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CASE REPORT
Heart failure

Inverted takotsubo syndrome complicated with cardiogenic shock requiring veno-arterial extracorporeal membrane oxygenation in a patient with bilateral pheochromocytoma: a case report

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Background Takotsubo syndrome (TS) is characterized by a transient left ventricular (LV) dysfunction and rarely presents with cardiogenic shock (CS). Inverted TS (ITS) is a rare entity associated with the presence of a pheochromocytoma.

Case summary We present a case of a young woman was admitted to the emergency department due to intense headache, chest discomfort, palpitations, and breathlessness. An ITS secondary to a pheochromocytoma crisis presenting with CS was diagnosed. The patient was managed with veno-arterial extracorporeal membrane oxygenation, until recovery of LV function. On the 35th day of hospitalization, open bilateral adrenalectomy was performed.

Discussion Takotsubo syndrome patients presenting with CS are challenging and clinicians should be aware of underlying causes. Specific triggers such as pheochromocytoma should systematically be considered particularly if ITS was presented. Extracorporeal life support devices could provide temporary mechanical circulatory support in patients with TS on refractory CS and help to manage complex cases with TS due to pheochromocytoma.

Keywords Takotsubo syndrome • Pheochromocytoma • Veno-arterial extracorporeal membrane oxygenation • Case report

Learning points

- Recognition of a rare entity such, as inverted takotsubo syndrome, and its association with specific aetiologies, which should be systematically investigated.
- The therapeutic management of a patient in cardiogenic shock (CS) secondary to the catecholaminergic crisis.
- The importance of mechanical circulatory support in patients with refractory CS, particularly in those with a potentially reversible cause.

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Introduction

Takotsubo syndrome (TS) is characterized by transient wall motion abnormalities of the left ventricle that typically involve the apical and midventricular segments (apical ballooning).[1] A variant, with akinesia of the basal and mid left ventricular (LV) segments and sparing of the apex, has been called inverted TS (ITS) and is associated with the presence of a pheochromocytoma. This variant is important to identify as it tends not to be recognized as readily as the apical presentation.[1,2]

Pheochromocytoma crisis (PC) is an endocrine emergency with a high mortality rate.[3,4] Inverted TS associated with PC is an unusual but reversible presentation and should be recognized as early as possible. There is a lack of evidence on the management of patients with TS and concomitant pheochromocytoma but proper and fast support could impact the patient's prognosis.

Timeline

Timeline	Description
Day 0	Patient admission in emergency department in a peripheral hospital. Probable diagnosis was made: inverted Takotsubo syndrome complicated with cardiogenic shock secondary to pheochromocytoma crisis
Day 0–6 h after admission	Transfer to hospital with extracorporeal membrane oxygenation (ECMO) capability
Day 0–8 h after admission	Patient started ECMO support
Day 10	Weaning ECMO support
Day 14	ECMO support removed
Day 35	Open bilateral adrenalectomy
Day 49	Hospital discharge

Case presentation

A 26-year-old woman was admitted to the emergency department due to intense headache, chest discomfort, palpitations, and breathlessness, with 4 h of evolution.

Physical examination showed tachypnoea, tachycardia (145 b.p.m.), blood pressure of 158/95 mmHg, no fever, and oxygen saturation on room air of 92%. Cardiac auscultation was normal but pulmonary auscultation revealed bilaterally dispersed crackles. She was pale, with cold and clammy extremities and decreased capillary refill time but peripheral pulses were easily palpable.

The patient had a personal history of migraine and had been submitted to periodontal surgery on the previous day. She was medicated with amoxicillin/clavulanic acid and prednisolone. No relevant family history was reported.

The electrocardiogram (EKG) revealed sinus tachycardia, left axis deviation, V4–V6 ST-segment depression, maximum 2 mm at V5, and an inverted T wave in aVL (*Figure 1*).

Transthoracic echocardiography showed severe LV systolic dysfunction with midbasal segments akinesia and hypercontractility of the apical segments (*Figure 2*, Supplementary material online, *Video S1*).

The patient underwent aortic computed tomography angiography that excluded an acute aortic syndrome, but identified signs of severe pulmonary oedema and two heterogeneous solid masses in both adrenal glands, the largest on the right adrenal gland, measuring $9.2 \times 9.2 \times 10.8$ cm, suggestive of a bilateral pheochromocytoma (*Figure 3*).

