ESC European Society of Cardiology

European Heart Journal - Case Reports (2021) **5**(8), 1–6
doi:10.1093/ehjcr/ytab270

CASE REPORT
Heart failure

Takotsubo syndrome: hyperthyroidism, pheochromocytoma, or both? A case report

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Received 17 January 2021; first decision 16 February 2021; accepted 18 May 2021

Background Takotsubo syndrome (TTS) is a transient left ventricular dysfunction usually with apical akinesia (classical pattern). Other less frequent variants have been described: the mid-ventricular pattern is characterized by hypokinesia of the mid-left ventricle and hypercontractile apical and basal segments; the inverted or basal pattern is characterized by basal and mid-ventricular segment hypokinesia or akinesia with preserved contractility or hypercontractility of apical segments and finally the focal pattern. There are also biventricular variants and forms with exclusive involvement of the right ventricle. There is a correlation between endocrine disorders and TTS, the one most frequently described is with pheochromocytoma. Catecholamine-mediated myocarditis, focal and diffuse myocardial fibrosis, and myocardial dysfunction are described in pheochromocytoma.

Case summary We describe a case of a 69-year-old patient with a recent diagnosis of hypertension and Graves' disease, hospitalized for persistent chest pain, hypertensive crisis, tachycardia, dyspnoea, and diaphoresis. Thyroid hormones, antibodies to TSH receptors, and hs-troponin I were increased. Electrocardiogram showed sinus tachycardia at 130 b.p.m., first-degree atrioventricular block, signs of left ventricular hypertrophy with inverted T wave in V4–V6. Echocardiogram demonstrated left ventricular apical and para-apical akinesia. Coronary angiography ruled out an obstructive coronary artery disease. Computed tomography angiogram aortic dissection ruled out aortic dissection but incidentally revealed a left adrenal mass compatible with a pheochromocytoma. Plasma and urinary metanephrines were increased. A TTS secondary to pheochromocytoma and hyperthyroidism was diagnosed. Pharmacological treatment included nitrates, urapidil and esmolol IV and methimazole at high doses. Type 2 multiple endocrine neoplasia has been excluded. After a complete haemodynamic stability on 20th day of hospitalization, the patient underwent an adrenalectomy.

Discussion High levels of catecholamines in pheochromocytoma can lead to myocardial dysfunction. Similarly, an excess of thyroid hormones with up-regulation of adrenergic system can lead to myocardial dysfunction. These two conditions, if both present, define a high haemodynamic risk profile. How do catecholamines interact with the thyroid gland? The clinical case is of interest as a relationship has been hypothesized between the incretion of plasma catecholamines and Graves' disease. We suppose an imbalance of the immune system with a predominance of the T helper-type 2 (Th2)-mediated response. Predominance of Th2-mediated immune response may induce humoral immunity causing Graves' disease. In addition Th2 cytokines are strong inducers of M2 macrophages (alternatively activated) that are involved in autoimmune diseases, myocarditis, and myocardial fibrosis. Knowing the interaction

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Handling Editor: Marta Cvijic
Peer-reviewers: Gonzalo Luis Alonso Salinas and Ching-Hui Sia
Compliance Editor: Brent Sydney Bernstein
Supplementary Material Editor: Fabienne Vervaat

between the cardiovascular system, immune response, and endocrine glands can help define the patient's risk class, possible complications, and follow-up.

Keywords Case report • Takotsubo syndrome • Pheochromocytoma • Graves' • disease • Catecholamines • Immune response • Cardiac fibrosis

Learning points

- To diagnose takotsubo syndrome (TTS), it is necessary to exclude other causes of acute chest pain.
- Emotional or physical triggers as well as neurological or endocrine disorders should always be sought in patients diagnosed with TTS in order to optimize therapy.
- Associations between pheochromocytoma and TTS, and Graves' disease and TTS are described individually but pheochromocytoma and Graves' disease can be associated together and with TTS.
- Excess catecholamines released by the pheochromocytoma could induce thyroiditis through immune dysregulation.
- Both pheochromocytoma and thyrotoxicosis can promote acute heart failure by adrenergic overactivation.
- Use of alpha and beta-blocker drugs associated with methimazole at high doses allows to stabilize the patient for the adrenalectomy.

