

Biventricular Takotsubo Cardiomyopathy as the Initial Manifestation of a Pheochromocytoma



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INTRODUCTION

Stress cardiomyopathy is a form of acute and transient myocardial injury characterized by regional systolic dysfunction.¹ Takotsubo cardiomyopathy (TTC) is a stress cardiomyopathy with a specific pattern of regional systolic dysfunction. It is classically induced by emotional or physical stress and often mimics an acute myocardial infarction.^{1,2} Regional wall abnormalities in TTC typically compromise the left ventricle (LV), extend beyond the coronary artery supply region, and have an apical and circumferential pattern of myocardial dysfunction that results in apical ballooning of the LV during systole.²

Among the medical conditions associated with TTC, pheochromocytomas represent a rare and controversial etiology.^{1,3,4} Limited evidence supports that patients with pheochromocytoma-induced TTC have distinct clinical features, present with different patterns of ventricular compromise, and have worse outcomes; therefore, they represent a clinical challenge.¹⁻³ Herein, we report the case of a patient with pheochromocytoma-induced TTC who presented with severe biventricular compromise detected by cardiovascular magnetic resonance imaging (CMR).

CASE PRESENTATION

A previously healthy, 21-year-old woman presented to the emergency department with sudden onset of severe, oppressive, substernal chest pain accompanied by diaphoresis and shortness of breath. On examination, blood pressure was 170/100 mm Hg, heart rate was 107 beats/minute, respiratory rate was 15 breaths/minute, and oxygen saturation was 97% at room air. Heart sounds were tachycardic but

regular. Cardiac examination was otherwise unremarkable, with no murmurs, gallops, or rubs. No neurologic deficits or other abnormal findings were present. The patient had no significant medical history. She reported an active lifestyle and was taking no medications. She was an occasional smoker but denied other substance use. There was no family history of cardiovascular disease.

The initial differential diagnosis of this young patient who presented with new-onset chest pain, dyspnea, tachycardia, and hypertension included panic attack, pulmonary embolism, acute coronary syndrome in the context of a spontaneous coronary artery dissection or coronary vasospasm (given her young age, coronary atherosclerotic disease was unlikely), aortic dissection, and inflammatory conditions such as pericarditis or myocarditis. An acute intoxication was also considered, even though there was no previous history of substance abuse.

Initial workup revealed normal renal and hepatic function, complete blood count, and electrolytes. A toxicological screening was negative. Upon arrival, an electrocardiogram showed sinus tachycardia and diffuse symmetric T-wave inversion (Figure 1). High-sensitivity troponin I concentration was 3.2 ng/mL (normal, <0.026 ng/mL), and, therefore, she was referred to the coronary care unit with a working diagnosis of acute coronary syndrome. In addition to acute coronary syndrome, the dramatic T-wave inversion added an apical variant hypertrophic cardiomyopathy to the working differential diagnoses. Coronary angiography showed no evidence of stenosis, although slow flow in the left anterior descending territory was present. This finding is characteristic of microvascular dysfunction (Video 1, Figure 2).

A bedside transthoracic echocardiogram showed LV akinesis in the mid and apical segments and a mild systolic dysfunction with left ventricular ejection fraction of 40% (Video 2). It also showed right ventricular apical akinesis and mild systolic dysfunction with a fractional area change (FAC) of 32%, tricuspid annular plane systolic excursion (TAPSE) of 1.5 cm, and tricuspid annular S' velocity of 18 cm/sec on tissue Doppler imaging (TDI; Video 3, Figures 3 and 4). A diagnosis of TTC was considered, and a subsequent CMR revealed LV akinesia in the mid and apical segments, with midsegment dyskinesia of the right ventricular free wall (Video 4). Additionally, there was evidence of myocardial edema in the T2 short tau inversion recovery (STIR) sequence and no late gadolinium enhancement (LGE) in the apical segments (Figure 5). The presence of mid and apical akinesis in the left and right ventricle, plus the evidence of apical edema without LGE in the same territory, is a classic finding of biventricular TTC. There was evidence of focal LGE in the basal septum, not related to the current episode. In the absence of any additional findings, we considered this to be related to a previous episode of myocarditis.