The patient progressed with respiratory failure and shock signs with poor peripheral perfusion, oligoanuria, and arterial hyperlactacidemia (41 mg/dL; normal range≤ 18 mg/dL), despite her hypertensive profile (mean arterial pressure 110–120 mmHg). At this stage, she was submitted to mechanical ventilation. Due to the rapidly deteriorated clinical status, she was referred and transported to the closest hospital with extracorporeal membrane oxygenation (ECMO) capability for immediate mechanical circulatory support.

The patient remained with veno-arterial ECMO (VA-ECMO) support for 14 days and progressive recovery of LV dysfunction was observed, enabling the weaning of the VA-ECMO support from the 10th day, without use of inotropics. There were no significant changes on the EKG on the following 2 days, with regression of repolarization changes at follow-up. The peak troponin I level was 1.73 ng/mL (normal range ≤0.015 mg/dL), on the first day of hospitalization with a slow but progressive fall and subsequent normalization.

Urinary catecholamines and metanephrines in 24-h urine were elevated (*Table 1*). Alpha-blockade was started with phenoxybenzamine and subsequently beta-blockade with metoprolol.

On the 35th day of hospitalization, open bilateral adrenalectomy was performed, without complications, and she began supplementation with gluco and mineralocorticoids. Anatomopathological examination confirmed the diagnosis of bilateral pheochromocytomas. The patient was discharged on the 49th day of hospitalization with complete recovery of the left ventricular systolic function and preserved neurologic status.

After discharge, the patient performed body scintigraphy with MIBG-123 that excluded pheochromocytoma metastases or synchronous tumours, but she was diagnosed with bilateral thyroid medullary carcinoma. Total thyroidectomy was performed and the diagnose of Type 2 multiple endocrine neoplasia (MEN) syndrome was established.

Discussion

Takotsubo syndrome is a reversible LV dysfunction triggered by a precipitating factor (emotional, physical, or combined) in about 70% of the patients and is thought to be caused by catecholamine-mediated injury. The exact mechanism is less well-understood, but it is probably the result of a combination of various mechanisms: coronary artery or microvascular spasms, direct cellular toxicity, and myocardial stunning due to receptor desensitization.[1,2,5]

Inverted TS has been reported in various situations such as antidepressant overdose, subarachnoid bleed, anaphylactic shock, and

