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Pheochromocytoma Induced Coronary Vasospasm and Takotsubo Cardiomyopathy

Aleksan Khachatryan[1*], Ashot Batikyan[2], Justin Brilliant[3], Mukta C. Srivastava[4], Margarita Sargsyan[5], Hakob Harutyunyan[6], Vahagn Tamazyan[7] and Joel Alejandro[8]

[1]*Department of Internal Medicine, University of Maryland Medical Center, Midtown Campus, Baltimore, USA.*

[2]*Department of Internal Medicine, North Central Bronx Hospital, New York, USA.*

[3]*Department of Cardiovascular Medicine, University of Maryland Medical Center, Baltimore, USA.*

[4]*Department of Cardiovascular Medicine, University of Maryland Medical Center, Baltimore, USA.*

[5]*Department of Cardiology, "HERATSI" HOSPITAL COMPLEX № 1, Yerevan, Armenia.*

[6]*Department of Internal Medicine, Maimonides Medical Center, New York, USA.*

[7]*Department of Internal Medicine, Maimonides Medical Center, New York, USA.*

[8]*Department of Internal Medicine, University of Maryland Medical Center, Midtown Campus, Baltimore, USA.*

***Corresponding author**

Aleksan Khachatryan, MD.,
PGY III Resident,
University of Maryland Medical Center, Midtown Campus,
827 Linden Ave, suite 3B Baltimore,
MD 21201.

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Abstract

Takotsubo cardiomyopathy (TTC) is characterized by transient left ventricular systolic dysfunction and can have various physical and emotional triggers, including pheochromocytomas. Pheochromocytoma is a rare neuroendocrine tumor associated with hypertension, orthostatic hypotension, tachyarrhythmias, myocardial infarction, and cardiomyopathies. TTC is a recognized complication of pheochromocytoma and can be life-threatening in severe cases, sometimes requiring mechanical circulatory support. One of the proposed mechanisms for pheochromocytoma-induced TTC is coronary vasospasm. This review includes a clinical observation illustrating coronary vasospasm leading to TTC and cardiogenic shock in a patient with pheochromocytoma. We conducted an extensive literature search to identify all the cases of TTC attributed to pheochromocytoma-induced coronary vasospasm. This review aims to provide a comprehensive summary of the latest research, encompassing the pathophysiology, diagnostic findings, and treatment approaches for TTC in the context of pheochromocytoma.

Keywords: tako-tsubo cardiomyopathy (TTC), pheochromocytoma, pheochromocytoma crisis, coronary vasospasm, apical ballooning, catecholamine, cardiogenic shock, VA-ECMO, left ventricular outflow tract obstruction (LVOT), doxazosin

Introduction

Takotsubo cardiomyopathy (TTC) is characterized by transient left ventricular (LV) systolic dysfunction not related to obstructive coronary artery disease or myocarditis and is marked by ECG changes and elevated cardiac biomarkers [1]. The hallmark finding of TTC is apical ballooning, although diverse wall motion abnormality patterns may be observed. Approximately 70% of TTC cases have an identifiable trigger, including pheochromocytomas [1,2].

Pheochromocytomas are mostly benign, rare neuroendocrine tumors arising from the adrenal medulla or any location of the sympathetic ganglia, known as paragangliomas or extra-adrenal pheochromocytomas [3]. The cardiovascular manifestations of pheochromocytomas are mediated by excessive catecholamine production from any adrenal or extra-adrenal sources, precipitating hypertension (HTN), cardiac arrhythmias, myocardial infarction, and cardiomyopathy [4]. The three well-described cardiomyopathies associated with this condition include dilated cardiomyopathy, hypertrophic cardiomyopathy, and TTC [5,6]. Pheochromocytoma, along with physical and emotional stressors, is a well-recognized trigger for TTC [1,7].

Although the Mayo Clinic diagnostic criteria established in 2004 initially excluded pheochromocytoma as a specific cause of TTC, recent literature acknowledges pheochromocytoma as a cause of TTC [1,8].