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Conflicts of Interest: None.

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VIDEO HIGHLIGHTS

Video 1: Coronary angiography, right anterior oblique projection. Coronary angiography was negative for obstructive coronary disease.

Video 2: Transthoracic echocardiogram, apical four-chamber view. Transthoracic echocardiogram showed mild left ventricular dysfunction, with akinesia of the apical segments of the left ventricle and hyperkinesia of the basal segments. The left ventricular ejection fraction was 40%.

Video 3: Transthoracic echocardiogram, right ventricle apical four-chamber view. Transthoracic echocardiogram showed moderate right ventricular dysfunction with akinesia of the apical segments. The FAC was 28%, the TAPSE was 1.5 cm, and the tricuspid annular *S'* velocity was 18 cm/sec on TDI.

Video 4: Cardiac magnetic resonance, four-chamber view cine. Cardiac magnetic resonance revealed left ventricular akinesia in the mid and apical segments, with midsegment dyskinesia of the right ventricular free wall.

View the video content online at www.cvcasejournal.com.

The patient's clinical course was characterized by severe, paroxysmal blood pressure elevations despite aggressive medical therapy. The presence of resistant malignant hypertension and marked blood pressure variability in a previously healthy young patient without risk factors made us suspect an underlying etiology. Thus, suspicion of secondary hypertension prompted a further workup. A 24-hour urine fractionated metanephrines test showed elevated levels of normetanephrine (141.3 $\mu\text{mol}/\text{day}$; reference range, 0.48-2.42 $\mu\text{mol}/\text{day}$) and metanephrine (76 $\mu\text{mol}/\text{day}$; reference range, 0.26-1.73 $\mu\text{mol}/\text{day}$) suggesting a hyperadrenergic state. Subsequent abdominal computed tomography showed a 55 × 40 × 37 mm well-defined mass with heterogeneous enhancement arising from the right adrenal gland (Figure 6). The imaging and serologic test findings were supportive of the diagnosis of a biventricular TTC secondary to a pheochromocytoma-induced adrenergic crisis. Urgent medical

management was initiated, and the patient was transferred to another institution for further medical and surgical management.

DISCUSSION

Since its first description in 1990 by Sato and colleagues,⁵ TTC has emerged as an increasingly recognized cause of transient ventricular dysfunction, especially in women without classic cardiovascular risk factors. Initially, the name was coined after the marked resemblance that the LV adopted during systole to that of a Japanese octopus trap during invasive left ventriculography.

Takotsubo cardiomyopathy typically presents in postmenopausal women with acute or subacute chest pain, classically, after severe emotional or physical stress. Although it is known for almost complete recovery of ventricular function and wall-motion abnormalities after the acute event, in some patients, TTC may lead to severe cardiovascular compromise, hypotension, cardiogenic shock, and requirement of ventricular assistance.²

Multiple theories and mechanisms have been proposed to describe the pathophysiological events and associated triggers in TTC.^{2,6} The international Takotsubo Registry Study showed that among 1,759 patients, 71.5% of the cases had a history of an emotional or physical trigger in the weeks that preceded the cardiovascular event.² Common emotional stressors include the death of a loved one, domestic abuse, financial losses, or unexpected medical diagnosis. On the other hand, frequently reported physical stressors include acute critical illness, surgery, and severe pain.⁶

Pheochromocytomas are rare catecholamine-secreting tumors of the adrenal medulla with an incidence of 0.05%.⁷ Features suggestive of pheochromocytoma include paroxysmal hypertension associated with episodic headache, palpitations, and sweating. Screening of pheochromocytoma should be considered in patients with malignant hypertension, poor response to antihypertensive treatment, and paradoxical hypertensive response to stress, pharmacologic provocation, or tumor manipulation (e.g., abdominal palpation). Correct diagnosis of pheochromocytoma requires a biochemical and imaging test to locate the tumor. The test of choice for screening is plasma-free metanephrines. This test has high sensitivity and, when elevated, should be followed by contrast-enhanced computed tomography or magnetic resonance imaging of the abdomen and pelvis. Surgical resection is the mainstay of treatment except in cases where the tumor is unresectable.

