Broken heart syndrome triggered by an obstructive goiter not associated with thyrotoxicosis

Syndrôme du cœur brisé déclenché par un goitre obstructif non associé à une thyrotoxicose

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Abstract

Purpose Takotsubo cardiomyopathy (TC) is described as transient ventricular dysfunction following emotional or physical trauma. A few reports have described patients with TC in association with various circumstances of thyrotoxicosis. We report an unusual case of TC in a patient with a large retrosternal goiter and normal thyroid function. We speculate that TC was triggered by compromise of tracheal flow induced by the goiter.

Clinical feature A 68-yr-old woman without primary heart disease presented with cardiorespiratory collapse requiring ventilatory and cardiovascular support, including placement of an intra-aortic balloon pump. She was diagnosed with a severe form of TC based on

characteristic echocardiography findings and clinical course. Within less than a week, her myocardial function completely normalized. The patient was later found to have a large retrosternal goiter compressing her trachea, though her thyroid function was normal. A total thyroidectomy was eventually performed, and she made a full recovery. Subsequently, the patient was found to have a positive JAK2 mutation for a myeloproliferative disorder.

Conclusions Takotsubo cardiomyopathy may be regarded as the final common pathway of cardiac dysfunction triggered by various stress conditions, in this case, a large retrosternal goiter not associated with thyrotoxicosis and likely exacerbated by severe leukocytosis related to a myeloproliferative disorder.

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Résumé

Objectif La cardiomyopathie de tako-tsubo (CT) est décrite comme un dysfonctionnement ventriculaire transitoire suivant un traumatisme émotionnel ou physique. Quelques comptes rendus ont décrit des patients souffrant de CT en association à diverses circonstances de thyrotoxicose. Nous rapportons un cas inhabituel de CT chez une patiente présentant un large goitre rétrosternal et une fonction thyroïdienne normale. Nous émettons l'hypothèse que la CT a été déclenchée parce que le débit trachéal a été compromis en raison du goitre.

Éléments cliniques Une femme de 68 ans sans cardiopathie primaire s'est présentée avec un collapsus cardiorespiratoire nécessitant une assistance ventilatoire et cardiovasculaire, y compris la mise en place d'un ballonnet intra-aortique. En se fondant sur des résultats d'échocardiographie caractéristiques et l'évolution clinique de la patiente, une forme grave de CT a été diagnostiquée. En moins d'une semaine, sa fonction

myocardique s'est complètement normalisée. Par la suite, on a découvert que la patiente avait un large goitre rétrosternal comprimant sa trachée, bien que sa fonction thyroïdienne soit normale. Une thyroïdectomie totale a finalement été réalisée, et la patiente s'est complètement rétablie. Par la suite, on a découvert que la patiente possédait une mutation positive du JAK2 pour un syndrome myéloprolifératif.

Conclusion *La cardiomyopathie de tako-tsubo peut être considérée comme la manifestation finale commune d'un dysfonctionnement cardiaque déclenché par différentes conditions de stress – dans ce cas, un large goitre rétrosternal non associé à une thyrotoxicose et probablement exacerbé par une leucocytose grave liée à un syndrome myéloprolifératif.*

Patients who present with life-threatening cardiorespiratory failure require urgent or emergent supportive care, and obtaining a definitive etiology may be delayed or elusive. We report a highly unusual case of stress-induced Takotsubo cardiomyopathy (TC) triggered by respiratory compromise resulting from a large retrosternal euthyroid goiter compressing the trachea and likely exacerbated by severe leukocytosis related to a myeloproliferative disorder.

Case report

Consent for publication was obtained from the patient. A previously healthy 68-yr-old woman (height, 157 cm; weight, 65 kg; body mass index, $26.4 \text{ kg}\cdot\text{m}^{-2}$) presented to our emergency room in respiratory distress. She had a history of fatigue, mild dysphagia, and progressive shortness of breath during the preceding two weeks. She had no significant medical history, took no medication, and had no allergies. Upon arrival, the patient was tachypneic ($> 35 \text{ breaths}\cdot\text{min}^{-1}$), hypoxic (tissue oxygen saturation 84% [pulse oximetry, room air]), and suffered from cold extremities. Her heart rate was $160 \text{ beats}\cdot\text{min}^{-1}$, systolic blood pressure (BP) measured $160/95 \text{ mmHg}$, and oral temperature was 37.4°C . She was in visible distress with laboured breathing, but no stridor or wheeze was detected. No goiter was evident on initial inspection and palpation. A transthoracic echocardiogram showed a left ventricular ejection fraction of 30% with severe apical hypokinesis and basal sparing of the left and right ventricles (LV and RV) (Video available as Electronic Supplementary Material). A 12-lead electrocardiogram showed atrial fibrillation with a ventricular rate of $170 \text{ beats}\cdot\text{min}^{-1}$, and a chest *x-ray* revealed small bilateral pleural effusions and mild

pulmonary edema. The patient's initial blood laboratory test results (compared with normal levels) were as follows: hemoglobin $127 (120\text{--}160) \text{ g}\cdot\text{L}^{-1}$, white blood cells $59 (4\text{--}11) 10^9\cdot\text{L}^{-1}$, platelets $659 (140\text{--}440) 10^9\cdot\text{L}^{-1}$, creatinine $95 (40\text{--}90) \mu\text{mol}\cdot\text{L}^{-1}$, lactate $9.7 (1\text{--}1.8) \text{ mmol}\cdot\text{L}^{-1}$, and troponin-I $0.24 (0.00\text{--}0.06) \text{ ng}\cdot\text{mL}^{-1}$.