There are several proposed mechanisms for pheochromocytoma -induced TTC(TTC-pheo), including direct toxicity and coronary vasospasm. In this review, we present an example of diffuse coronary vasospasm complicated by TTC and cardiogenic shock in the setting of pheochromocytoma crisis. We also conducted an extensive literature search to group all cases of TTC-pheo or TTC-like presentations attributed to pheochromocytoma-induced coronary vasospasm, visualized spontaneously on coronary angiography or during provocative testing. We searched articles published in PubMed, Google Scholar, and other sources until April 2024, using the search terms "pheochromocytoma and coronary vasospasm/vasoconstriction" and "coronary vasospasm, pheochromocytoma, and takotsubo cardiomyopathy." This review outlines the pathogenesis, diagnosis, and treatment approaches of TTC-pheo based on contemporary literature.

Review

Clinical Observation

A 25-year-old postpartum female with a history of HTN, recent diagnosis of pheochromocytoma, preeclampsia, and anxiety disorder presented with abdominal pain, chest pain, nausea, vomiting, and diaphoresis, all of which began on the day of presentation. The pheochromocytoma was diagnosed approximately six weeks prior. Her home medications included doxazosin, hydralazine, and nifedipine ER, though she was not taking doxazosin. There was no reported history of smoking, alcohol use, or drug abuse. Her peak troponin level was 89.6 ng/L (reference range <14 ng/L) and her NT-proBNP level was 7,550 pg/mL (reference range 20.0 - 95.0 pg/mL). The initial ECG was significant only for sinus tachycardia.

Transthoracic echocardiography (TTE) revealed severe biventricular systolic dysfunction involving the mid to apical segments, with hyperkinetic basal segments and an ejection fraction (EF) of 10-15%, consistent with stress cardiomyopathy as shown in Video 1 (View video here: https://www.youtube.com/watch?v=MdZUAKrs8EI; the upper two videos, captured from the parasternal long-axis view during the initial presentation, demonstrate hyperdynamic basal segments, while the bottom two videos, obtained during the VA-ECMO, shows akinetic mid to apical segments in the parasternal long-axis view {bottom left video} and the apical four-chamber view {bottom right video}).

Importantly, the stress cardiomyopathy pattern was also present in the right ventricle (RV) with moderately reduced systolic function (tricuspid annular plane systolic excursion (TAPSE) of 12 mm).

Despite initial treatment with phentolamine and labetalol for a presumed pheochromocytoma crisis, the course was complicated by multiorgan failure and cardiogenic shock necessitating the initiation of venoarterial extracorporeal membrane oxygenation (VA-ECMO) and intubation for worsening hypoxic respiratory failure. Shortly after the initiation of VA-ECMO, the repeat ECG demonstrated pronounced ST segment elevations in the inferior and anterolateral precordial leads as illustrated in Figure 1.

