Takotsubo Myocardiopathy and Hyperthyroidism: A Case Report and Literature Review

Authors' Contribution:
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Data Interpretation D
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Conflict of interest: None declared

Patient:	**Male, 34**
Final Diagnosis:	**Takotsubo myocardiopathy and hyperthyroidism**
Symptoms:	**Chest pain • dyspnea**
Medication:	**—**
Clinical Procedure:	**—**
Specialty:	**Cardiology**

Objective: Rare co-existance of disease or pathology

Background: Takotsubo cardiomyopathy (TM), also called stress myocardiopathy or transient left ventricular apical ballooning syndrome, is characterized by acute left ventricular dysfunction with reversible wall motion abnormalities. TM resembles acute coronary syndrome (ACS) in the absence of coronary artery disease (CAD).
In several reports, TM has been described in association with hyperthyroidism, suggesting the potential role of thyrotoxicosis in the pathophysiology.

Case Report: We present the case of a 34-year-old man with TM associated with hyperthyroidism caused by Graves' disease. In this case, TM was also preceded by an emotional trigger.
The diagnosis of TM was based on clinical manifestations, electrocardiographic and echocardiographic abnormalities, and the absence of coronary artery disease (CAD) in the angiography. A diagnosis of hyperthyroidism was made based on hormonal and antibody measurements. The patient had a favorable outcome, and the cardiac and thyroid disorders resolved.

Conclusions: Our case illustrates that thyroid disease, mainly hyperthyroidism, should be considered in patients with TM with or without previous emotional triggers. As in our patient, the outcome in TM is usually favorable, with reversibility of cardiac abnormalities.

MeSH Keywords: **Cardiomyopathies • Hyperthyroidism • Takotsubo Cardiomyopathy • Thyroid Diseases**

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Background

Takotsubo (TM) or stress cardiomyopathy (SC) was first described in Japan in the early 1990s by Sato, as an entity mimicking acute myocardial infarction (AMI). The term Takotsubo syndrome is due to the shape of the heart as seen in the ventriculogram, similar to the Japanese name for an octopus trap [1].

The clinical presentation is similar to AMI with normal coronary arteries in the angiography, and it is a reversible cause of acute heart failure. The ventriculography usually shows alterations of apical contractility with hypercontractility of the basal segments. It is commonly preceded by physical or emotional stress [1,2].

Several cases have been reported linking TM with different thyroid disorders. However, the causal association of thyroid disorders and SC has not been fully established [1].

We present a case of TM in a patient diagnosed with hyperthyroidism.

Case Report

A 34-year-old man with a history of smoking (20 packs/year) was admitted to our institution complaining of chest pain and dyspnea. One month prior to admission, he had had atrial fibrillation (AF) with high ventricular response that required electrical cardioversion. Four months earlier, his wife and daughter had died in a motor vehicle accident.

His presenting symptoms were oppressive retrosternal chest pain at rest, and dyspnea (NYHA functional class III), which disappeared with the administration of sublingual nitroglycerin.

On admission, physical examination revealed a normal state of consciousness, anxiety, mild tremor, heart rate 110 bpm, and blood pressure 120/80 mmHg, and the other findings were unremarkable.

The electrocardiogram showed sinus tachycardia with negative T waves in DIII, AVF, and V5–6. His hemoglobin level was 13.5 gr/dL (VN: 13–16 gr/dL), white blood cell count was 7.2×10^9/L (VN: $5–10 \times 10^9$/L), and platelet count was 220×10^9/L (VN: $150–400 \times 10^9$/L). C-reactive protein was 0.5 mg/dl (VN: 0.1–0.5 mg/dl) and his erythrocyte sedimentation rate (ESR) was 20 mm/h. Plasma creatinine, urea, liver function tests (LFT), and proteinogram were normal. Troponin I was 0.03 ng/ml (VN: less than 0.01 ng/ml).