Introduction

Takotsubo syndrome (TTS) is a transient left ventricular dysfunction that is typically observed as apical ballooning with cardiac imaging. Emotional or physical triggers as well as endocrine or neurological disorders are the most recognized causes of this syndrome. The most common symptoms of TTS are acute chest pain, dyspnoea, and syncope which initially can mirror an acute myocardial infarction. We describe a case of TTS in a patient with a complex endocrine disorder.

Timeline

Day 0	Mild symptoms (occasional episodes of palpitations associated with sweating). Diagnosis of Graves' disease and start of therapy with methimazole
Day 2	Worsening symptoms and chest pain. Patient admission at emergency department. Echocardiogram reports left ventricular apical and para-apical akinesia with an estimated left ventricular ejection fraction (EF) of 23% and a global longitudinal strain (GLS) of -8.1%. High serum fT4 and fT3. Left adrenal mass at computed tomography scan. Probable diagnosis of Takotsubo syndrome associated with pheochromocytoma and hyperthyroidism. Start of therapy with urapidil, esmolol, and high doses of methimazole
Day 3	Partial recovery of EF (41%) and GLS (-11.2%) of the left ventricle at echocardiogram
Day 22	Achieving of complete haemodynamic stability and adrenalectomy
Day 24	Hospital discharge
Month 3	Full recovery of left ventricle function (EF of 50.5% and GLS of -16.4% at echocardiogram)
Month 6	Cardiac magnetic resonance detected normal EF and a mild meso-subepicardial late gadolinium enhancement in inferolateral segments with normal EF. No oedema was found.

Continued

Case presentation

A 69-year-old male was admitted to the emergency department for oppressive chest pain with wheezing and sweating. His past medical history was significant for smoking and arterial hypertension. Two days earlier, the patient was diagnosed with hyperthyroidism linked to Graves's disease. Before then, he reported occasional episodes of palpitations associated with sweating. Ultrasound analysis of the thyroid gland documented intense vascularization. Thyroid hormones and antibodies to TSH receptors were increased. His medical therapy included bisoprolol 1.25 mg, olmesartan 20 mg, and for 2 days methimazole 5 mg t.i.d. On admission, his blood pressure was 250/130 mmHg. The electrocardiogram showed sinus tachycardia at 130 b.p.m., first degree atrio-ventricular block, signs of left ventricular hypertrophy with inverted T wave in V4–V6. The echocardiogram revealed left ventricular apical and para-apical akinesia with an estimated left ventricular ejection fraction (EF) of 23% and a global longitudinal strain (GLS) of -8.1%. Initial serum hs-troponin I level was 1211 ng/dL (n.v. < 34). Urapidil, nitrate, and diuretic therapy were commenced. As oppressive chest pain associated with diaphoresis and elevated blood pressure values persisted, coronary angiography and computed tomography (CT) angiogram were performed in order to rule out an obstructive coronary artery disease and aortic dissection, respectively. Both exams resulted in negative. Interestingly, a CT scan incidentally demonstrated a left adrenal mass which was compatible with a pheochromocytoma (non-contrast density greater than 10 HU and absolute washout less than 60%; *Figure 1*, see arrow) and an enlarged thyroid gland with an uneven appearance. The patient was transferred to the cardiac intensive care unit. Burch–Wartofsky score was highly suggestive of thyroid storm