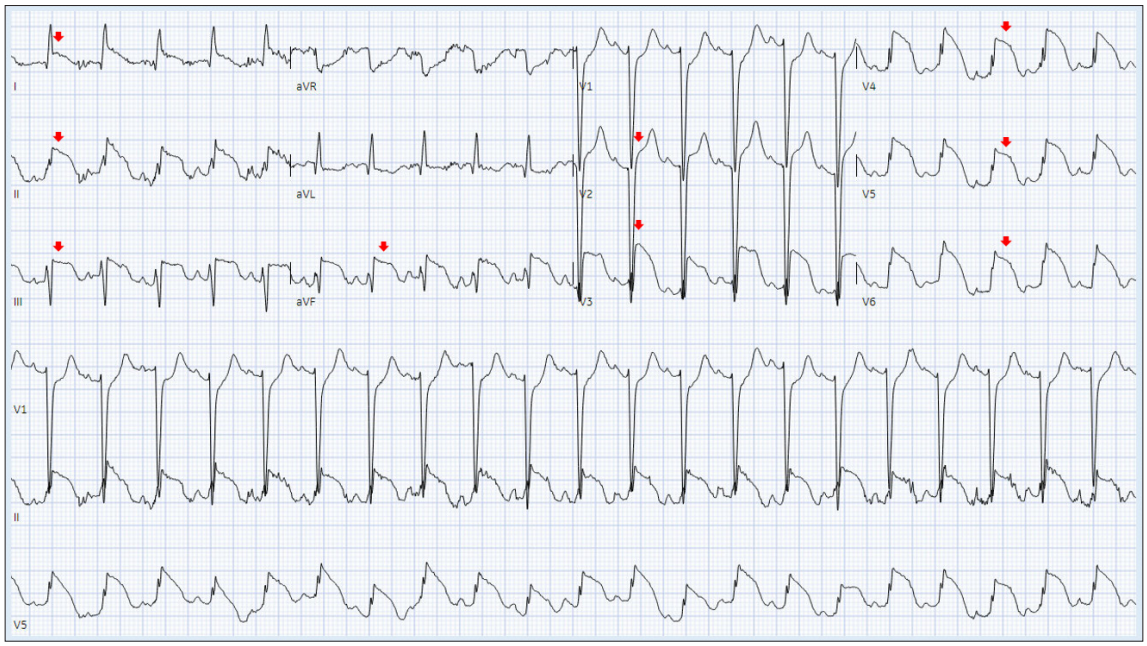

Figure 1: ECG depicting ST elevations
The red arrows indicate ST segment elevations in leads I, II, III, aVF, and V2-V5.

The patient subsequently underwent left heart catheterization (LHC), which revealed diffuse coronary vasospasm without a culprit coronary lesion. The vasospasm resolved after intracoronary nitroglycerin administration (Figure 2).

