Case Reports

Recurrent Takotsubo Cardiomyopathy Related to Recurrent Thyrotoxicosis

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Takotsubo cardiomyopathy, or transient left ventricular apical ballooning syndrome, is characterized by acute left ventricular dysfunction caused by transient wall-motion abnormalities of the left ventricular apex and mid ventricle in the absence of obstructive coronary artery disease. Recurrent episodes are rare but have been reported, and several cases of takotsubo cardiomyopathy have been described in the presence of hyperthyroidism. We report the case of a 55-year-old woman who had recurrent takotsubo cardiomyopathy, documented by repeat coronary angiography and evaluations of left ventricular function, in the presence of recurrent hyperthyroidism related to Graves disease. After both episodes, the patient's left ventricular function returned to normal when her thyroid function normalized. These findings suggest a possible role of thyroid-hormone excess in the pathophysiology of some patients who have takotsubo cardiomyopathy. ***(Tex Heart Inst J 2016;43(2):152-5)***

Key words: *Hyperthyroidism/complications; takotsubo cardiomyopathy/diagnosis/physiopathology/therapy; thyroid diseases/physiopathology; thyroid function tests; thyrotoxicosis/complications; treatment outcome; ventricular dysfunction, left/diagnosis/etiology*

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Takotsubo cardiomyopathy (TC) is a form of acute heart disease in which patients present with symptoms that resemble acute myocardial infarction (MI) in the absence of obstructive coronary artery disease (CAD).[1] In the classic form of TC, symptoms are precipitated by a stressful event, and the left ventricle (LV) is characterized by hyperkinesis of the basal wall segments, dyskinesis of the midventricular segments, and apical ballooning. Most of these abnormalities spontaneously resolve after resolution of the stressful event and the initiation of heart-failure therapy. Although many reports and case series about TC have been published during the past 20 years, recurrent TC has been identified only sporadically.[1,2] Furthermore, several investigators have noted a link between thyroid disease and TC[3,4]; however, to our knowledge, recurrent TC related to thyroid dysfunction has not been described. We report a case of recurrent TC's potential link with recurrent hyperthyroidism.

Case Report

In 2013, a 55-year-old black woman with hypertension, diabetes mellitus, hyperlipidemia, and sarcoidosis was transferred from another hospital to our facility, with a diagnosis of non-ST-segment-elevation acute MI. She had received news about the death of a close family friend and subsequently had chest pain and dyspnea. Two aspirin tablets had brought no relief. Upon presentation at her local emergency department, her initial blood pressure was 107/75 mmHg and her heart rate was 102 beats/min. Physical examination yielded nothing remarkable. Her electrocardiogram (ECG) showed premature ventricular beats and nonspecific ST changes in the anteroseptal leads (Fig. 1). Her initial creatine kinase (CK) level was 109 U/L (normal range, 30–200 U/L), her CK-MB fraction was 8.8 U/L (normal level, <6.6 U/L), and her troponin I level was 1.85 ng/mL (normal level, <0.032 ng/mL).

In view of our concern about acute MI, the patient was given oxygen, clopidogrel, metoprolol, sublingual nitroglycerin, intravenous morphine, a bolus of intravenous heparin, and furosemide intravenously for dyspnea. Coronary angiograms revealed diffuse luminal irregularities with all stenoses ≤30% in severity. The left ventriculogram revealed severe systolic dysfunction with apical ballooning. This was confirmed by a follow-up echocardiogram, which showed an estimated LV ejection fraction (LVEF) of 0.30 and akinesis of the mid-to-distal anterior, lateral, inferior, and septal walls, as well as the apex (Fig. 2A). On the basis of these findings, the patient was

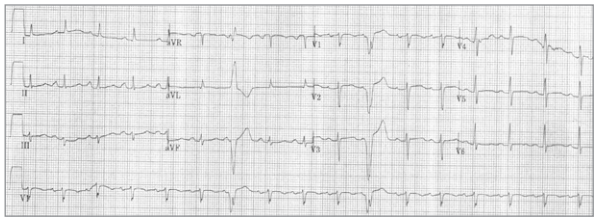

Fig. 1 *Electrocardiogram on initial admission shows sinus rhythm with premature ventricular complexes, left atrial enlargement, and nonspecific T-wave changes.*

diagnosed with TC, or apical ballooning syndrome, thought to be secondary to emotional stress.

Further evaluation revealed abnormal thyroid function: the patient's thyroid-stimulating hormone (TSH) level was <0.004 μIU/mL (normal range, 0.35–4.94 μIU/mL), her free thyroxine (FT_4) level was 1.6 ng/dL (normal range, 0.7–1.5 ng/dL), her total triiodothyronine (T_3) level was 211 ng/dL (normal range, 45–137 ng/dL), and her free T_3 level was 5.6 pg/mL (normal range, 1.5–3.5 pg/mL). Her thyroid ultrasound test showed a superior left thyroid nodule without evidence of malignancy. A radioactive iodine uptake scan revealed a mildly enlarged thyroid gland with diffuse homogeneous uptake of 80%, indicating hyperactive thyroid function. Her thyroid-stimulating immunoglobulin level was 231% (normal value, ≤139%), yielding the definitive diagnosis of Graves disease. The patient was discharged from the hospital with instructions to take 10 mg of methimazole 3×/d and 40 mg of furosemide 2×/d, in addition to standard cardiomyopathy medication (200 mg of metoprolol succinate and 100 mg of losartan daily).