The patient was transferred to the intensive care unit where her condition rapidly deteriorated. Her systolic BP declined to $< 90 \text{ mmHg}$, and she was started on a norepinephrine infusion titrated to maintain systolic BP $> 100 \text{ mmHg}$. Following oral tracheal intubation (7.5 mm endotracheal tube) and initiation of mechanical ventilation, vasopressin and epinephrine infusions were begun to maintain adequate systemic pressure. Intubation was easily accomplished, and no anomalies were detected in the airway. At that time, arterial blood gas analysis (F_iO_2 0.5%) indicated $\text{pH} = 7.13$, $\text{PaO}_2 = 73$, $\text{PaCO}_2 = 47$, and $\text{HCO}_3 = 15 \text{ mmol}\cdot\text{L}^{-1}$. A pulmonary artery catheter was inserted through the right internal jugular vein, and her cardiac index was measured to be 1.2. After inserting an intra-aortic balloon pump (IABP) through a femoral artery and initiating a milrinone infusion, the cardiac index increased to 2.1. Cardiac catheterization showed normal coronary vessels with no atherosclerotic disease. Continuous venovenous hemofiltration was instituted within 24 hr of admission as the patient became anuric. The diagnosis of septic shock was postulated and broad-spectrum antibiotics were started. In the next 24 hr, the lactate level peaked at $18 \text{ mmol}\cdot\text{L}^{-1}$, international normalization time at 6.8, alanine aminotransferase $2,670 \text{ U}\cdot\text{L}^{-1}$, and troponin-I at $1.40 \text{ ng}\cdot\text{mL}^{-1}$, suggesting multiple organ failure.

Over the course of a few days, the patient's condition gradually improved; she was weaned off all vasopressor and inotropic drug support, and the IABP was removed. An echocardiogram performed on the third day of admission showed near recovery of myocardial function with decreased right apical ventricular function and normal LV contraction. Complete normalization was observed by the following week. The white blood cell count increased as high as $136 10^9\cdot\text{L}^{-1}$ with marked left shift, and the neutrophil count increased as high as $131.5 10^9\cdot\text{L}^{-1}$. Repeated blood smears showed only reactive changes. Eventually, a JAK2 V617F mutation screening test came back positive, suggesting a myeloproliferative disorder.

Following weaning from mechanical ventilation and extubation, acute respiratory decompensation occurred on two occasions over the course of the next several weeks. This relapse required reinstitution of the supportive respiratory therapy, including eventual tracheostomy. The patient was asymptomatic with her tracheostomy. Bronchoscopy showed subglottic stenosis with tracheal constriction to a 3-mm diameter at the level of

Figure Magnetic resonance imaging of the cervical region, axial (A) and coronal views (B) showing a partially collapsed trachea by (and) a large multinodular goiter

approximately 3.5 cm below the vocal cords. Magnetic resonance imaging of the cervical region confirmed a partially collapsed trachea due to a large multinodular goiter (Figure). The right thyroid lobe measured almost $9 \times 3 \times 3$ cm with caudal extension displacing the submandibular gland anteriorly. The left lobe had similar dimensions ($8.5 \times 4.5 \times 4.5$ cm), and multiple nodules, some calcified, were seen in both lobes. The gland also extended retrosternally (2 cm from the aortic arch). Thyroid function tests were consistently normal, and thyrotropin receptor and thyroid peroxidase antibody titers were negative.

Following six months of physical rehabilitation, the patient underwent a total thyroidectomy, and several weeks later, the tracheostomy was successfully reversed. The thyroid gland weighed 120.8 g in its entirety. Pathology showed multiple follicular nodules consistent with a multinodular goiter and papillary microcarcinomas in the isthmus of an oncocyctic follicular variant. The foci were unencapsulated and no vascular invasion was identified. The patient made a full recovery and was discharged from hospital on a beta-blocker and thyroid replacement.

Discussion

We report an unusual case of stress-induced TC triggered by upper airway obstruction secondary to a large goiter. Hyperthyroidism is the only thyroid disease that has been implicated in triggering TC.¹⁻⁵ While the potential for respiratory compromise secondary to the mechanical effects of a large goiter on the airway is a known but

rare occurrence, we draw attention to the possibility of concomitant stress-induced cardiomyopathy.

