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Pheochromocytoma-induced takotsubo syndrome: what does an intensivist need to know?

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Dear Editor,

Takotsubo syndrome (TTS) is a specific form of transient myocardial dysfunction primarily associated with sudden adrenergic discharge [1–5]. In particular, pheochromocytoma might arise as a subtle trigger of TTS, potentially leading to a variety of unfavorable outcomes [1–5]. These unfavorable outcomes have been associated with more severe degrees of adrenergic discharge as well as delayed diagnosis of pheochromocytoma in this context [2, 3]. The recent article by Odierna *et al*. [1] describes a case of pheochromocytoma-induced TTS complicated by persistent hemodynamic compromise in a relatively young female patient. Based on this report [1], I would like to highlight certain aspects of pheochromocytoma-induced TTS, particularly in the intensive care setting.

First, certain diagnostic clues in the context of a TTS presentation should raise the possibility of an existing pheochromocytoma, and mandate further investigation [2, 3, 6]. These clues include certain demographic features including young age, male gender and admission characteristics including the presence of an atypical TTS pattern (midventricular, inverted, etc.), severe hypertension and hemodynamic compromise along with a history indicative of pheochromocytoma (tachycardia bouts, headache, etc.) and absence of an overt TTS trigger [1–6] (most of which conform to the features of the reported patient [1]). However, the authors seemed to coincidentally detect the adrenal mass on computed tomography (CT) [1]. In TTS cases highly suggestive of having a pheochromocytoma, specifically focusing on adrenal glands with ultrasonographic (USG) examination might be harnessed as a routine initial strategy [4] particularly where emergency CT is unavailable. However, the absence of an adrenal mass might not safely rule out a highly likely pheochromocytoma [1], potentially warranting further imaging of non-adrenal locations (with e.g., nuclear imaging).

Second, intensive care clinicians should be particularly alert to potential complications including malignant arrhythmias and mechanical complications including acute left ventricular outflow tract (LVOT) obstruction [2–6] in patients with a suspected pheochromocytoma-induced TTS. These complications are mostly attributable to more pronounced adrenergic discharge in these patients [2–6] (compared with those suffering from a classical emotionally triggered TTS). Moreover, extreme adrenergic discharge in this context might also lead to acute coronary microvascular dysfunction generally emerging in the form of a coronary slow pattern (CSF) on coronary angiogram [2, 3]. Therefore, TTS cases with a CSF pattern might be particularly prone to coronary ischemic complications, and hence should receive intensive anti-ischemic therapy as part of their intensive care management [7]. I wonder about the presence of a CSF pattern and emerging LVOT gradient in the patient.

Notably, as the patient had only modest involvement of the myocardium, her hemodynamic collapse might

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be potentially associated with a new-onset LVOT obstruction [1]. LVOT obstruction in this context is dynamic in nature, and is potentially augmented by LVOT hypercontractility, hypovolemia and reductions in systemic arterial resistance [2, 5]. Importantly, inotropic support (noradrenaline, levosimendan, etc.) further augments even a trivial degree of LVOT gradient associated with TTS, and hence should be avoided in this context [2, 5]. Mechanical support devices such as a temporary left ventricular assist device (LVAD) (except for intraaortic balloon counterpulsation) might be the only therapeutic option in the setting of a severe LVOT gradient that is refractory to fluid loading and alpha-adrenergic agonists (phenylephrine) [5]. Interestingly, doxazosin (an α1 receptor blocker also used in the patient [1]) used for the management of a potential pheochromocytoma might also trigger or further augment the LVOT gradient (if any) in the setting of TTS [1]. Therefore, serial evaluation of LVOT velocity in echocardiography seems to be necessary in patients with a pheochromocytoma-induced TTS to whom alpha receptor blockers are initiated. In those cases complicated by an LVOT obstruction, cessation (or deferral) of alpha receptor blocker use until the complete recovery of TTS seems a plausible strategy in the preoperative setting of pheochromocytoma.

Third, intensive care clinicians should particularly avoid adrenergic substances as part of inotropic support in the setting of TTS (even in the absence of an LVOT gradient), largely due to their adverse effects on the stunned myocardium (leading to prolonged recovery, etc.) [2, 5]. In this context, levosimendan (a non-adrenergic inodilator agent) along with mechanical support was previously suggested as an efficient option in the setting of hemodynamic collapse due to TTS after exclusion of an emerging LVOT gradient [2, 5, 8]. Interestingly, the detrimental impact of adrenergic substances might be even more substantial in patients with a pheochromocytoma-induced TTS [2]. Therefore, I wonder why the authors tried to combat hemodynamic compromise with adrenergic substances including noradrenaline and dobutamine in their patient [1]. On the other hand, excessive fluid loading (crystalloids, etc.) without supporting cardiac pumping might only temporarily improve blood pressure values usually at the cost of worsening pulmonary edema, and hence should also be avoided.

Fourth, intensive care clinicians should also be familiar with another pheochromocytoma-related condition, namely 'catecholamine-induced myocarditis' (chemical myocarditis) [2, 3, 9]. In patients with pheochromocytoma, this phenomenon might mimic TTS, and might even co-exist with TTS in certain settings [2, 3]. As expected, an existing myocarditis in this context is more likely to be associated with complications including hemodynamic compromise (due to more extensive involvement) along with a substantial troponin rise and incomplete myocardial recovery (as might be detected with magnetic resonance imaging) [2, 3].

Finally, morphological patterns might rapidly alternate in the setting of pheochromocytoma-induced TTS [2, 3, 6]. For instance, a midventricular TTS variant might transform into a global or apical variant within just a day in this context [3, 6]. This form of rapidly alternating TTS pattern is known as 'fast wandering TTS' [2, 10], and is more likely to be encountered in patients with pheochromocytoma [2, 6]. This may warrant frequent evaluation of wall motion abnormalities in echocardiography in patients with a suspected pheochromocytoma-induced TTS in an effort to timely detect and manage new-onset pathologies (including LVOT obstruction and acute mitral regurgitation, etc.) [2, 5]. I also wonder about the frequency of echocardiographic evaluation in the patient [1].

In conclusion, the article by Odierna *et al.* [1] presents a variety of important didactic points in the setting of pheochromocytoma-induced TTS. In particular, intensivists should be familiar with important aspects and potential implications of pheochromocytoma-induced TTS for the establishment of proper diagnostic and therapeutic strategies.

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