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# The Heart of the Issue: A Case Report of Recurrent Reversible Stress-Induced Cardiomyopathy

## Authors' Contribution:

Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

BCDEF 1 **Patrick Platzer**  
ABDEF 2 **Martin A. Espinosa Ginic**  
DEF 3 **Silvia Potenziani Pradella**

1 St Thomas Health Department of Internal Medicine, University of Tennessee Health Sciences Center, Nashville, TN, U.S.A.  
2 St Thomas Heart, Ascension Health, Nashville, TN, U.S.A.  
3 Anatomic and Clinical Laboratory Associates, P.C., Nashville, TN, U.S.A.

**Corresponding Author:** Patrick Platzer: e-mail: [pplatzer@uthsc.edu](mailto:pplatzer@uthsc.edu)

**Conflict of interest:** None declared

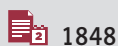
**Patient:** Female, 69-year-old  
**Final Diagnosis:** Pheochromocytoma  
**Symptoms:** Anxiety • headache • hearing impairment • hypertensive crisis • paresthesia • pulmonary edema • slurred speech  
**Medication:** —  
**Clinical Procedure:** Adrenalectomy • coronary angiography • echocardiography  
**Specialty:** Cardiology • Endocrinology and Metabolic • General and Internal Medicine

**Objective:** Mistake in diagnosis  
**Background:** Stress-induced cardiomyopathy is an increasingly recognized reversible cardiovascular condition. This type of cardiomyopathy usually occurs as an isolated event, and recurrent episodes are rare. Oftentimes, the underlying trigger is not recognized or definitively diagnosed. The differential diagnosis for reversible cardiomyopathy is extensive. A supraphysiologic catecholamine release from a pheochromocytoma can precipitate a recurrent and reversible cardiomyopathy. The highly variable clinical presentation of catecholamine-producing tumors can make timely recognition very challenging.  
**Case Report:** We present an exceptional case of recurrent reversible stress-induced cardiomyopathy triggered by an unrecognized pheochromocytoma with unusual clinical features. Our patient presented primarily with nonspecific neurological complaints, medication intolerance, and anxiety. The underlying etiology was not discovered until her fourth presentation of stress-induced cardiomyopathy.  
**Conclusions:** Pheochromocytomas can have a highly variable clinical presentation with a broad spectrum of signs and symptoms. Our case highlights the importance of performing an exhaustive search for a definitive underlying cause in the setting of recurrent “stress-induced” cardiomyopathy. Providers should consider an underlying catecholamine-producing tumor when presented with recurrent reversible cardiomyopathy. We recommend using plasma, rather than urine, catecholamine studies to screen for the presence of a pheochromocytoma.

**MeSH Keywords:** Cardiomyopathies • Neuroendocrine Tumors • Pheochromocytoma • Takotsubo Cardiomyopathy

**Abbreviations:** ACS – acute coronary syndrome; CAD – coronary artery disease; CT – computed tomography; CTA – computed tomography angiography; CVA – cerebrovascular accident; HU – Hounsfield units; LVEF – left ventricular ejection fraction

**Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/924876>



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## Background

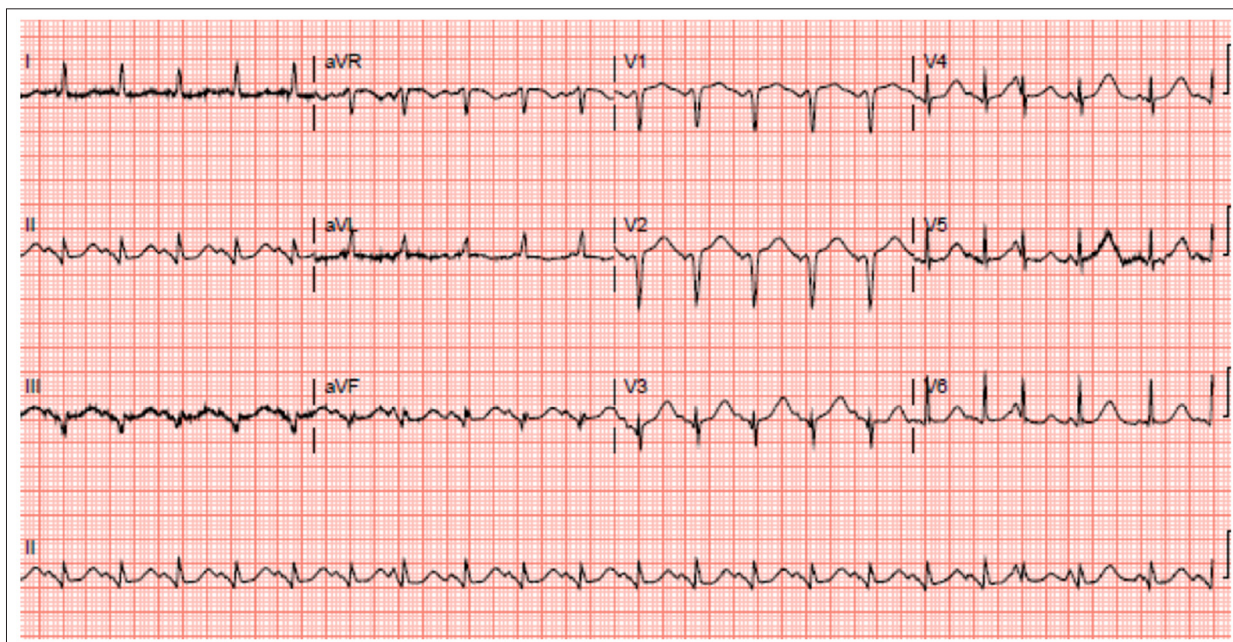
One of the most common causes of reversible cardiomyopathy is takotsubo cardiomyopathy, which is often referred to as stress-induced cardiomyopathy. The differential diagnosis of reversible cardiomyopathy is extensive and includes inflammatory, infectious, metabolic, arrhythmogenic, and sympatho-excitation-induced pathologies [1,2]. Stress-induced cardiomyopathy is increasingly recognized as a reversible cardiovascular condition. Although frequently underdiagnosed, there has been a noted increase in the incidence of stress cardiomyopathy (15–30 cases per 100 000 per year) [1]. This condition usually occurs as an isolated event with an identifiable trigger, although the specific underlying etiology is not always recognized. Classical takotsubo cardiomyopathy demonstrates an “apical ballooning” pattern on echocardiogram, with apical hypokinesis or akinesis and basal hyperkinesis [1]. While the majority of cases demonstrate classical apical ballooning, cases of reverse stress cardiomyopathy have been reported, in which there is basal hypokinesis/akinesis and the apex is hyperkinetic [1]. Right ventricular ballooning has also been reported [1]. Almost all cases extend beyond a single epicardial vascular distribution, but rare cases of “focal ballooning” have also been reported [1]. Stress cardiomyopathy is a diagnosis of exclusion; therefore, when a cardiomyopathy that is thought to be a stress cardiomyopathy recurs without a clear identifiable trigger, a more extensive search should be performed for a previously unrecognized trigger. A catecholamine-producing tumor can induce a recurrent and reversible cardiomyopathy. The clinical presentation of a pheochromocytoma can be highly variable, making clinical recognition

challenging at times. Interestingly, it has been described that cardiac symptoms often preceded the diagnosis of pheochromocytoma or paraganglioma by 3 and 5 years, respectively [2].