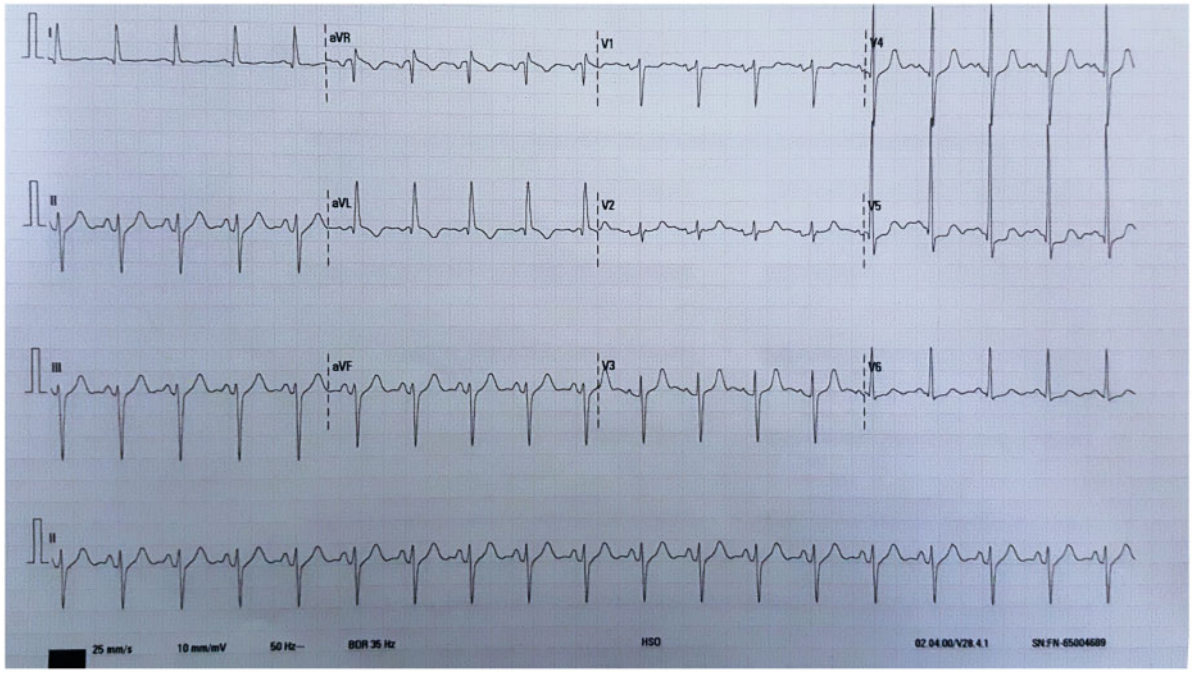

Figure 1 Admission electrocardiogram revealed sinus tachycardia, left axis deviation, V4–V6 ST-segment depression, maximum 2 mm at V5, and an inverted T wave in aVL.

also in association with pheochromocytoma, so these conditions should be considered in this particular setting.[1,6] Even though the original Mayo Clinic Diagnosis Criteria considered pheochromocytoma as an exclusion criterium for the diagnosis of TS, this was never universally accepted. The diagnostic criteria of the Heart Failure Association of the European Society of Cardiology (ESC) and more recently, the new InterTAK Diagnosis Criteria, identified pheochromocytoma as a trigger for TS and this concept was integrated in the current ESC consensus position paper on TS.[1,7]

This clinical case highlights that, despite similar pathophysiological causes to typical TS, ITS is associated with a different patient profile and presenting symptoms. Compared with typical TS, patients with ITS more frequently have a stress trigger and present at a younger age, which may be due to the abundance of adrenoreceptors at the base of the heart in young individuals and the apex in older ones.[2]

Contrarily to previous data that shows that ITS patients may present with less pulmonary oedema and cardiogenic shock (CS) than patients with classic TS, our case presented with CS, highlighting that CS in ITS should also raise the suspicion of a PC.[1,2]

Pheochromocytomas are rare catecholamine-secreting neuroendocrine tumours in the adrenal medulla, with an incidence of 2-9 cases per 1 000 000 adults. Usually sporadic (90%), they also can appear earlier in the context of neurofibromatosis, Von Hippel–Lindau or MEN syndromes.[8]

Pheochromocytoma crisis has reported mortality as high as 85% and about 10–20% of cases present with TS.[3,4]

CS is defined as systemic tissue hypoperfusion due to inadequate cardiac output despite the adequate circulatory volume.[9] CS is a life-threatening complication in TS, with an incidence between 2.8% and 12.4%.[10] In this case, although haemodynamic measurements of cardiac output or index could not be obtained, the presence of severe systolic dysfunction and signs of peripheral poor perfusion, oligoanuria, and hyperlactacidemia corroborate the diagnosis of CS. High blood pressure can be explained by the intense vasoconstriction caused by catecholaminergic discharge, increasing the afterload and contributing to the shock.

In TS presenting with CS, it is crucial to assess whether the shock is caused by LV outflow tract obstruction or primary pump failure. In primary pump failure, treatment with VA-ECMO or an LV assist device should be considered as a bridge to recovery.[5,7] Catecholamine inotropics should be avoided, especially if the TS is triggered by PC, as they could exacerbate the clinical condition.[5,7]

In this patient, the presence of headaches, palpitations, a large abdominal mass, and an ITS complicated with CS, despite sustained hypertension, constituted red flags to the diagnosis of pheochromocytoma and a PC precipitated by an elective surgery and the glucocorticoid therapy.[4]

Although coronary angiography should be considered in every patient with TS and/or unexplained CS, especially in cases of ST-segment deviation, in this case, coronary heart disease was not excluded. The patient was a very young female with no cardiovascular risk factors, an almost normal EKG on admission, no electrocardiographic evolution, or troponin rise compatible with an acute coronary syndrome and there was an early suspicion of pheochromocytoma with abdominal imaging confirmed afterwards with elevated urinary catecholamines.

