JACC: CASE REPORTS VOL. 1, NO. 2, 2019

EDITORIAL COMMENT

Takotsubo Cardiomyopathy With Pheochromocytoma

When an Imitator Meets a Masquerader*

Vikram Agarwal, MD, MPH

Takotsubo cardiomyopathy (TTC) is a clinical syndrome that closely mimics acute coronary syndrome (ACS) and presents with chest pain and dyspnea, dynamic ST/T changes, elevated myocardial necrosis biomarkers, and regional left ventricular wall motion abnormalities, without significant coronary artery disease (CAD). Because TTC is a great imitator of ACS, these patients are often misdiagnosed and treated as ACS. In fact, it is estimated that TTC accounts for 1% to 3% of all patients presenting with suspected ST-segment elevation myocardial infarction (1). However, the defining hallmark of TTC is the functional recovery occurring within weeks of initial presentation.

Pheochromocytoma, also known as the "great masquerader" is a rare, catecholamine-secreting neuroendocrine tumor. It gets its reputation as a masquerader because of its highly variable clinical presentation, including paroxysms of hypertension, with headache, sweating, anxiety, or palpitations. Because pheochromocytomas secrete excess catecholamines, often episodically, they can have both, an acute presentation with severe cardiomyopathy, and subtle chronic myocarditis with global left ventricular dysfunction (2).

In this issue of *JACC: Case Reports,* Kiamanesh et al. (3) present the case of a 45-year-old woman, who rapidly developed cardiogenic shock, after initial complaints of chest pain and headache. Her work up revealed hyperdynamic left ventricular apex, with basal- and mid-ventricular hypokinesis, without significant CAD. Her clinical course was complicated by labile blood pressures with hemodynamic instability, which required mechanical support with veno-arterial extracorporeal membrane oxygenation. Although initially suspected to have fulminant myocarditis, she was subsequently diagnosed with TTC and associated pheochromocytoma (TTC-pheo). After hemodynamic stabilization, and 2 weeks of therapy with α-blockers, she underwent successful adrenalectomy, with good intermediate outcome at 2 months.

SEE PAGE 85

This case by Kiamanesh et al. (3) illustrate the challenges and pitfalls faced in the appropriate diagnosis and management of TTC-pheo patients. It is now generally accepted that TTC is a distinct cardiomyopathy that is precipitated by a state of catecholaminergic excess, and may be triggered by a variety of stressors. Despite markedly similar clinical features, there has been endless debate regarding whether TTC-pheo should be considered as a separate clinical entity from TTC without underlying pheochromocytoma. While the pros and cons of this debate are beyond the current purview, the recently released InterTAK (International Takotsubo Registry) Diagnostic Criteria no longer considers the presence of pheochromocytoma as an exclusion criteria for the diagnosis of TTC (1).

Although the overall prognosis of patients with TTC is generally considered good (4), it is important to note that the complication rates are markedly higher in TTC-pheo patients. Almost two-thirds of TTC-pheo patients develop cardiac complications as compared to only one-fifth of patients without

*Editorials published in *JACC: Case Reports* reflect the views of the authors and do not necessarily represent the views of *JACC: Case Reports* or the American College of Cardiology.

From St. Luke's Heart and Vascular Institute, Chesterfield, Missouri. Dr. Agarwal has reported that he has no relationships relevant to the contents of this paper to disclose.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2019.07.004

pheochromocytoma (5,6). Given its profound impact on management, pheochromocytoma should be systematically considered in TTC patients and/or unexplained cardiogenic shock. Although a high index of suspicion is needed, as highlighted in this case, due consideration to certain clinical features can often point us in the right direction.

At initial presentation, it is important to distinguish TTC from underlying ACS. Despite regional wall motion abnormalities in both entities, it is important to correlate these abnormalities with CAD severity. TTC may also occasionally present with high-grade CAD, but the degree and extent of myocardial dysfunction is markedly out of proportion to the underlying CAD. In TTC, although there is a modest rise of cardiac necrosis biomarkers, there is discordant elevation of serum B-type natriuretic peptide and/or N-terminal B-type natriuretic peptide levels, which is commensurate with the degree of myocardial dysfunction. Also, the regional wall motion abnormalities of TTC do not follow the typical distribution of an epicardial coronary artery and are often noted in a circumferential pattern.

Although, the diagnosis of pheochromocytoma is often chanced upon after the incidental finding of an adrenal mass on an imaging study, certain clinical clues in TTC-pheo patients can alert us toward the presence of an undiagnosed pheochromocytoma. As opposed to TTC patients without pheochromocytoma, TTC-pheo patients are relatively younger age, presenting in the fourth or fifth decade of life. Underlying precipitating factors are often not identified in TTC-pheo patients. Classical clinical features of pheochromocytoma, including hypertension, headache, palpitations, and diaphoresis, are often masked by the acute cardiac presentation. Although TTC by itself can have a highly dynamic and variable clinical course given the marked variability in myocardial involvement, labile blood pressures during the early stages of presentation in the absence of significant mechanical complications should alert the clinician to the presence of pheochromocytoma.

