leads to increased myocardial vulnerability, which may raise the risk of Torsades de pointes [11]. Episodes of polymorphic ventricular tachycardia (VT) are usually preceded by early afterdepolarizations, especially in the presence of QT interval prolongation and concurrent electrolyte disturbances, such as hypokalemia. The heterogeneous ventricular refractoriness resulting from the heterogeneous myocardial structural remodeling and the degree of mucopolysaccharide deposition in the interstitium predisposes to QT dispersion and, consequently, to ventricular tachyarrhythmia in patients with hypothyroidism.

Despite the fatal outcome, the presented clinical case raises several questions. What is the risk of sudden death in patients with significant myocardial hypertrophy as a result of severe endocrine disorders? Unfortunately, we were unable to conduct additional imaging studies, such as cardiac magnetic resonance imaging (MRI) with late gadolinium enhancement to assess myocardial fibrosis. Also, computed tomography angiography or conventional coronary angiography could have answered the hypothesis of ischemic heart disease, which may coexist with endocrine pathology. Possible ischemia could lead to further electrical instability of the myocardium and contribute to triggering ventricular tachyarrhythmia.

## 4. Conclusion

Hypothyroidism is a common endocrine disease, more frequently affecting females, and has both direct and indirect effects on the cardiovascular system. Timely diagnosis allows for the initiation of replacement therapy and the prevention of potential negative outcomes. Hypertrophic cardiomyopathy as a phenotypic manifestation of severe myxedema is a rare presentation of the disease but can have serious negative consequences for the affected patient.

## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

### *Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.

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