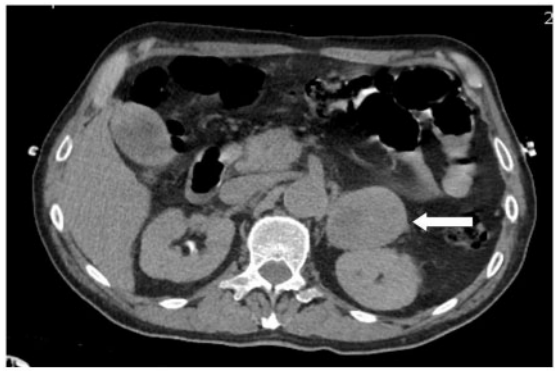


Figure 1 Computed tomography showing left adrenal mass of approximately 52 mm × 43 mm (see arrow).

(65 points). Urapidil and esmolol infusion and high doses of oral methimazole prompted symptomatic improvement and normalization of blood pressure and heart rate. Partial recovery of EF (41%) and GLS (-11.2%) of the left ventricle was documented at 2D echocardiography after 24 h of alpha and beta-blocker therapy. The use of illicit drugs has been excluded. A panel of blood and urinary tests was performed to better evaluate the adrenal and thyroid function: normetanephrine 5.30 mg/24 h (n.v. 0.08–0.45), metanephrine 15.80 mg/24 h (n.v. 0.05–0.34), TSH <0.01 µUI/mL (n.v. 0.35–4), fT4 2.00 ng/dL (n.v. 0.7–1.48), fT3 3.60 pg/mL (n.v. 1.71–3.71), free urinary cortisol 150 ug/24 h (n.v. 4.30–176), and normal plasma aldosterone levels, spot and 24 h sodiuria and potassiuria. Calcium, phosphorus, alkaline phosphatase, vitamin D3, parathyroid hormone, calcitonin, were found within normal limits, therefore excluding a type 2 multiple endocrine neoplasia. The patient continued his hospitalization to better monitor symptoms and vital parameters. After 20 days of antithyroid and alpha and beta-blocker therapy, the patient has achieved complete haemodynamic stability and he underwent left adrenalectomy. The histological examination of the specimen confirmed the diagnosis of pheochromocytoma. Hyperthyroidism was well controlled with medical therapy and radioactive iodine and surgery were excluded. After 2 days, the patient was discharged with the following therapy: methimazole 5 mg t.i.d., ramipril 5 mg, and bisoprolol 5 mg.

Further improvement of left ventricular contractility occurred 3 months later with an EF of 50.5% and a GLS of -16.4% (*Figure 2*).

A cardiac magnetic resonance (CMR) performed after 6 months detected normal EF and mild meso-subepicardial late gadolinium enhancement (LGE) in inferolateral segments. No oedema was found (*Figure 3*).

After 9 months the patient is asymptomatic, with good control of thyroid and heart disease and is continuing the discharge therapy. An annual follow-up has been scheduled.

Discussion

The relationship between endocrine disorders and TTS has been widely documented in the literature; however, the precise frequency of this association remains unknown.[1] Several publications report on the association between pheochromocytoma and thyroid disorders and these data support the most accredited pathophysiological theory whereby TTS can be promoted by sympathetic hyperactivity.

Inappropriate release of high levels of catecholamines in pheochromocytoma induces direct cardiotoxic damage secondary to increased intracellular calcium and oxidative stress resulting in inflammation, ischaemia, contraction band necrosis, and fibrosis with consequent excitation–contraction decoupling and transient stunning of the myocardium.[1–3] Other pheochromocytoma-related conditions are catecholamine-mediated myocarditis and focal/diffuse myocardial fibrosis.[4]

Similarly, myocardial dysfunction can be induced by an excess of thyroid hormones since thyroid hormones enhance the chronotropic and inotropic myocardial response to catecholamines through an up-regulation of adrenergic receptors.[5]