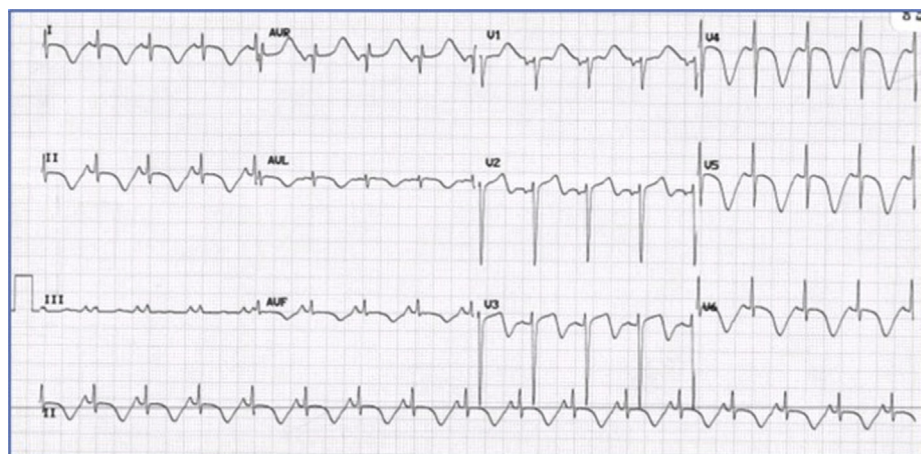


Figure 1 Electrocardiogram showing sinus tachycardia and diffuse symmetric T-wave inversion.

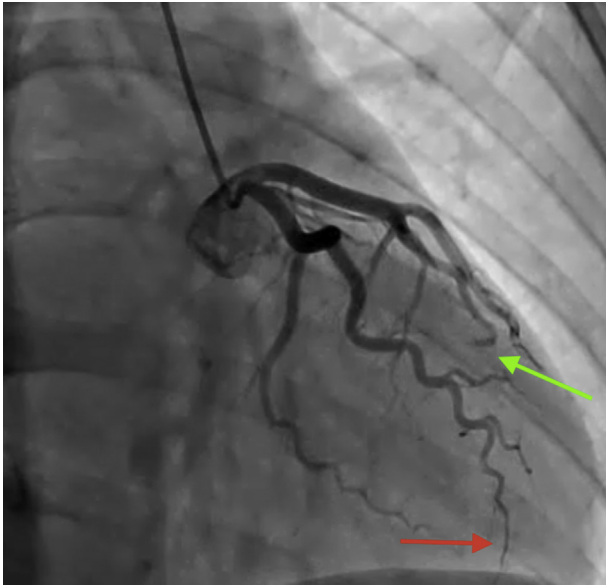


Figure 2 Coronary angiography demonstrating slow flow in the left anterior descending (LAD) coronary territory. The red arrow shows normal filling of the obtuse marginal artery up to the cardiac apex. The green arrow shows partial filling of the LAD.

The causal relationship between an adrenergic crisis secondary to pheochromocytoma and TTC has been widely debated and surrounded by controversy.^{1,3,8,9} Multiple investigators and previously proposed diagnostic criteria explicitly excluded pheochromocytoma as a potential cause of TTC and categorized the occurrence of ventricular wall-motion abnormalities in the setting of an adrenergic crisis, even in the presence of the characteristic imaging findings of TTC, as a separate and distinct syndrome.¹⁰ However, current statement positions from the International Expert Consensus on Takotsubo Cardiomyopathy have supported the link between pheochromocytoma and TTC, as long as specific clinical and imaging criteria have been fulfilled.¹