Plasma thyrotropin (TSH) was under 0.005 µU/mL (0.35–55 µU/mL, by chemiluminometric assay) and total serum thyroxine (T4) was 15.9 µg/dl (5.4–11.7 µg/dl, by chemiluminometric assay). Thyrotropin receptor antibodies (TRAb) were positive, and the thyroid echography showed mild enlargement of the thyroid gland, without nodules.
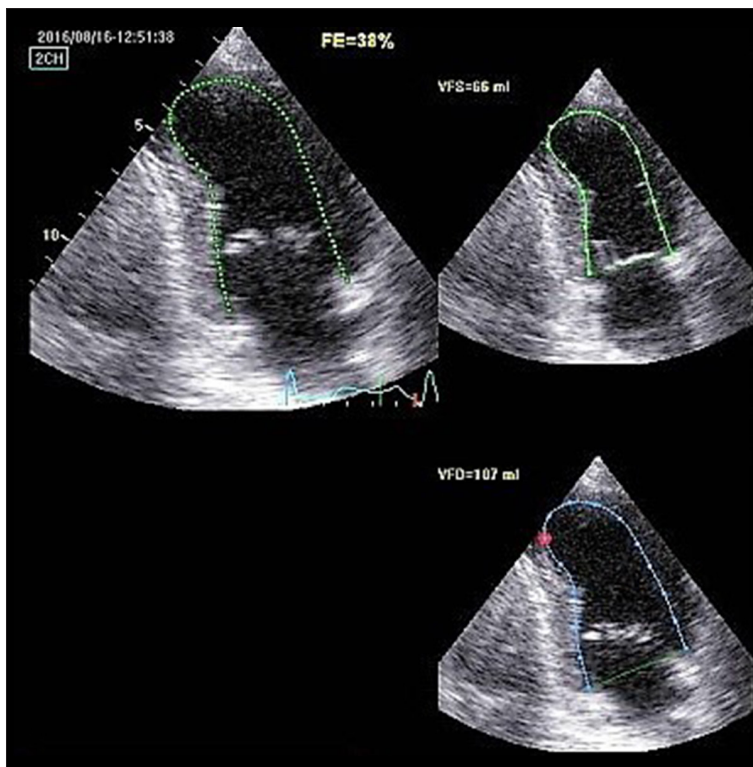

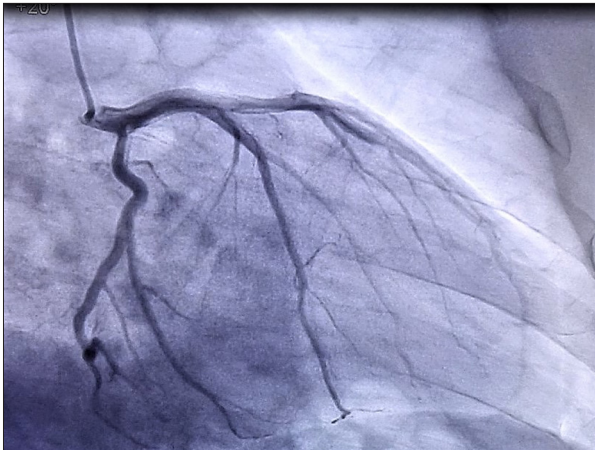**Figure 1.** Echocardiogram: apical hypokinesia.

Figure 2. Coronary Angiography: coronary tree without significant lesions.

The Doppler echocardiogram showed severe apical and moderate anterior hypokinesis and the left ventricular (LV) ejection fraction was 40%. Right ventricle (RV) size was preserved, and function was within the lower normal limit (TAPSE 16 mm) (Figure 1).

As coronary artery disease (CAD) was suspected, coronary angiography and ventriculography were done. These studies showed a coronary tree without significant lesions, and the LV presented moderately decreased ejection fraction and apical akinesis compatible with TM (Figures 2, 3). Based on the diagnosis of TM and hyperthyroidism secondary to Graves' disease, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and methimazole were started.

The clinical evolution was favorable, and 1 week later, the patient was discharged.

Six weeks later, the patient remained asymptomatic and showed normalization of the echocardiographic abnormalities

and TSH serum levels. The patient continued treatment at another hospital.

Discussion

TM represents approximately 2% of the cases in which the clinical presentation is suggestive of AMI. The precise incidence of TM is unknown. It is considered a rare syndrome, but at present its incidence is increasing due to better diagnosis and screening. In 2006, the American Heart Association included TM in the classification of cardiomyopathies [3].

TM evidences left ventricular wall motion abnormalities in both echocardiography and ventriculography. In the classical form of the condition, hypokinesis, akinesis, or dyskines of the apical and mid-ventricular segments are typically observed. Several other forms of TM have also been described: basal (or Takotsubo inverted), mid-ventricular, focal, biventricular, and right ventricular TM [3].

TM is more common in postmenopausal women, with women accounting for as much as 80–100% of cases in several reports [2–4]. In a review of 1750 cases, 89.8% were women with a mean age of 66.8 years [2]. TM has also been reported in younger women, pregnant women, and in males. [5–7].