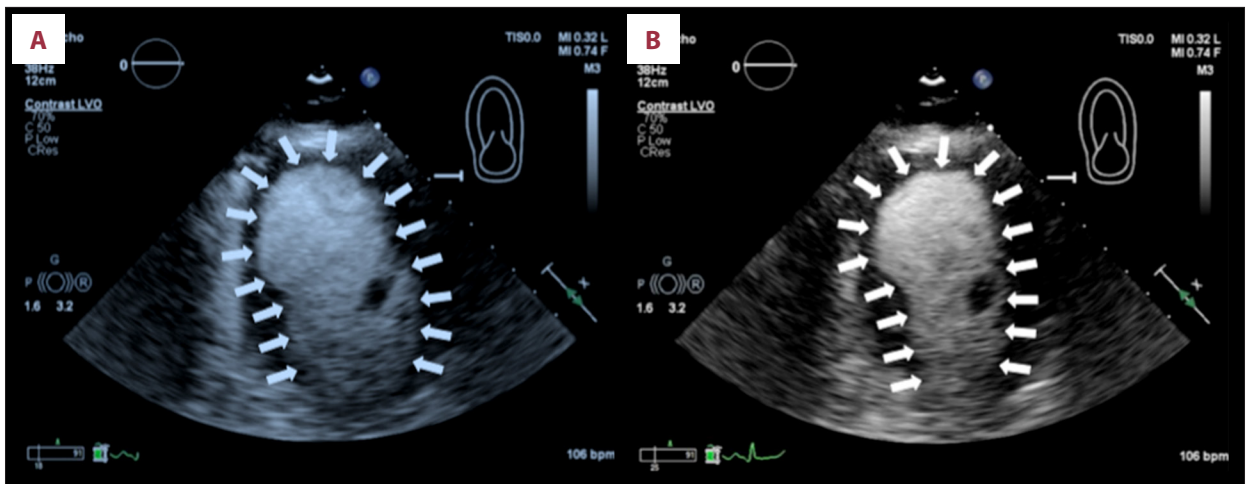
## Case Report

A 69-year-old woman presented with concerns that she was having a stroke. She reported labile blood pressure, recurrent headaches, paresthesias, lightheadedness, decreased hearing, garbled speech, and word-finding difficulties. She also endorsed episodic thoracic back pain and dyspnea. She was in hypertensive emergency and had pulmonary edema. The initial troponin was 0.02 ng/mL, peaking at 6.77 ng/mL. This was thought to be due to demand ischemia, as she had a very recent angiogram with patent coronary arteries. An ECG showed non-specific anterolateral and inferior ST changes, a transient left bundle branch block, and QT prolongation (Figure 1). An echocardiogram revealed moderate concentric left ventricular hypertrophy and wall motion abnormalities consistent with apical ballooning syndrome with akinesis of the mid- to apical left ventricular myocardium, and a left ventricular ejection fraction (LVEF) of 37% (Figure 2).

The patient had a past medical history of hypertension and anxiety. She was a former smoker, having quit approximately 35 years ago. The patient denied alcohol use and illicit drug use, but was previously noted to consume 1–3 glasses of wine daily, but she had quit 2 months prior due to concerns for worsening her heart function. She denied drug use. Her mother died from “heart disease” in her 50’s, her father died from



**Figure 1.** ECG on day 1: Sinus rhythm with marked QT prolongation and left bundle branch block.



**Figure 2.** 2D echocardiogram with Definity® ultrasound contrast. Two-chamber view showing left ventricular apical ballooning and normal base contractility. (A) Systole, (B) diastole.

bladder cancer, and her brother had a stroke. Otherwise, her family history was negative for any form of genetic syndromes.

She had a history of 3 prior episodes of reversible stress-induced cardiomyopathy, labile hypertension, nonspecific neurological complaints (paresthesias, word-finding difficulties, garbled speech), generalized anxiety disorder, and an intolerance to beta-blockers.

She was first diagnosed with takotsubo cardiomyopathy 3 years prior, when she presented to an outside hospital with chest pain. No trigger was identified. An echocardiogram showed an LVEF of 20% with apical dyskinesia. A coronary angiogram showed minimal non-obstructive CAD. A 3-month follow-up echocardiogram showed complete resolution of wall motion abnormalities and normalization of her LVEF to 55–65%.

The second episode of cardiomyopathy occurred 21 months later when she presented to another outside facility with a hypertensive emergency and pulmonary edema. Her LVEF was again 20% with new apical dyskinesia and a hyperkinetic base. Again, no cause was found. A repeat echocardiogram 1 month later was normal, without wall motion abnormalities, and normal LVEF.

The patient had a third hospital presentation 14 months later (1 month prior to the current admission) with nonspecific neurological complaints (decreased hearing, slurred speech, facial and right upper extremity paresthesias), uncontrolled hypertension, and pulmonary edema. Her blood pressure had been very labile since the prior admission. An echocardiogram showed an LVEF of 40% with severe basal hypokinesia and preserved function of the apical myocardium, suggestive of reverse takotsubo. A repeat angiogram was unchanged. A CT/CTA of the chest showed no significant vascular abnormalities, but

incidentally noted an “irregular heterogenous lesion along the left adrenal gland”. Outpatient follow-up was arranged. A 24-hour urine collection showed an elevated level of epinephrine at 230  $\mu\text{g}$  (normal range: 1–7), normal norepinephrine (46  $\mu\text{g}$ ), normal cortisol (17.2  $\mu\text{g}$ ), and normal dopamine (117  $\mu\text{g}$ ). These results were interpreted as non-diagnostic for a catecholamine-producing tumor.