Takotsubo cardiomyopathy, as the initial presentation of pheochromocytoma, is a rarely described scenario.^{2,4,10} Recent research has highlighted the relevant epidemiological, clinical, and imaging differences between pheochromocytoma-induced TTC and TTC due to other stressors.^{2,3,10} Patients with pheochromocytoma-induced TTC are generally younger (mean age of 46 vs 66 years), are frequently male (30% vs 10%), have a decreased frequency of the typical apical ballooning pattern (44% vs 83%), and have increased prevalence of global and basal ventricular compromise (20% and 30%, respectively, vs 0% and 2.2%).^{2,10} They also have significantly higher complication rates compared to the entire TTC population (68% vs 21.8%) and,

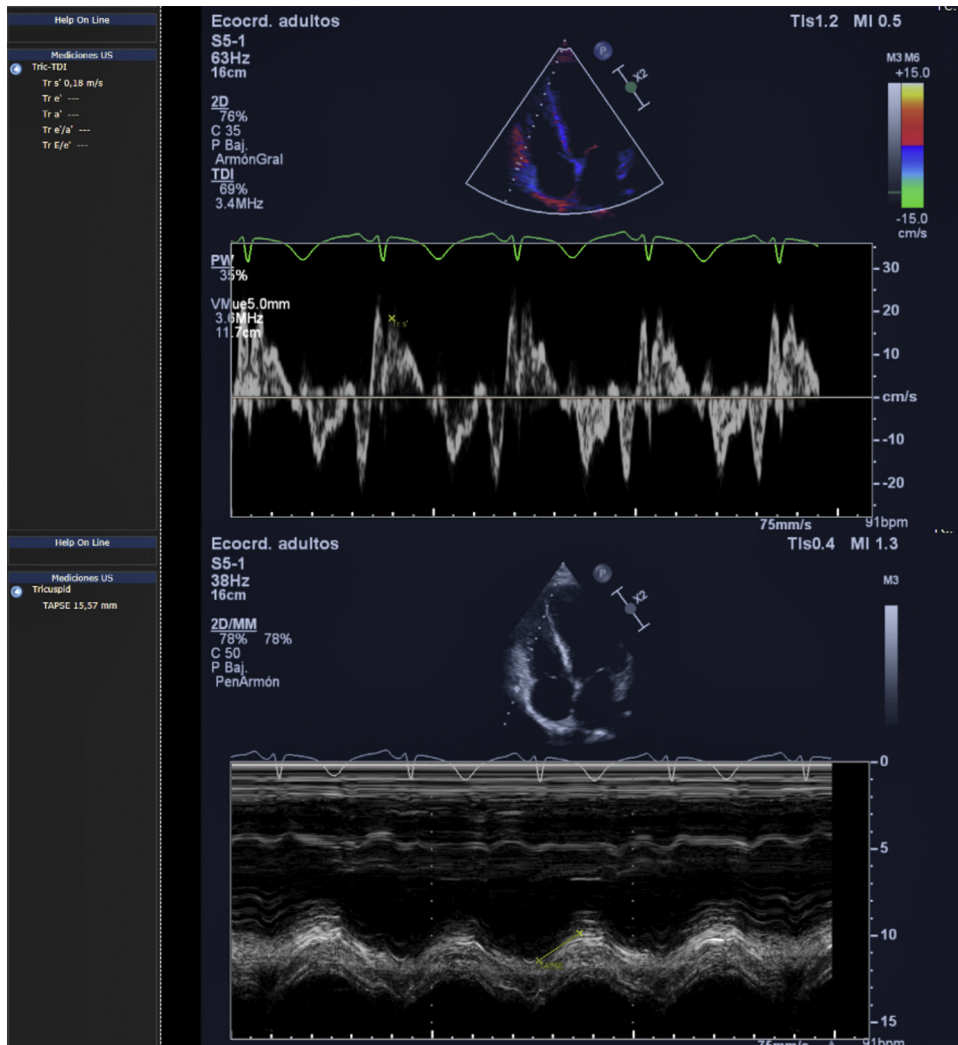


Figure 3 Transthoracic echocardiogram. The TAPSE was 1.5 cm, and the tricuspid annular S' velocity was 18 cm/sec on TDI.