The reason why TM is more prevalent in females is unknown. It may be related to sex differences in myocardial sensitivity to catecholamines and the potentially important role of estrogens in the pathogenesis of this entity [1–4,8]. Our patient, unlike most reported cases, was young and male.

Clinically, TM usually presents with chest pain and dyspnea, and the most important differential diagnosis is AMI [1–4].
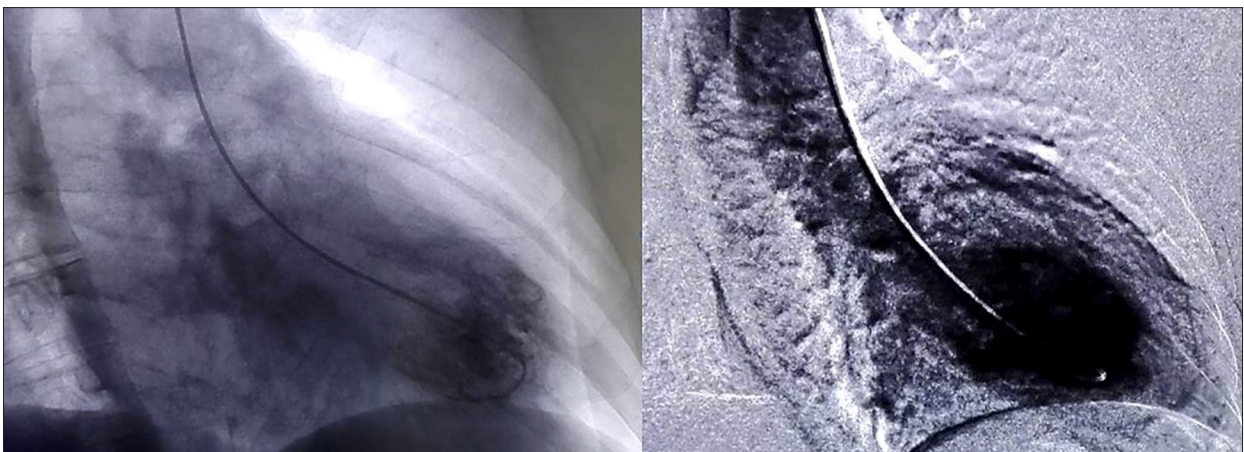

Figure 3. Ventriculography: image of apical ballooning.

In TM, electrocardiographic changes may include either ST-segment elevation or T-wave inversion and troponin elevation, but usually in lower values as compared to AMI [9,10].

Moreover, the apical motility disorder shown in the echocardiogram and ventriculogram with normal coronary arteries is the most characteristic marker of TM [1,2]. Magnetic resonance imaging (MRI) may also be a useful tool to differentiate between TM and AMI. In TM, the MRI may show an isolated mid-wall or subepicardial pattern of late gadolinium enhancement (LGE), whereas either subendocardial or transmural LGE is observed in AMI [11,12].

Considering the above, a diagnosis of TM should be suspected in the presence of clinical manifestations, echocardiographic and ventriculographic changes and the absence of coronary disease. However, there is no universal diagnostic definition of TM, and several diagnostic criteria have been proposed.

The Mayo Clinic diagnostic criteria were originally proposed in 2004 and modified in 2008 [4,13].

These criteria considered (all criteria must be present):
• Transient akinesis, hypokinesis or dyskinesis of the left ventricular apical and mid-ventricular segments;
• Absence of obstructive coronary disease as shown in the angiography;
• Electrocardiographic abnormalities (either ST-segment elevation or T-wave inversion);
• Absence of pheochromocytoma and myocarditis.

Although the Mayo Clinic criteria are frequently used, there are other useful criteria for TM diagnosis, such as the Gothenburg criteria, proposed in 2013, as follows [14]:
• Transient hypokinesis, akinesis, or dyskinesis in the left ventricular segments and commonly, but not always, the presence of an either physical or emotional stress-related trigger;
• The absence of other pathological conditions (e.g., ischemia, myocarditis, toxic, damage, and tachycardia) that may reliably account for regional dysfunction;
• Normal or near-normal filling pressure.

More recently, in 2014, Madias proposed new diagnostic criteria for TM [15]:
• Transient hypokinesis/akinesis/dyskinesis of the left and/or right ventricular myocardial segments, particularly in postmenopausal women, associated frequently, but not always, with a stress-related trigger (physical or emotional);
• The absence of other pathological conditions (e.g., ischemia, myocarditis, toxic damage, and tachycardia) that may reliably account for the regional dysfunction;
• "Milder forms" or *formes frustes* of Takotsubo syndrome may exist, characterized by transient hypokinesis, akinesis,

or dyskinesis in the left and/or right ventricular myocardial segments, and/or T-wave inversions and QTc prolongation at follow-up;
• TM may be a comorbidity with a variety of illnesses, including acute coronary syndromes (ACS).