Her home medications included a beta-blocker and a losartan/hydrochlorothiazide combination, she was not on any alpha-blockade. The patient had self-discontinued the carvedilol as she believed it was the cause of her neurological symptoms. She had previously been intolerant of metoprolol and nebivolol, as she believed these caused her anxiety to worsen, decreased hearing, and caused slurred speech, paresthesias, and word-finding difficulties. Her blood pressure during this time was very labile and difficult to control, requiring multiple medication changes.

Upon admission to our facility, an extensive workup was performed to evaluate the cause of her neurological symptoms and recurrent cardiomyopathies. Stroke was ruled out with dedicated CT and MRI scans. Renal artery stenosis was considered as it can present with hypertensive emergency and pulmonary edema, but this was ruled out with a renal artery duplex ultrasound. Given the recent non-revealing coronary angiograms, this was not repeated. A CTA of the chest was performed to evaluate her thoracic back pain in the setting of hypertensive emergency. This showed no acute findings, but again noted an irregular heterogeneous lesion along the left adrenal gland. Lab work revealed normal blood counts, metabolic panel, thyroid function, ANA, negative HIV serology, and drug screen. Plasma aldosterone was normal (10.7 ng/dL). This time plasma metanephrines, rather than urine catecholamine levels, were performed. The plasma normetanephrine level

was elevated at 15.1 nmol/L (normal range: 0.00–0.89), plasma metanephrine was elevated at 12.8 nmol/L (normal range: 0.00–0.49). A thin-slice CT of the abdomen/pelvis with contrast was performed to characterize the adrenal mass. This showed a 7.3×4.8×7.1 cm left adrenal mass with intrinsic cystic areas and layering fluid. The lesion measured 38 Hounsfield units (HU) on pre-contrast imaging, 59 HU on portal venous imaging, and 72 HU on delayed phase imaging.

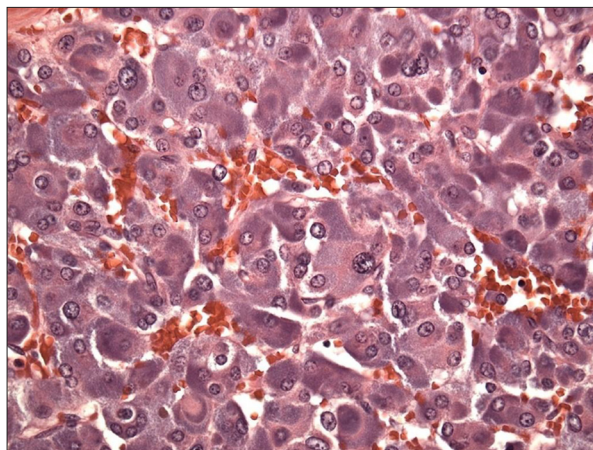
The patient was admitted to the intensive care unit. The hypertensive emergency and severe anxiety were managed with a nicardipine drip, IV labetalol, and lorazepam. Upon discovering the elevated plasma metanephrines and confirming the presence of an adrenal mass, the patient was started on an alpha-blocker (prazosin) in addition to the labetalol.

An uncomplicated left laparoscopic adrenalectomy was performed on hospital day 12. Pathology confirmed the diagnosis of pheochromocytoma (Figure 3). Postoperatively, the patient was hypotensive and briefly required norepinephrine. The patient recovered well from the surgery, with normalization of her blood pressure, resolution of neurological symptoms, and ECG normalization. She was discharged on post-operative day 3 on metoprolol for her cardiomyopathy.

After discharge she was seen at 1, 6, and 12 months. She reported no recurrence of symptoms, her anxiety had greatly improved, and she was tolerating the metoprolol well. Repeat serum metanephrines were normal. A repeat echocardiogram showed normalization of the left ventricular function with no residual wall motion abnormalities. Her ECG was unremarkable.