At her follow-up visit one month after hospital discharge, the patient's FT_4 level had decreased to 1 ng/dL, although her TSH level remained <0.004 μIU/mL. Two months after hospital discharge, an echocardiogram showed the resolution of the cardiomyopathy (LVEF, 0.75) and normalization of the wall-motion abnormalities (Fig. 2B). The patient was asymptomatic and specifically reported no chest pain, dyspnea, orthopnea, or paroxysmal nocturnal dyspnea. Examination revealed no signs of fluid overload, and furosemide was discontinued. The FT_4 and TSH levels had both normalized by this time (1.1 ng/dL and 1.021 μIU/mL, respectively). Three weeks later, the patient began experiencing symptoms of hypothyroidism, and laboratory results revealed that her FT_4 level had decreased from 1.1 to 0.6 ng/dL. On the basis of the symptoms and low FT_4 level, methimazole was withheld with the intention of restarting it several weeks later at a lower dose, after the thyroid hormone levels had normalized.

Twenty days after stopping the methimazole, the patient returned to the emergency department with progressively worsening dyspnea while lying in bed.

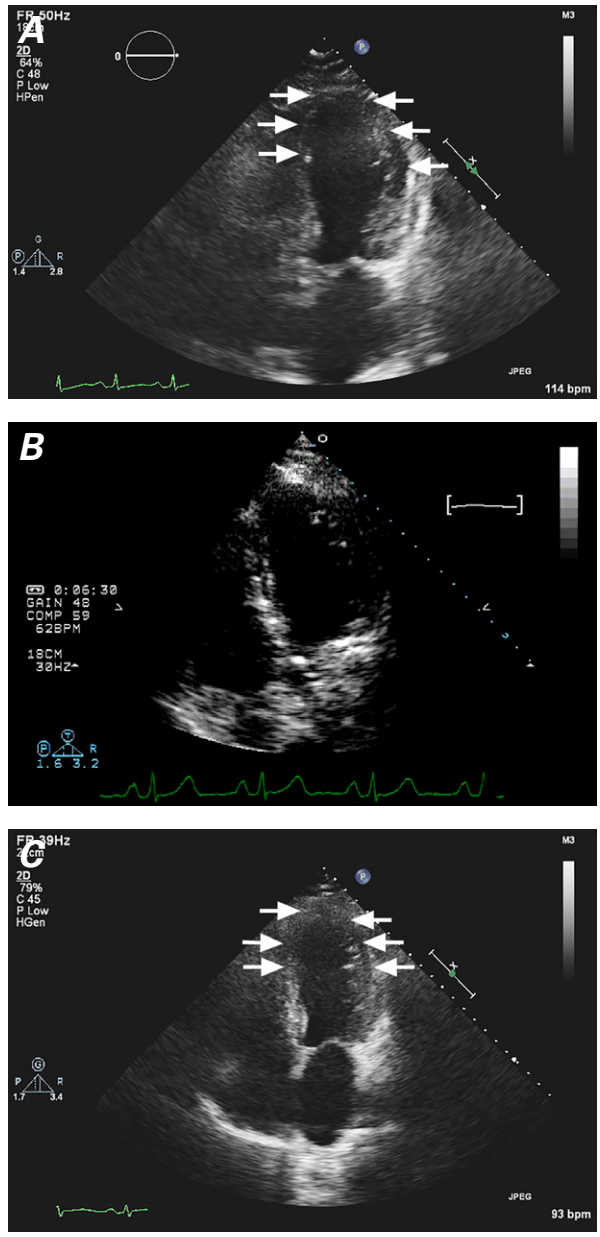

Fig. 2 *Systolic frames (4-chamber echocardiographic views) show **A**) hyperkinetic basal segments with akinesis of the left ventricular apical segments upon initial presentation, **B**) normalization of apical wall motion after 2 months of therapy for thyroid disease and cardiomyopathy, and **C**) recurrence of those wall-motion abnormalities with relapse of hyperthyroidism. Arrows highlight the poor contractility of the mid-to-apical segments typical of takotsubo cardiomyopathy.*

Supplemental motion images are available for Figures 2A, B, and C.

She reported no antecedent chest pain, palpitations, presyncope, or syncope. Initial examination revealed a systolic blood pressure of 230 mmHg, jugulovenous pulsations 5 cm above the clavicle, and bibasilar rales on chest auscultation. The patient was started on noninvasive positive-pressure support for respiratory distress and was admitted to the cardiovascular intensive care unit

for further therapy, including nitroglycerin and intravenous furosemide. An ECG showed sinus rhythm with nonspecific T-wave abnormalities. Initial troponin and CK-MB values were within normal limits. However, subsequent cardiac biomarkers trended upward (troponin, 1.54 ng/mL; and CK-MB, 8.7 ng/mL). A repeat ECG showed new, deep, symmetric T-wave inversions (Fig. 3). Coronary angiograms revealed unchanged nonobstructive CAD, and an echocardiogram showed an LVEF of 0.40 with akinesis of the apex and distal anterior, lateral, inferior, and septal walls (Fig. 2C).