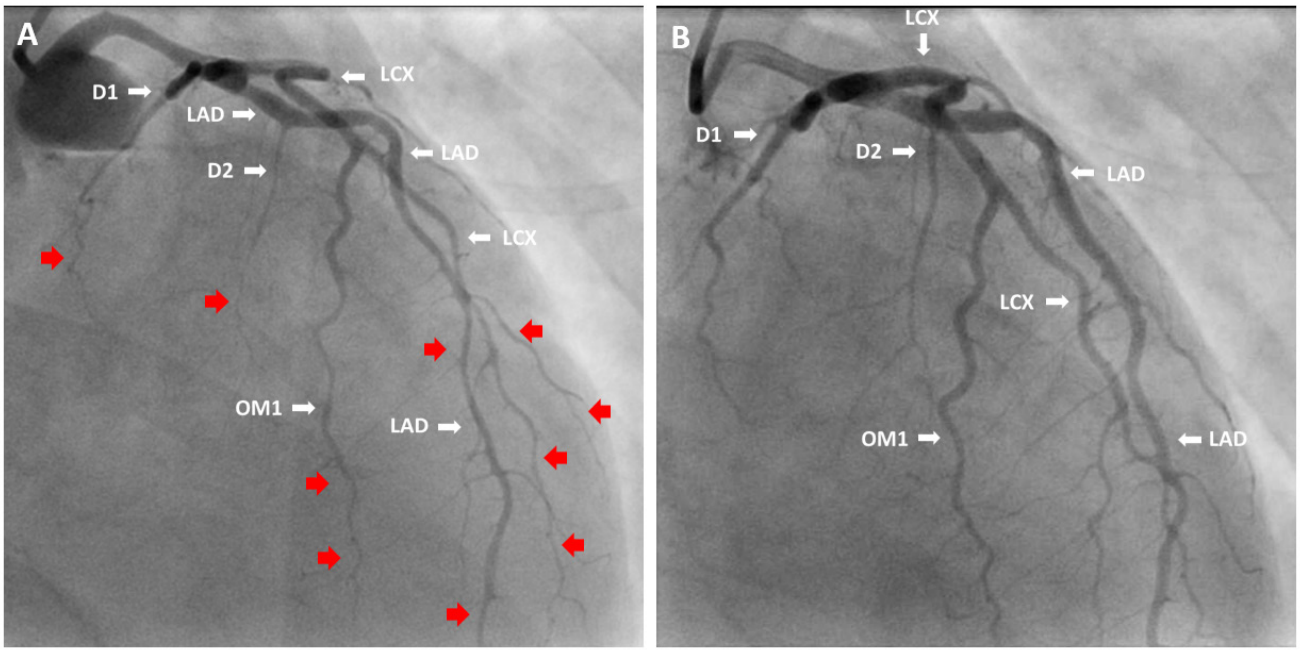

Figure 2: Left heart catheterization revealing diffuse coronary spasm
A) RAO cranial view shows diffuse coronary spasm involving LAD, D1, D2, LCX, and OM1 arteries as indicated by red arrows. B) The severe, diffuse coronary vasospasm improves after intracoronary nitroglycerin administration.
RAO: right anterior oblique; LAD: left anterior descending artery; D1: diagonal 1; D2: diagonal 2; LCX: left circumflex artery; OM1: obtuse marginal 1

Management with doxazosin and nicardipine resulted in improved EF and successful decannulation from VA-ECMO after five days. A repeat TTE demonstrated normal biventricular systolic function. The patient later underwent a successful laparoscopic right adrenalectomy, with pathological confirmation of pheochromocytoma. Her symptoms improved dramatically post-surgery, and she was switched to monotherapy with metoprolol succinate. Interestingly, the genetic workup revealed Von Hippel-Lindau syndrome (VHL).

Discussion

Based on the systolic dysfunction pattern involving the mid and apical segments, elevated cardiac biomarkers, ST elevations on the ECG, and findings from LHC revealing diffuse coronary spasm, a diagnosis of TTC secondary to coronary vasospasm associated with a pheochromocytoma crisis was established. It is important to note that peripartum cardiomyopathy was also considered in the differential diagnosis, given that the patient was two months postpartum. However, the presence of pheochromocytoma, the detection of diffuse coronary spasm, rapid improvement with nitroglycerin, nicardipine, and alpha-antagonist therapy, and the resolution of HTN and other symptoms following adrenalectomy strongly supported the diagnosis of TTC-pheo. Additionally, the workup confirmed the presence of VHL syndrome. This case also illustrates that severe coronary vasospasm can be effectively managed with intracoronary nitroglycerin administration in the catheterization laboratory, followed by nicardipine and alpha antagonist therapy to prevent recurrent, diffuse coronary vasospasm in patients with pheochromocytoma.

As a result of our literature search, we identified three cases of TTC secondary to coronary vasospasm attributed to pheochromocytoma [9-11]. Notably, the number of identified cases was limited due to stringent selection criteria, which required the detection of vasospasms during coronary angiography or with provocative measures. Cases presumed to be due to coronary vasospasm without objective evidence were excluded from consideration. The clinical characteristics of the identified cases are summarized in Table 1.

Author	Bhasin D et al. [9]	Sato K et al. [10]	Jarasunas J et al. [11]	Our Case
Year	2021	2020	2013	2024
Journal	Circulation	European Heart Journal	Lithuanian Surgery	JMC Case Reports
Age	25	44	42	25
Sex	F	F	M	F
Type of tumor	Left adrenal pheo	Right adrenal pheo, normetanephrine	Right adrenal pheo	Right adrenal pheo, normetanephrine
Presenting symptom	Chest pain	Chest pain, dyspnea	Chest pain, dyspnea, nausea	Chest pain, abdominal pain, N/V
ECG changes	ST elevation in all leads except for aVF	---	ST elevation in leads III, aVF	ST elevations in V2-V6, I, II, III, aVF
LVEF	<30%	---	<20%	<15%
TTC pattern	Apical	Apical, basal, global	Apical	Apical (biventricular)
Vasospasm	POA	Acetylcholine provocation	POA	POA
Coronary angiography results	No CAD	No CAD	No CAD	No CAD
Complications	---	Pulmonary edema	Pulmonary edema,	Pulmonary edema, AKI, liver injury,
Cardiogenic shock	---	---	Cardiogenic shock,	Cardiogenic shock
Treatment	Left adrenalectomy	Right adrenalectomy	IABP, Inotropes, adrenalectomy	VA-ECMO, adrenalectomy
Outcome	Complete resolution of ECG and LV function	Resolution of the symptoms	Partial recovery of LV function to mid-range	Complete recovery