The association between pheochromocytoma and thyrotoxicosis has already been reported.[6] An increase in thyroid volume with subsequent diagnosis of pheochromocytoma was first documented in 1947.[7] Thyroid gland is enlarged in 6% of pheochromocytomas and infusion of norepinephrine in experimental models can induce a volumetric increase of the thyroid gland.[8] Based on this evidence, a pathophysiological interaction between thyroid hormones, catecholamine receptors, and the immune system has been hypothesized.[9]

We speculate that the excessive production of catecholamines by the pheochromocytoma in our patient might have induced a thyroiditis via immune dysregulation. The action of the catecholamines seems to be mediated via the β2 adrenergic receptors located on the antigen-presenting cells and T helper 1 lymphocytes (Th1).[10] Activation of the β2 adrenergic receptors determines inhibition of the cellular immune response and activation of the humoral immune response mediated by T helper 2 lymphocytes (Th2) leading to an imbalance between Th1 and Th2 (*Figure 4*).[11] Predominance of Th2-mediated immune response may induce humoral immunity causing Graves' disease.[11, 12]

On the other hand, it has been described that an imbalance of the immune response towards Th2 results in a transition from M1 (classically activated) to M2 (alternatively activated) macrophage polarity with the maturation of monocyte precursors to fibroblast resulting in fibroblast-derived collagen synthesis and fibrosis via IL-4 and IL-13 cytokines.[13, 14]

These processes also involve the heart and are responsible for myocardial fibrosis.[15]

In our case, acute heart failure might have been triggered by the sympathetic hyperactivation secondary to adrenal and thyroid endocrine disorders. Optimization of a combined anti-thyroid therapy and alpha and beta-blocker therapy allowed an immediate improvement of the left ventricular systolic function.

The subsequent complete recovery of the systolic function of the left ventricle confirmed the diagnosis of TTS [the echocardiogram at the time of diagnosis documented typical apical akinesia (*Video 1*), while the echocardiogram (*Video 2*) and CMR performed at the follow-up confirmed a normal EF (*Video 3*)].

The mild meso-subepicardial LGE in inferolateral segments is compatible with myocarditis which is another possible complication when catecholamines are released in the presence of an adrenal mass compatible with pheochromocytoma.[16]