Cardiac imaging, including echocardiogram, play a key role in management. Echocardiography not only helps identify the pattern and extent of TTC, but it also helps assess mechanical complications, including dynamic left ventricular outflow tract obstruction (LVOTO), with or without systolic anterior motion of the mitral leaflets, and/or functional mitral valve regurgitation. Whereas the apical ballooning pattern, with dyskinetic apex and hyperdynamic basal- and mid-ventricular segments is the most common form of TTC (80%), among patients with catecholaminergic excess, including pheochromocytoma, there is a disproportionately high percentage of "inverted Takotsubo" presentation with apical hyperkinesis associated with basal- to mid-ventricular hypokinesis (30% vs. 2.2%). Right ventricle, which may be involved in up to one-fourth of TTC patients should also be closely assessed. Hence, it is crucial to not rely solely on left ventriculogram for myocardial function assessment. When the diagnosis is uncertain, cardiac magnetic resonance imaging with its ability to characterize myocardial tissue can differentiate TTC from myocarditis and ischemic cardiomyopathy. On cardiac magnetic resonance imaging, TTC demonstrates high-intensity signal on T_2-weighted sequences in a transmural distribution, without significant macroscopic late gadolinium enhancement, in regions with wall motion abnormalities. Occasionally patients with pheochromocytoma may have underlying lymphocytic myocarditis and small foci of late gadolinium enhancement (2). Again, in TTC patients, it is important to note the significant discrepancy in the late gadolinium enhancement distribution vis-à-vis ventricular wall motion abnormalities.

Timely and aggressive hemodynamic stabilization is the key to successful patient care in cardiogenic shock. Additionally, when managing patients with suspected TTC-pheo, certain caveats should be paid attention to. Given the high catecholaminergic state, judicious initiation and utilizing lowest possible dosages of inotropes and pressors is warranted. In patients with the appropriate nidus for LVOTO, indiscriminate use of these agents may precipitate LVOTO and worsen cardiogenic shock. Whereas β-blockers are selectively used in patients with LVOTO, their use in pheochromocytoma can precipitate hypertensive crisis due to unopposed α-receptor stimulation. Failure to achieve adequate hemodynamic stability with routine measures should prompt early consideration of mechanical support devices as a bridge to recovery, and timely access to these devices can be lifesaving. Depending on the clinical requirements, the use of intra-aortic balloon pump, Impella system (Abiomed, Danvers, Massachusetts), the TandemHeart device (LivaNova, London, United Kingdom), or veno-arterial extracorporeal membrane oxygenation may be considered. Once the diagnosis of pheochromocytoma is suspected, appropriate biochemical and imaging work-up should be pursued.

Despite its initial dramatic presentation, once hemodynamic stability is achieved, these patients have good long-term outcomes. Given its high complication rate, even in the absence of classical clinical features, pheochromocytoma should be actively

sought for in TTC patients. It all begins with a high index of clinical suspicion, after all we are trying to figure out the meeting of an imitator with a great masquerader.

ADDRESS FOR CORRESPONDENCE: Dr. Vikram Agarwal, St. Luke's Heart and Vascular Institute, Chesterfield, Missouri 63017. E-mail: vagarwal@post.harvard.edu.

REFERENCES

1. Ghadri JR, Wittstein IS, Prasad A, et al. International expert consensus document on Takotsubo syndrome (part I): clinical characteristics, diagnostic criteria, and pathophysiology. Eur Heart J 2018;39:2032–46.

2. Ferreira VM, Marcelino M, Piechnik SK, et al. Pheochromocytoma is characterized by catecholamine-mediated myocarditis, focal and diffuse myocardial fibrosis, and myocardial dysfunction. J Am Coll Cardiol 2016;67:2364–74.

3. Kiamanesh O, Vu EN, Webber DL, et al. Pheochromocytoma-induced takotsubo syndrome treated with extracorporeal membrane oxygenation: beware of the apical sparing pattern. J Am Coll Cardiol Case Rep 2019;1:85–90.

4. Pelliccia F, Pasceri V, Patti G, Tanzilli G, Speciale G, Gaudio C, Camini PG. Long-term prognosis and outcome predictors in Takotsubo syndrome: a systematic review and meta-regression study. J Am Coll Cardiol HF 2019;7:143–54.

5. Agarwal V, Kant G, Hans N, Messerli FH. Takotsubo-like cardiomyopathy in pheochromocytoma. Int J Cardiol 2011;153:241–8.

6. Y-Hassan S. Clinical features and outcome of pheochromocytoma-induced Takotsubo syndrome: analysis of 80 published cases. Am J Cardiol 2016;117:1836–44.

KEY WORDS pheochromocytoma, stress-induced cardiomyopathy, Takotsubo cardiomyopathy