Table 1: Characteristics of identified cases

Pheo: pheochromocytoma; POA: present on admission; CAD: coronary artery disease; IABP: intra-aortic balloon pump; VA-ECMO: venoarterial extracorporeal membrane oxygenation; AKI: acute kidney injury

The majority of cases involve female patients, with chest pain being the most common presenting symptom. The vasospasm in identified cases is predominantly described in younger individuals compared to the general TTC population, where it is observed in the 60s. The most frequent TTC pattern is apical ballooning, observed in all cases, supporting the theory that coronary vasospasm was the most likely underlying mechanism. In coronary vasospasm, the blood supply is more likely to be compromised in the distal apical segments of the myocardium, leading to the development of apical ballooning. In the case reported by Sato et al., diverse TTC patterns were observed during different hospitalizations. The ST elevation pattern described by Bhasin et al. had a distribution similar to that of our case. However, among all the cases, ours is the only one that required VA-ECMO due to severe, multi-vessel coronary vasospasm, which led to significant biventricular dysfunction.

History and Epidemiology

Catecholamine-induced cardiomyopathy is a rare and life-threatening complication of pheochromocytoma. TTC was identified in the early 1990s by Japanese researchers as reversible stress-induced cardiomyopathy, initially referred to as TTC, and later as an apical ballooning syndrome and broken heart syndrome [12,13]. The first case of TTC-pheo was reported in 1989 by Iga and colleagues [14]. In a retrospective study conducted by Giavarini, only 11% of patients with pheochromocytoma or paraganglioma developed catecholamine-induced cardiomyopathy, which includes three common types: TTC, dilated cardiomyopathy, and hypertrophic cardiomyopathy [6,15]. In another review, it is reported that TTC-like cardiomyopathy is observed in around 3% of catecholamine-secreting tumors [16]. Approximately 1-2% of patients presenting with a primary diagnosis of acute coronary syndrome or myocardial infarction were found to have TTC [17]. TTC most commonly affects women (~90%) in the sixth decade of life, although it can occur in any age group [18]. It has been shown that TTC-pheo patients are, on average, 19.87 years younger than the general TTC population, with a predominance of female patients [19,20]. Unlike other causes of TTC, TTC-pheo is less commonly associated with triggering stressors [21].

Although previous diagnostic criteria for TTC excluded cases of pheochromocytoma, the contemporary International Expert Consensus Document on Takotsubo Syndrome recognizes pheochromocytoma as a known trigger for TTC [1,17].

Pathophysiology

Despite multiple postulated hypotheses, there is no conclusive explanation for the mechanisms of TTC. Catecholamines play a central role in the pathophysiology of TTC, as it is frequently

triggered by sudden unexpected stress, major trauma, or physical illness, including pheochromocytoma. This has been supported by several pieces of evidence. It has been shown that the plasma catecholamine levels in patients with TTC are up to three times higher compared to those presenting with acute myocardial infarction and post-infarction heart failure [22]. Notably, some data indicate that iatrogenically administered catecholamines (epinephrine, dobutamine) can directly trigger TTC [23]. Moreover, the administration of high catecholamine doses in preclinical models can reproduce TTC features, such as reversible apical and midventricular, and in some experiments, a basal or inverted pattern of hypokinesis [24-27]. Intracranial processes, such as subarachnoid hemorrhages, are well-known triggers for TTC, supporting the role of increased circulating catecholamines in its pathogenesis. Finally, multiple cases of TTC have been reported attributed to underlying catecholamine-secreting tumors [16,19].