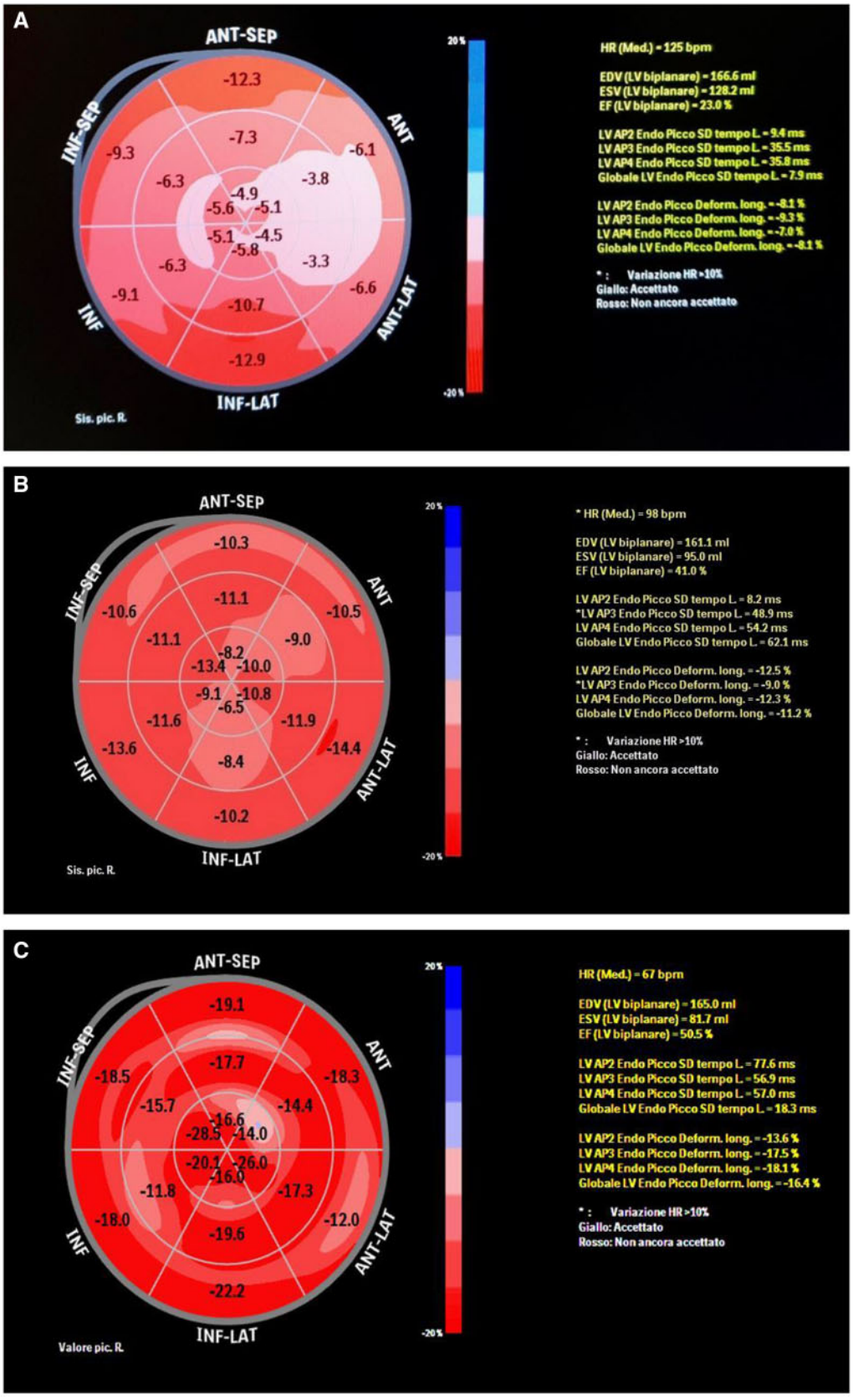


Figure 2 Longitudinal strain bull's eye plot at admission (*A*), after 24 h of alpha and beta-blocker therapy (B) and after 3 months (C).

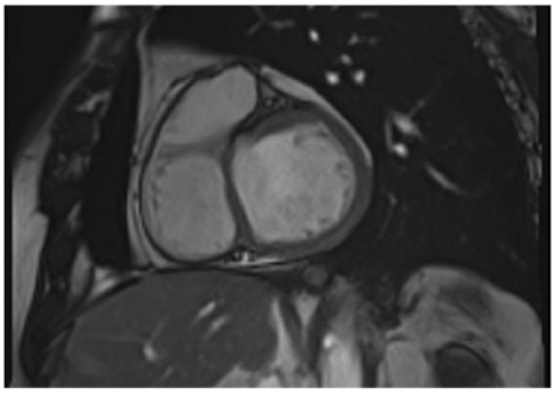


Figure 3 Cardiac magnetic resonance showing meso-subepicardial late gadolinium enhancement in inferolateral segments.

