

An Unusual Case of Takotsubo Cardiomyopathy in Pheochromocytoma

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Afana and colleagues¹ have presented a case that illustrates the complex interaction between transient takotsubo cardiomyopathy (TC) and pheochromocytoma, which merits discussion.

Some authors have accepted the idea that catecholamine surges are the biochemical cause of TC.² However, others view this explanation as simplistic and have suggested additional considerations, as follows.

1) Frequently, patients presenting with TC complicated by hypotension have been empirically treated with those hormones, usually effectively. In addition, among the many patients who have no tachycardia or hypertension but have TC, very few typically undergo studies of catecholamine blood levels, meaning that this testing is not considered to be clinically useful or revealing.

2) Experimental findings in animal models^{3,4} have *not* shown that catecholamines cause typical TC manifestations. However, these hormones can precipitate TC, most likely in the presence of predisposing conditions.⁴ Thus far, TC has been reproduced in human beings only by means of acetylcholine testing.⁵ Early after a patient presents with TC, an acetylcholine challenge frequently evokes echocardiographic TC recurrence, chest pain, and diffuse coronary spasm, all of which can be rapidly and consistently resolved by infusing intracoronary nitroglycerin.⁶ This response is absolutely specific—that is, an acetylcholine challenge provokes a response only in individuals with a history of TC. This observation suggests that acetylcholine is an effective marker of a predisposition to TC (usually called endothelial dysfunction) and may actually be a mediator of clinical occurrences when locally secreted by nerve endings in otherwise normal hearts.

3) In a large clinical series of patients with pheochromocytoma or paraganglioma,⁷ TC was diagnosed in only about 2.6% of patients, and TC in pheochromocytoma typically presented only after several years of severe hypertensive episodes caused by the pheochromocytoma. This suggests that a spontaneous increase in catecholamine levels is not sufficient by itself to induce TC. Endothelial dysfunction may be the underlying requirement.

4) Independent of pheochromocytoma surgical excision, all forms of TC usually resolve spontaneously, and most do not recur, even in the presence of persistent catecholamine elevation. The observed “vaccination effect” from one TC episode is currently unexplainable. Consistent with this, Afana and colleagues¹ reported no TC in their patient before her sole episode or during her month of recovery before pheochromocytoma excision.

5) In an in-depth review in 2016, Y-Hassan⁸ compared 80 patients with pheochromocytoma-associated TC with 1,750 cases of all patients with TC and found that the former occurs at younger ages (median age, 46 vs 66 yr), more often in men than does TC alone (30% vs 10%), and more often in the basal left ventricle (LV) than in the LV apex (50% vs 2%). In addition, TC in pheochromocytoma was more often associated with tachycardia (mean heart rate, 115 vs 87 beats/min), shock and congestive heart failure (50% vs 2%), and recurrence (18% vs 3%). Because these data were obtained from multiyear databases with different protocols in different hospitals, many potentially relevant variables were unavailable, such as prior LV function and late-recovery

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status, catecholamine levels upon presentation, and time of tumor removal. Nevertheless, the distinctly different presentations of TC indicate specific baseline changes that can be secondary to a chronic hypercatecholamine state.

6) In a systematic review of the literature, Batisse-Lignier and colleagues⁹ analyzed LV dysfunction associated with pheochromocytoma in a comparison of patients with and without TC. They suggested that congestive heart failure or cardiomyopathy without coronary artery disease can present chronically (assumed to be due to high catecholamine levels from pheochromocytoma) or acutely (probably due to TC). Notably, of 135 patients, 36% of pheochromocytoma carriers had chronic cardiomyopathy and 7% had acute cardiomyopathy. Chronic cardiomyopathy resolved after medical therapy alone in 50% of those patients and in 82% of patients who also underwent tumor removal⁹; conversely, pheochromocytoma-induced TC almost always resolved rapidly even without tumor removal, as in Afana and colleagues' patient.¹

In most patients, with or without pheochromocytoma, transient endothelial dysfunction probably causes TC. The nebulous underlying mechanism can hardly be assumed to be neurogenic and related to some hypothetical neurologic dysfunction that would also be expected to affect the heart so transiently. In nature, acetylcholine is a local effector of the parasympathetic system. The predisposing factor for TC in pheochromocytoma—sometimes a high catecholamine blood level—is active before and especially during tumor removal, and the risk of TC recurrence will be high if acetylcholine test results are positive. Accordingly, acetylcholine testing after a TC episode is important

in cases like that of Afana and colleagues.¹ Details are available on how to perform acetylcholine tests safely.⁴⁻⁶

The above considerations indicate that much about TC remains to be clarified beyond the simplest explanations of its precipitating causes, especially in association with pheochromocytoma.

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