In pheochromocytoma, the excessive release of catecholamines can lead to overexcitation of catecholamine receptors, increasing inotropic and chronotropic activities in the heart and resulting in a supply-demand mismatch [6]. Catecholamines may be directly involved in various pathological processes such as cardiomyocyte dysfunction, arrhythmias, irreversible cellular injury via calcium overload, production of reactive oxidative species, and mitochondrial dysfunction [28]. Epinephrine at low to medium levels exerts positive inotropic effects through β1 and β2 adrenoreceptors; however, at high levels, it has a negative inotropic effect, which may play a role in TTC-pheo. The highest density of β1 and β2 adrenoreceptors is found at the apex compared to the basal segments, potentially explaining the apical involvement in TTC-pheo caused by high levels of circulating catecholamines [29]. Sympathetic overactivation is associated with an interstitial mononuclear inflammatory response and may cause contraction band necrosis, a hallmark of catecholamine toxicity [22].

Another possible mechanism involved in TTC could be acute transient myocardial ischemia due to coronary vasospasm, particularly in pheochromocytoma, which may precipitate a massive surge of catecholamines into the systemic circulation [22,30]. In their original report, Dote et al. hypothesized that TTC was caused by multivessel coronary vasospasm, as 4 of 5 patients in their series had spontaneous or inducible coronary vasospasm found on coronary angiography [31]. Several other studies have highlighted the importance of coronary vasospasm in patients with TTC [32,33]. In one prospective study, acetylcholine caused severe coronary vasospasm associated with echocardiographic evidence of transient LV systolic dysfunction, supporting the multivessel spasm theory as a mechanism of TTC [34].

Coronary vasospasm was possibly the underlying cause of TTC both in our case and in other cases we identified. The involvement of apical segments in all cases supports the contribution of vasospasm to TTC development, given the higher degree of compromised distal coronary circulation supplying the mid to apical segments of the myocardium during coronary vasospasm. It should be noted that not all patients with TTC-pheo demonstrate evidence of epicardial vasospasm, even with the use of provocative tests. Since vasospasm is not a lasting condition, it is challenging to determine whether the absence of vasospasm at the time of coronary angiography reliably excludes the possibility of prior vasospasm. However, theoretically, coronary vasospasm is less likely to be the underlying mechanism for the basal pattern of TTC.

In addition to epicardial vasospasm, coronary microvascular dysfunction could play a role in TTC, as several studies have demonstrated abnormal coronary microvascular responses using both non-invasive and invasive diagnostic tools [35-39]. Conversely, there is clinical and experimental evidence against the "microcirculatory hypothesis." Christensen et al. have shown in their positron-emission tomography perfusion study that the primary abnormality in TTC is hyperperfusion in the basal segments and normal perfusion in the apical akinetic segments [40]. Another postulated mechanism of TTC involves the direct effect of elevated endothelin-1, a potent vasoconstrictor, inducing microvascular spasm [41].

Clinical Presentation

In a cohort of 80 TTC-pheo cases, the most common presenting symptom was chest pain, followed by abdominal pain, dyspnea, headache, palpitations, cough, and dizziness. Approximately two-thirds of the patients developed complications, with the most common being heart failure, pulmonary edema, cardiogenic shock, and respiratory failure. Mechanical ventilation was required in 21% of cases, and extracorporeal life support (ECLS) treatment in 18% of cases [19]. Notably, patients may develop symptoms of heart failure, cardiogenic shock, arrhythmias, and even sudden cardiac death.