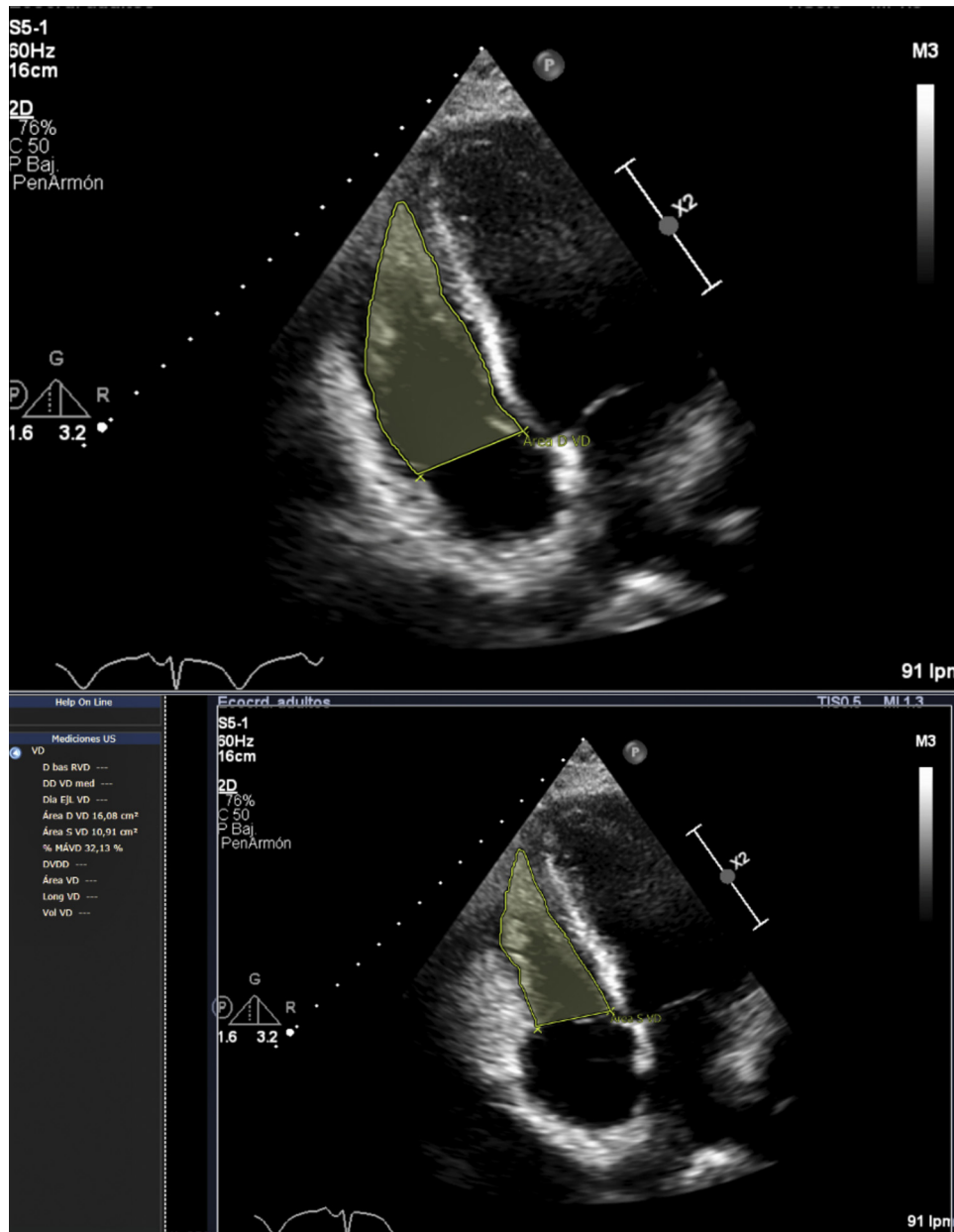


Figure 4 Transthoracic echocardiogram shows mild right ventricular systolic dysfunction with an FAC of 32%.