According to the Mayo Clinic criteria for the diagnosis of TM, pheochromocytoma must be ruled out. Other criteria state that pheochromocytoma should be considered, and this diagnosis must not be disregarded. However, it is not mandatory to always measure catecholamine levels when suspecting TM. These tests should be done only in select cases when there is no clear explanation for this diagnosis [3,16].

In our case, 2 possible causes are related to the diagnosis of TM: hyperthyroidism and the previous emotional trigger. In accordance with the criteria mentioned, the diagnosis of pheochromocytoma in our patient was not to be ruled out. Actually, catecholamine levels may be elevated in TM cases, as in cases of AMI [3,17,18].

TM may be preceded by a physical or an emotional event. Emotional factors were more prevalent among women, while physical factors were more common among males [2]. Several stressful situations have been associated with TM. The emotional stressors include exposure to a stressful event, commonly a relative's disease or death. In a TM review, physical triggers were more common than emotional triggers, and in 28.5% of the cases, no evident trigger was found [2].

In our case, 2 possible triggers – emotional and physical – were identified: grief related to the recent death of relatives and hyperthyroidism.

With respect to hyperthyroidism, the previous episode of AFib was suggestive of this diagnosis and then confirmed by hormonal and antibody measurements.

Thyroid disease has been associated with TM in many reports [2,8,19–24]. In 2004, Miyakazi et al. first described TM associated with thyrotoxicosis when demonstrating myocardial stunning by scintigraphy and the use of thallium-201 and Tc 99m-pyrophosphate [8].

Templin et al. reported that 17.7% of TM cases were associated with thyroid disorders, 5.9% were hyperthyroid, and 11.8% were associated with hypothyroidism [2].

In another study of 78 patients with TM, 27 (34.6%) had hypothyroidism and 5 (6.4%) had hyperthyroidism [5]. TM has been also described in mild and apathetic hyperthyroidism [23,24].

There are several hypotheses that may explain the relationship between TM and thyroid diseases. The thyroid and the adrenergic axes are closely related. Elevated levels of thyroid hormones cause exaggerated inotropic and chronotropic responses to catecholamines. There is over-regulation of beta-adrenergic receptors by thyroid hormones in many tissues, including the heart [8,19–21].

Although most reported cases of TM with thyroid dysfunction are considered thyrotoxicosis due to Graves–Basedow disease, cases related to hypothyroidism also have been described [2].

Hypothyroid patients may present alterations of the autonomic nervous system, coronary artery spasm, and decreased coronary reserve.

Several pathophysiological mechanisms have been proposed in TM: spasm of multiple epicardial vessels, deterioration of the coronary microvasculature, and microvascular spasm resulting in myocardial stunning [3].

At present, the most accepted theory focuses on the role of endogenous catecholamines in the induction of myocardial dysfunction. Contraction band necrosis is the histological pattern observed in TM and other hyperadrenergic conditions [21,22].

In agreement with a recent publication, we conclude that the pathogenesis of TM includes alterations in different factors: myocardial perfusion, stunning, abnormal cardiac sympathetic innervation, high circulation catecholamine toxicity, and regional receptor distribution in the left ventricle [25].

In terms of TM prognosis, it is a reversible acute myocardiopathy. Although the clinical presentation is similar to MI, the prognosis is much better; however, in some cases, it may be complicated by serious events such as cardiac rupture, pulmonary edema, and cardiac arrest [26].

No randomized trials or guidelines are available for the management and treatment of TM. The use of ACE inhibitors or angiotensin receptor blockers may be associated with better survival, but beta blockers are not effective for prevention or treatment [2,27].

Conclusions

TM is considered a rare cardiac syndrome, but in recent years this disorder has been recognized and diagnosed more frequently. It may be preceded by a physical or an emotional event, and it is usually associated with a favorable prognosis.

Given the association of thyroid disorders, both hyperthyroidism and hypothyroidism, we suggest that the measurement of thyroid hormones should be included in the armamentarium when studying this entity. In cases related to these endocrine disorders, management of the endocrine disorder is necessary for cardiomyopathy resolution.

Conflict of interest

None.

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