At this point, the patient was diagnosed with recurrent TC, although during this clinical presentation she had no known recent stressful events to precipitate the cardiomyopathy. Laboratory results included a TSH value of 0.017 μIU/mL, FT_4 of 1.6 ng/dL, and FT_3 of 6.9 pg/mL, consistent with recurrent hyperthyroidism. Methimazole was restarted, and the patient's symptoms improved after diuresis. Two weeks after discharge from the hospital, she underwent definitive radioiodine ablation of the thyroid. Over the next 9 months, she remained clinically and chemically euthyroid on supplemental thyroid hormone replacement. A follow-up echocardiogram after normalization of her thyroid hormone panel showed improvement in LVEF to 0.55 and normalization of LV wall motion. She had no further heart-failure symptoms or hospitalizations during the subsequent 3 years of outpatient monitoring.

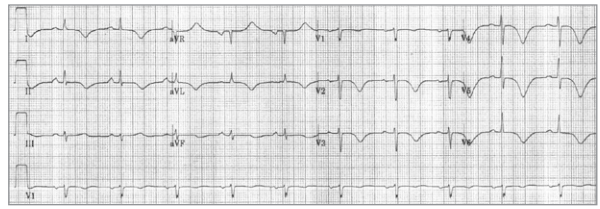

Fig. 3 *Electrocardiogram on readmission shows sinus rhythm, left atrial enlargement, and deep, symmetric T-wave inversions that were new in comparison with previous electrocardiograms.*

Discussion

Takotsubo cardiomyopathy is a rather newly described disease; Iga and colleagues published the first description in 1989, in a case of pheochromocytoma.[5] Takotsubo—the Japanese term for "octopus pot," which describes the apical ballooning morphology of the LV—was coined by Sato and associates in 1990.[6] This disease accounts for approximately 2% of all cases of suspected MI, and cases predominantly occur in postmenopausal Asian or white women.[2] In 2004, Bybee and co-authors proposed the following diagnostic criteria: 1) transient hypokinesis, dyskinesis, or akinesis of the LV mid segments, with or without apical involvement, and in a distribution beyond the vascular distribution of a single epicardial coronary artery, often triggered by a stressful event; 2) absence of obstructive CAD or acute plaque rupture; 3) new ECG changes (generally ST-segment elevation, T-wave inversion, or both) or modest elevation of troponin levels; and 4) the absence of head trauma, pheochromocytoma, or myocarditis.[1] Our patient met all 4 criteria.

Multiple mechanisms have been proposed regarding the pathophysiology behind TC, including multivessel coronary artery vasospasm, microvascular impairment, neurogenic-stunned myocardium, and catecholamine-mediated toxicity to the myocardium via intracellular calcium overload.[2] In 2004, Miyakazi and colleagues described thyrotoxicosis-associated TC by demonstrating myocardial stunning with use of thallium-201 and 99m Tc-pyrophosphate scintigrams.[7] The effect of T_3 on the myocardium is profound, because T_3 up-regulates the transcription of calcium-ATPase protein and β-adrenergic receptors.[8] In certain populations, such as postmenopausal women who tend to be predisposed to TC, calcium influx in addition to ATPase up-regulation might lead to wall-motion abnormalities consistent with TC.

Although these mechanistic theories ultimately cannot prove whether thyroid hormones can cause TC, the "natural experiment" described in our case study might lend credibility to this relationship in a subset of patients who have newly identified TC. Even if the hyperthyroidism itself was not the direct mediator of cardiomyopathy, an extreme catecholaminergic state (perhaps related to the rapid return of hyperthyroidism) could explain the severe hypertension and recurrent TC at the patient's 2nd presentation. In addition, the initiation of antithyroid therapy in conjunction with standard heart-failure medications seemed to reverse the cardiomyopathy on both occasions in our patient, with no complications or recurrence after a stable euthyroid state was achieved. Therefore, our case study lends credibility to the previous observation that hyperactive-thyroid disorders might be responsible for TC in some patients. Our patient's clinical course suggests that thyroid testing should be performed in all patients who present with TC—consistent with current guidelines for the evaluation of patients with heart failure. In addition, the definitive treatment of thyroid disease might help to prevent recurrences of TC.

In summary, we identified a patient with hyperthyroidism-associated TC, in whom treatment of the thyroid disease, along with standard heart-failure therapies, resulted in resolution of the cardiomyopathy. Furthermore, recurrent hyperthyroidism resulted in a 2nd acute presentation with TC, which again resolved after the patient returned to a euthyroid state. Accordingly, screening for and treatment of underlying thyroid dysfunction in patients presenting with TC is warranted.

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