notably, are more prone to develop cardiogenic shock (33% vs 9.9%).^{2,10}

Most cases of TTC from any cause have only LV involvement; however, biventricular compromise is not uncommon. Right ventricle involvement has been reported in approximately 25% to 42% of patients diagnosed with TTC.^{11,12} Interestingly, there are scarce data concerning biventricular compromise in pheochromocytoma-induced TTC, with only a few cases reported worldwide.^{3,10} Such cases are usually characterized by a severely compromised ventricular function, early clinical deterioration, and higher risk of complications and require more intensive and aggressive management.¹⁰ Our patient differs from those cases with respect to the course of hospitalization, which progressed without development of respiratory or heart failure, pleural effusion, or cardiogenic shock or the requirement of any form of advanced life support.

In our case, multimodal imaging, and specifically CMR, was key to eliminating other potential causes of regional LV systolic dysfunction, provided a comprehensive evaluation of both ventricles, and supported a final diagnosis of TTC as the most likely etiology. It is worth noting that CMR has been proposed as an invaluable tool in the diagnostic workup of atypical cases, such as this one. Gravina and colleagues¹³ suggested that it may even allow diagnosing both stress cardiomyopathy and pheochromocytoma in a single imaging session.

CONCLUSION

Clinicians should be aware of uncommon etiologies of TTC, especially when atypical features such as young age, atypical clinical signs, and unusual wall-motion abnormalities are present. A high degree of suspicion should be held when initiating workup. In our case, a young

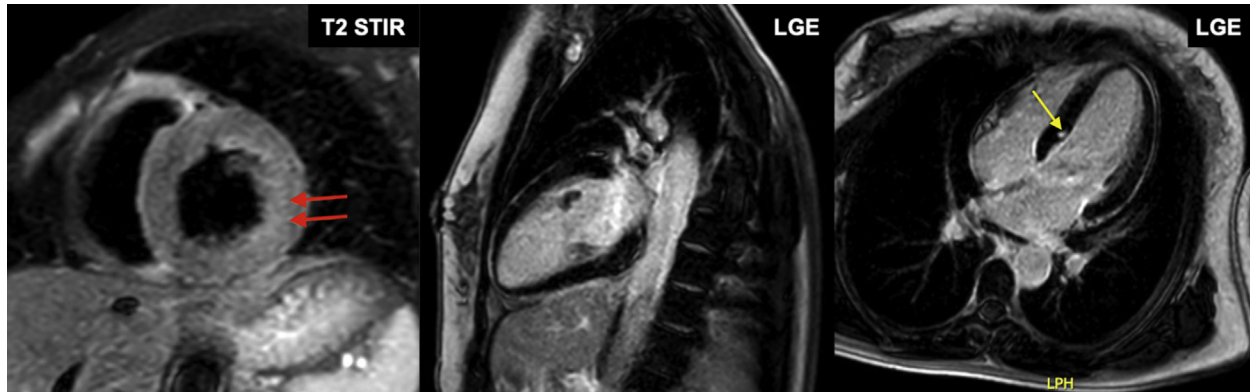


Figure 5 Cardiac magnetic resonance: STIR and LGE sequences. Short-axis STIR sequence, showing myocardial edema (red arrows). There was evidence of focal LGE in the basal septum (yellow arrow), not related to the current episode. In the absence of any additional findings, we considered this to be related to a previous episode of myocarditis.



Figure 6 Abdominal computed tomography showing a well-defined mass in the right adrenal gland (black arrow).

patient presented with malignant hypertension and imaging evidence of biventricular dysfunction plus the typical segmental wall-motion abnormalities seen in TTC. The concomitant presence of an unusual form of Takotsubo and malignant hypertension in a young patient without risk factors prompted further follow-up. Laboratory results suggested the presence of a hyperadrenergic state, and imaging studies confirmed the presence of a pheochromocytoma. Although unusual, clinical and laboratory findings pointed toward a biventricular Takotsubo as the initial presentation of pheochromocytoma.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.case.2021.09.007>.

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