Diagnosis

Several clinical manifestations, such as chest pain, abdominal pain, and dyspnea, combined with symptoms indicative of catecholamine excess including pallor, profuse sweating, tremulousness, palpitations, labile blood pressure, and headache should alert clinicians to the possibility of pheochromocytoma as the underlying cause of TTC. It is important to note that the diagnostic workup for pheochromocytoma includes the measurement of urine and plasma fractionated metanephrines and catecholamines, followed by imaging studies to localize the hormonally active tumor [42,43].

In TTC, troponin levels are typically elevated, although peak values are lower than in ST-segment elevation myocardial infarction (STEMI). Conversely, BNP and NT-proBNP levels are significantly higher than in myocardial infarction cases. Common ECG abnormalities in TTC include ST-segment elevation, T wave inversions, left bundle branch block, and QT prolongation [44]. In a review article, almost all the cases exhibited ST/T wave abnormalities and elevated cardiac biomarkers, while the coronary angiography results were unremarkable [19].

TTE is crucial for evaluating LV wall motion abnormalities and detecting complications such as left ventricular outflow tract obstruction (LVOTO) and intraventricular thrombi [45,46]. Coronary angiography is highly supportive of TTC diagnosis, revealing normal or nonobstructive coronary findings. Left ventriculography typically confirms TTC by showing the characteristic ballooning of the ventricle [1].

TTC can be categorized into four major types based on regional wall motion abnormality pattern: apical ballooning (typical, occurring in 81.7% of cases), mid-ventricular, basal, and focal. Other variants include biventricular (apical type and RV involvement), isolated RV, and global [1,20]. The basal subtype is common in TTC-pheo, occurring in 30% of cases, although both in our case and in the cases we identified, the apical pattern was prevailing probably due to coronary vasospasm [19]. Cardiac magnetic resonance imaging is essential in demonstrating intense myocardial edema, differentiating TTC from myocardial infarction or myocarditis in challenging cases [47].

Treatment

Given the transient nature of TTC-pheo, treatment is primarily supportive during the acute phase of the disease [4]. Timely diagnosis of pheochromocytomas and initiation of targeted therapy, followed by surgical resection once clinically stable, is essential. Management of TTC-pheo involves stabilizing blood pressure using α-adrenoceptor antagonists, followed by β-adrenoceptor antagonists to prevent unopposed α-adrenergic action, which may precipitate a hypertensive crisis [48].

In acute decompensated heart failure precipitated by TTC-pheo, intravenous boluses of phentolamine are preferred over phenoxybenzamine due to phentolamine's rapid onset of action and short half-life, which ensures that any adverse effects, such as hypotension, are short-lasting. Once cardiovascular stability is achieved following the initiation of phentolamine bolus, phenoxybenzamine or other selective alpha antagonists can be introduced, with dosage up-titration in the subsequent days to reach the target blood pressure [49,6].

When the course is complicated by cardiogenic shock, it is crucial to distinguish between primary pump failure and LVOTO, as they require different treatments. Beta-blockers are recommended for LVOTO but should only be administered after achieving adequate alpha blockade. However, beta-blockers are not appropriate for primary pump failure. In both LVOTO and pump failure, cautious fluid administration may be appropriate, provided there is no pulmonary congestion. Inotropic support (adrenalin, noradrenalin, dobutamine) is contraindicated for both types of cardiogenic shock particularly due to the adrenergic nature of the complication. Specifically, in LVOTO, inotropes can exacerbate the systolic anterior motion of the anterior mitral valve [50]. Recent studies suggest that levosimendan, a calcium sensitizer, might be safe in these situations [51,52]. In severe cases, extracorporeal membrane oxygenation (ECMO), left ventricular assist devices and intra-aortic balloon pumps can be used as a bridge to recovery [53,19]. Hekimian et al. reported that pheochromocytoma-induced cardiogenic shock requiring mechanical support, predominantly ECMO, has a mortality rate of 7% [54].