## Discussion

The conditions associated with reversible cardiomyopathy include: inflammatory/infectious (viral myocarditis, sepsis), metabolic (hyperthyroidism; thiamine, selenium, and carnitine deficiencies), arrhythmia-induced (PVC and tachycardia-mediated), auto-immune (peripartum), toxic (alcohol and cocaine), chronic disease (obesity, cirrhosis, uremia), and sympathoexcitation-induced (stress-induced, catecholamine-induced from medications or tumors) [1,3,4]. The most common cause of sympathoexcitation-induced cardiomyopathy is takotsubo cardiomyopathy (stress-induced), which can occur secondary to physical and emotional triggers, although in 30–35% of cases no identifiable trigger is found [4]. Catecholamine-producing tumors are another known trigger of sympathoexcitation-induced cardiomyopathy. Takotsubo cardiomyopathy usually occurs as a single and reversible event, and multiple recurrent episodes are uncommon.



**Figure 3.** Photomicrograph: Pheochromocytoma demonstrating sheets of large polygonal cells with abundant basophilic, granular cytoplasm and focal nuclear pleomorphism (hematoxylin-eosin, original magnification 400×).

There have been other reported cases of pheochromocytoma-induced cardiomyopathy, but we are unaware of any published cases in which a catecholamine-producing tumor caused both a classical and reverse Takotsubo cardiomyopathy in the same patient. Additionally, our case is unique in the number of recurrences during an unusually long period of time prior to definitive diagnosis. Our patient had 4 episodes over a 3-year timespan.

Neuroendocrine tumors can generate a massive catecholamine surge which overwhelms the body's compensatory mechanisms. However, the exact mechanism of sympathoexcitation-induced cardiomyopathy is not completely understood. The current leading hypotheses involve acute coronary microvascular impairment and catecholamine-induced cardiotoxicity via increasing intracellular calcium levels [4]. The left ventricular apex is more prone to being affected by a catecholamine surge due to a greater concentration of  $\beta$ -adrenoreceptors than in surrounding tissue [4]. It has been reported that pheochromocytoma-induced cardiomyopathy cases more frequently express the atypical inverse ballooning phenomenon, which occurs in approximately one-third of cases [5].

The signs and symptoms of pheochromocytomas are related to the actions of its secreted catecholamines [6]. Typical signs and symptoms include paroxysmal hypertension, tachycardia, pallor, headaches, anxiety, hyperglycemia, and flushing [6]. Less prevalent symptoms include paresthesias, nausea, vertigo, and chest pain. It should be noted that these symptoms can mimic those of an emotionally or physically stressful situation, such as the triggers in takotsubo cardiomyopathy.

Recent evidence suggests that plasma metanephrine tests are more sensitive than urine metanephrines for screening

of pheochromocytoma [7]. If suspicion remains high after an indeterminate plasma test, it is recommended to repeat the plasma test, or obtain a 24-hour urine collection. CT and MRI both have excellent sensitivity [8]. Imaging of the thorax, abdomen, and pelvis should be performed in search of a catecholamine-producing tumor (pheochromocytoma or extrarenal paraganglioma).

Medical management in pheochromocytoma cases should include alpha- and beta-blockade prior to surgery, even in patients who are normotensive. Beta-blockers should be avoided prior to alpha-blockade due to the possibility of unopposed alpha-adrenergic effects. This explains why our patient was unable to tolerate beta-blockers. Even patients with good pre-operative management may experience intra-operative hypertension due to physical stress on the tumor [8]. Postoperatively, patients can experience profound hypotension.

The *American College of Cardiology Expert Consensus on Takotsubo Syndrome* published in June 2018 indicated the possible connection with high-output catecholaminergic states such as a pheochromocytoma, but no recommendations are provided regarding the diagnostic approach [9]. We recommend obtaining plasma metanephrines when considering the diagnosis of a neuroendocrine tumor as the possible cause of reversible cardiomyopathy.

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Stress-induced cardiomyopathy is usually transient, and management is largely supportive. As in our case, the wall motion abnormalities and systolic dysfunction resolve with treatment of the underlying cause.

## Conclusions

Pheochromocytomas can present as recurrent sympathoexcitation-induced cardiomyopathy and can have a highly variable clinical presentation with a broad spectrum of signs and symptoms. Providers should consider an underlying catecholamine-producing tumor when presented with a patient with recurrent reversible cardiomyopathy. Beta-blocker intolerance can be an important clue to an underlying neuroendocrine tumor. Screening for an underlying neuroendocrine tumor with serum metanephrines should be considered in patients with reversible cardiomyopathy.

## Conflicts of interest

None.