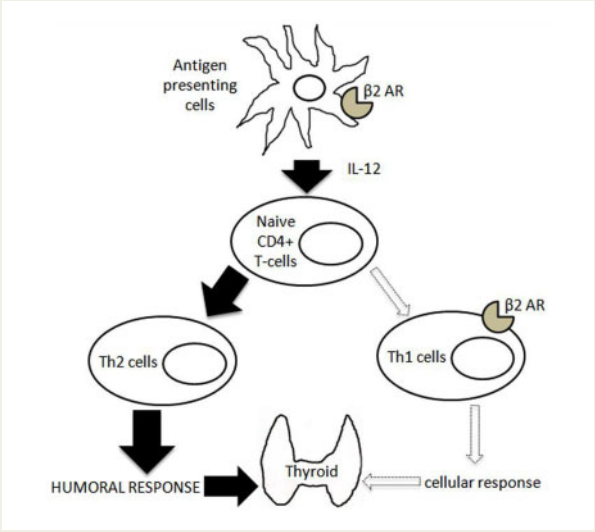
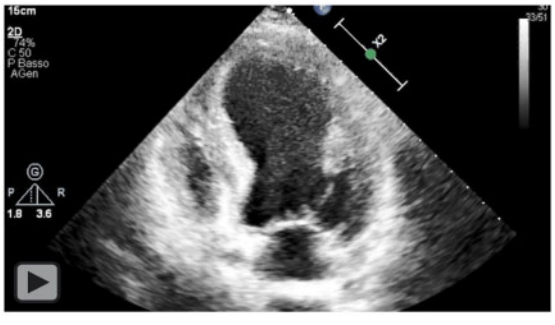
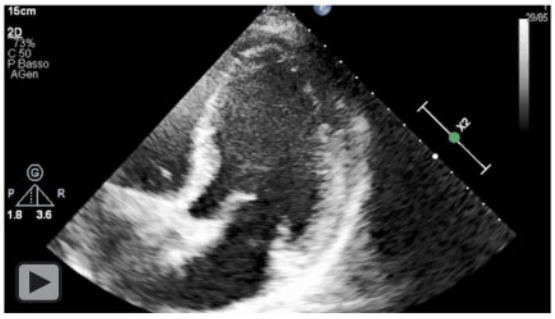


Figure 4 Role of catecholamines in cellular and humoral immune response and thyroiditis. Dark lines = stimulation; white lines = inhibition. β2 adrenergic receptor (β2 AR).



Video 1 Echocardiogram performed at the diagnosis showing the typical apical akinesia of classical takotsubo syndrome.



Video 2 Echocardiogram performed at follow-up showing shows a complete recovery of the ejection fraction.

Acute heart failure therefore appears to be mainly due to TTS and minimally to myocarditis.

Conclusion

In patients with a suspected diagnosis of TTS, it is necessary to identify the underlying causes in order to optimize therapy. All possible causes must be considered. In our case, it was necessary to add high-dose methimazole to the alpha/beta-blockade to achieve hemodynamic stability. Subacute pathological conditions could manifest in the course of excess of catecholamines through mechanisms in which the immune system could play a role. The review of the mechanisms underlying myocardial fibrosis and the regulation of the immune response secondary to the release of catecholamines have made it possible to define a risk profile and plan a follow-up for the patient.

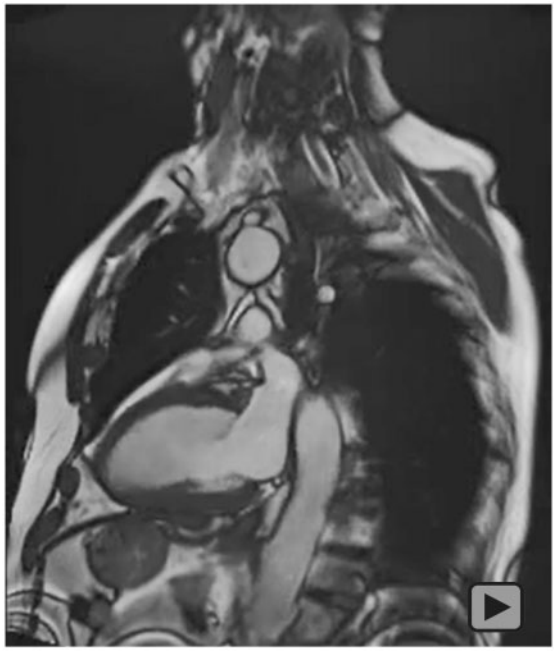
Lead author biography

Gaetano Marino was born in Cariati, Italy on 26 October 1990. He studied Medicine at Sapienza University of Rome, where completed his Master's degree in 2016. Since 2017, he is Cardiology resident at AOU Sant'Andrea. His main interests include echocardiogram, haemodynamic assessment, and intensive cardiac care.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as Supplementary data.