Elective adrenalectomy is the ideal option for pheochromocytoma treatment, accompanied by appropriate preoperative medical

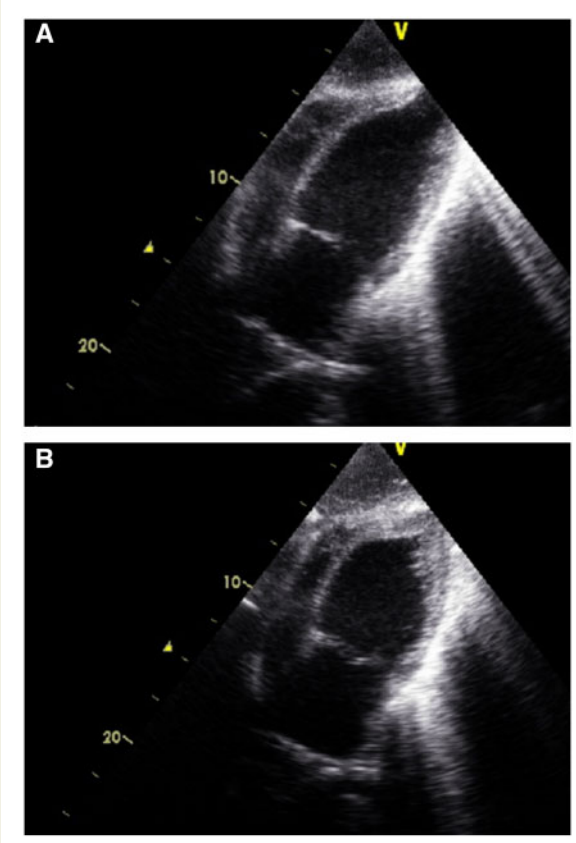

Figure 2 Admission echocardiography showing subcostal view of the left ventricle at end-diastole (*A*), and end-systole (*B*).

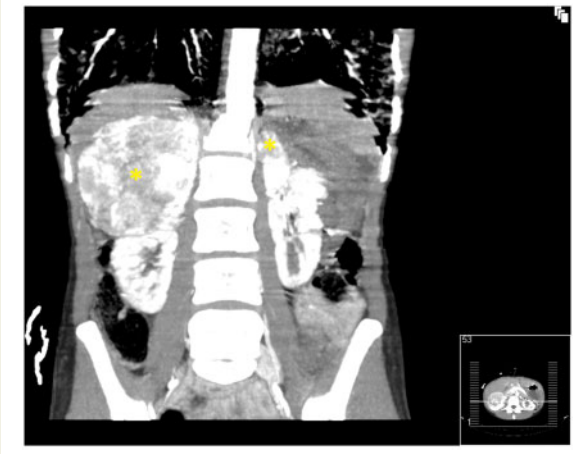

Figure 3 Computed tomography scan showing two heterogeneous solid masses (*), on the right (9.2 × 9.2 × 10.8 cm) and left (2.3 × 2.8 × 3.3 cm) adrenal gland.

treatment. Alpha-blockade before elective surgery is associated with reduced mortality, shorter hospital stays, and fewer post-operative complications.[5,8] Beta-blockers should never be administered without appropriate alpha-blockade as this could worsen hypertensive episodes by exacerbating vasoconstriction while inhibiting vasodilation.[3]

In our case, alpha-blockers were gradually introduced, followed by beta-blockers once cardiac systolic function had recovered and ECMO support had been removed. Adrenalectomy was deferred until myocardial recovery.

Table 1 Urinary catecholamines and metanephrines in patient with bilateral pheochromocytoma

Catecholamines and metanephrines in 24-h urine	Results (μg/h)	Reference range (μg/h)
Norepinephrine	13 144/24	<97/24
Epinephrine	3064/24	<27/24
Dopamina	1118/24	<500/24
Normetanephrine	15 689/24	<390/24
Metanephrine	15 000/24	<320/24

Conclusion

Takotsubo syndrome patients presenting with CS are challenging and clinicians should be aware of possible underlying causes. Specific triggers such as PC should systematically be considered for patients with TS, particularly ITS complicated by CS.

For the most severe cases, ECMO support can be a life-saving therapy, allowing myocardial recovery. After haemodynamic stabilization, treatment should include alpha-blockade followed by beta-blockade, with elective adrenalectomy after myocardial recovery.

Lead author biography

Bebiana Manuela Monteiro Faria was born in Guimarães, Portugal on 7 April 1988. She studied Medicine at University of Porto—Institute of Biomedical Sciences Abel Salazar where completed her Master's degree in 2013. Since 2015 she is Cardiology resident at Hospital Senhora da Oliveira Guimarães. With a particular interest in Emergency Medicine she also works as an Emergency Physician in the National Institute of Medical Emergency since 2017.

Supplementary material

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

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

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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