First described in 1991, stress-induced cardiomyopathy, also known as broken heart syndrome and apical ballooning syndrome, may present as transient LV apical dysfunction following emotional or physical trauma. It is also referred to as Takotsubo cardiomyopathy because the LV may resemble the shape of a Japanese octopus trap (tako tsubo) during systole.⁶ The prevalence of TC in patients with suspected acute coronary syndrome is in the order of 1-2%. Postmenopausal women constitute 90% of patients affected by TC.⁷ Symptoms can vary from chest pain and dyspnea to frank cardiogenic shock on rare occasions. This condition is usually accompanied by non-specific electrocardiogram changes and/or a rise in troponin. Clinical diagnosis of TC is made in the absence of obstructive coronary disease.⁸ Many mechanisms are postulated to explain this phenomenon, but the most plausible is a rise in catecholamine levels and decreased blood flow in the myocardial microcirculation.⁹ Right ventricular dysfunction may occur in approximately 25% of patients. This typically occurs in more severe cases, and patients may require IABP support.¹⁰ The primary treatment of stress-induced cardiomyopathy is supportive care. Beta-blockade is recommended after recovery of myocardial function to prevent recurrence of TC.⁹ The prognosis of TC is generally favourable, although fatal cases have been reported due to ventricular free-wall rupture.¹¹ Recurrence has been reported as high as 11%.^{12,13}

We hypothesize that TC was triggered in our patient by compromise of tracheal air flow induced by the goiter. The etiology of her goiter was likely endemic iodine deficiency

given that she lived over 50 years in an endemic area. Endemic goiters tend to be multinodular,¹⁴ and once established, they tend not to regress even in the presence of iodine supplementation, such as emigration to a region replete with iodine, as was the case of our patient.¹⁵ Our patient resided in Canada for 16 years and did not have a family physician. Nodular goiters typically enlarge insidiously and may cause progressive dyspnea and dysphagia by compressing respiratory and digestive structures. Acute life-threatening airway obstruction produced by benign goiters is rare (1%), and they typically present with bilateral thyroid enlargement and retrosternal extension.¹⁶ Following surgical treatment by thyroidectomy, airway compromise can still ensue secondary to tracheomalacia and edema.¹⁷ Thorough assessment of the airway is essential for patients presenting with goiter, and pending airway obstruction secondary to tracheal compression by an enlarged goiter mandates urgent intervention. In almost all cases, the compressed trachea easily extends with the passage of a regular but preferably slightly smaller endotracheal tube. Incidental papillary microcarcinoma occurs in up to 20% of benign thyroid tumours. They are considered to be nonaggressive tumours, and patients have an excellent prognosis following their excision.¹⁸

Sepsis, myocardial infarction, acute myocarditis, hyperthyroidism, and pheochromocytoma were considered as possible etiologies, but these causes were soon rejected. Bacterial and viral cultures (nasal swabs, bronchial aspirations, blood samples, urine and stool) were negative, and the excessive leukocytosis was likely secondary to stress and exaggerated by the patient's underlying myeloproliferative disease. Angiography showed normal coronary vessels. In the context of full myocardial recovery in less than two weeks and the echocardiographic findings (severe apical hypokinesis with basal sparing), acute myocarditis did not seem plausible. Normal thyroid function eliminated the possibility of hyperthyroidism. Pheochromocytoma did not seem to be a likely diagnosis as the patient did not have uncontrolled hypertension and no adrenal mass was seen on abdominal CT scan. A 24-hr urine metanephrine level was in the normal range but the normetanephrine level was twice the normal value. This most likely was caused by stress, as these levels were taken just after the patient's trachea was urgently intubated for respiratory distress. Subsequent 24-hr urine catecholamine levels were normal.

Myeloproliferative disorders (MPDs) are a heterogeneous group of chronic hematologic diseases characterized by an excessive myeloid cell growth in the peripheral blood. The JAK2 V617F mutation is a molecular marker that occurs in 95% of patients with polycythemia vera.^{19,20} Our patient's extreme leukocytosis was thought to be a leukemoid reaction secondary to her MPD and presumed to be exacerbated by

stress and a single intravenous dose of hydrocortisone 100 mg that she received at initial presentation. This condition may have aggravated or directly contributed to the development of TC by compromising the microcirculation of the myocardium.

A number of studies have shown disturbances in coronary microcirculation and local metabolic abnormalities in patients with TC. Using thallium-201 myocardial single-photon emission computed tomography and 18F-fluorodeoxyglucose myocardial positron emission tomography, Yoshida reported impaired coronary perfusion and severe local metabolic abnormalities in patients with TC.²¹ It remains unclear, however, whether these changes are causal or rather a consequence of the mechanical wall stress related to apical ballooning.

In conclusion, we propose that TC may be regarded as the final common pathway of cardiac dysfunction triggered by various stress conditions, in this case, a large retrosternal goiter causing airway obstruction in a patient with extreme leukocytosis due to an underlying MPD. While the potential for respiratory compromise secondary to the mechanical effects of a large goiter on the airway is a known but rare occurrence, this case shows that attention to the possibility of concomitant stress-induced cardiomyopathy is also warranted. We recommend that all patients with goiter be properly assessed for airway involvement, as this could be a life-threatening condition. In severe forms of TC with complete cardiovascular collapse, IABP should be used if readily accessible. To prevent further episodes, beta-blockers should be considered once the patient is hemodynamically stable.

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