Video 3 Cardiac magnetic resonance two-chamber view performed at follow-up showing a normal ejection fraction.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

Funding: None declared.

References

1. Gupta S, Goyal P, Idrees S, Aggarwal S, Bajaj D, Mattana J. Association of endocrine conditions with takotsubo cardiomyopathy: a comprehensive review. *J Am Heart Assoc* 2018;**7**:e009003.
2. Kume T, Kawamoto T, Okura H, Toyota E, Neishi Y, Watanabe N et al. Local release of catecholamines from the hearts of patients with tako-tsubo-like left ventricular dysfunction. *Circ J* 2008;**72**:106–108.
3. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005;**352**:539–548.
4. Ferreira VM, Marcelino M, Piechnik SK, Marini C, Karamitsos TD, Ntusi NAB et al. Pheochromocytoma is characterized by catecholamine-mediated myocarditis, focal and diffuse myocardial fibrosis, and myocardial dysfunction. *J Am Coll Cardiol* 2016;**67**:2364–2374.
5. Polikar R, Burger AG, Scherrer U, Nicod P. The thyroid and the heart. *Circulation* 1993;**87**:1435–1441.
6. Suzuki K, Miyake T, Okada H, Yamaji F, Kitagawa Y, Fukuta T et al. Thyrotoxic and pheochromocytoma multisystem crisis: a case report. *J Med Case Rep* 2017;**11**:173.
7. Bauer J, Belt E. Paroxysmal hypertension with concomitant swelling of the thyroid due to pheochromocytoma of the right adrenal gland; cure by surgical removal of the pheochromocytoma. *J Clin Endocrinol Metab* 1947;**7**: 30–46.
8. Fatma M, Wafa BO, Dorra G, Mouna E, Bs D, Mohamed A. Pheochromocytoma/ganglioneuroma and auto-immunity: report of two cases. *J Endocrinol Thyroid Res* 2019;**4**:555636.
9. Silva JE, Bianco SD. Thyroid–adrenergic interactions: physiological and clinical implications. *Thyroid* 2008;**18**:157–165.
10. Panina-Bordignon P, Mazzeo D, Lucia PD, D'Ambrosio D, Lang R, Fabbri L et al. Beta2- agonists prevent Th1 development by selective inhibition of interleukin 12. *J Clin Invest* 1997;**100**:1513–1519.
11. Furmaniuk A, Demarquet L, Klein M, Weryha G, Feigerlova E. Subacute thyroiditis revealing a pheochromocytoma. *AACE Clin Case* Rep 2016;**2**:161–166.
12. Tsatsoulis A. The role of stress in the clinical expression of thyroid autoimmunity. *Ann N Y Acad Sci* 2006;**1088**:382–395.
13. Trial J, Cieslik KA, Haudek SB, Duerrschmid C, Entman ML. Th1/M1 conversion to th2/m2 responses in models of inflammation lacking cell death stimulates maturation of monocyte precursors to fibroblasts. *Front Immunol* 2013;**4**:287.
14. Mylonas KJ, Jenkins SJ, Castellan RF, Ruckerl D, McGregor K, Phythian-Adams AT et al. The adult murine heart has a sparse, phagocytically active macrophage population that expands through monocyte recruitment and adopts an 'M2' phenotype in response to Th2 immunologic challenge. *Immunobiology* 2015;**220**: 924–933.
15. Kong P, Christia P, Frangogiannis NG. The pathogenesis of cardiac fibrosis. *Cell Mol Life Sci* 2014;**71**:549–574.
16. de Miguel V, Arias A, Paissan A, de Arenaza DP, Pietrani M, Jurado A et al. Catecholamine-induced myocarditis in pheochromocytoma. *Circulation* 2014;**129**: 1348–1349.