When treating heart failure in the context of pheochromocytoma, the beta-blockers should be used either after the tumor resection or following the initiation of alpha blockade before resection [6,48]. Angiotensin-converting enzyme inhibitors are also recommended since their use has been shown to accelerate recovery [55].

According to Shams et al., among six patients with TTC-pheo complicated by thromboembolism, five had an apical pattern of TTC [19]. An interesting study demonstrated that elevated troponin I levels (>10 ng/mL) and apical ballooning were strongly associated with the occurrence of left ventricular thrombus (LVT), underscoring the importance of prophylactic anticoagulation in such cases [46]. Oral anticoagulants for three months should be considered when cardiac troponin I levels exceed 10 ng/mL in high-risk patients with apical ballooning to prevent LVT formation. In contrast, for other patients (those with midventricular and/or basal ballooning and troponin I levels <10 ng/mL), routine oral anticoagulation is not recommended due to the relatively low incidence of LVT formation [46]. Generally, patients with documented LVT, thromboembolic complications, or extensive mid-apical ballooning may require therapeutic anticoagulation for two to three months [56].

The definitive treatment for pheochromocytoma is surgical resection. Traditionally, nonselective alpha antagonists, such as intravenous phentolamine (a reversible nonselective alpha antagonist) and phenoxybenzamine (an irreversible nonselective alpha antagonist), have been used to prepare patients for surgery. However, the use of nonselective alpha antagonists has been associated with several adverse effects, including orthostatic hypotension, reflex tachycardia, nasal congestion, dizziness, and syncope. Due to these adverse effects, selective alpha 1-antagonists, such as doxazosin, are preferred because they have a more favorable side effect profile and a shorter half-life [57,58]. It is crucial to up-titrate alpha-antagonists to achieve the maximally tolerated doses to prevent perioperative complications [48]. Preoperative blood pressure and heart rate targets are generally based on observational studies, and there is no consensus on the optimal values. One source recommends achieving a preoperative blood pressure of 130/80 mm Hg or less while sitting and about 100 mm Hg systolic while standing (not less than 80/45 mm Hg), with a target heart rate of about 60-70 bpm when sitting and 70-80 bpm when standing [59]. At least 1-2 weeks of alpha blockade is recommended before surgery, although it may take up to six weeks to achieve the desired level of blockade [48]. Minimally invasive surgery is recommended in most cases, although open resection is preferred for large (>6 cm) or invasive pheochromocytomas [48]. Improvement of myocardial dysfunction can vary, ranging from 1-2 weeks to several months [60].

To the best of our knowledge, the scenario we presented is the first reported case of postpartum TTC-pheo with biventricular involvement secondary to diffuse coronary spasm. RV involvement in TTC is relatively common, occurring in up to 34% of cases [61]. However, there are only a few documented cases of TTC-pheo with biventricular compromise. RV involvement in TTC is typically associated with early clinical deterioration and an increased risk of complications, necessitating aggressive management [62,63].

Conclusions

The pheochromocytoma crisis is a life-threatening condition that can progress to cardiogenic shock due to TTC, often necessitating mechanical circulatory support. The underlying mechanisms of TTC remain unclear. Coronary vasospasm is a potential cause of TTC-pheo, although not all patients exhibit documented vasospasm on angiograms. It is important to note that vasospasm is transient and its absence during coronary angiography does not entirely rule out its occurrence. Conversely, coronary vasospasm in isolation is not explanatory for the basal type of TTC indicating that no single pathophysiological mechanism can elucidate all TTC patterns. Prompt recognition and management of TTC-pheo is crucial and can be life-saving. The management is complex due to the lack of well-validated resources. Prioritizing the use of alpha antagonists is essential, as they can prevent further complications, contribute to the reversal of the condition, and prepare for tumor resection. Cardiogenic shock in this context requires careful assessment of the underlying mechanism, as treatment approaches differ for LVOT and pump failure. Inotropic agents are generally contraindicated in both scenarios, making the timely initiation of mechanical circulatory support imperative.

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