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Case Report

Pheochromocytoma and Takotsubo's Cardiomyopathy Requiring Extracorporeal Membrane Support: A Report of Two Cases and Review of Takotsubo's Cardiomyopathy Subtypes

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Abstract

Pheochromocytoma/Paraganglioma (PPGL) are rare neuroendocrine catecholamine secreting tumours that may vary widely in their clinical presentation. Previous case series describe 12% of PPGL patients initially presenting with cardiac complications. Pheochromocytoma-related Takotsubo's cardiomyopathy has been well described in the literature and may present with primarily basal dyskinesis (inverted subtype), apical dyskinesis (classic subtype), or global dyskinesis. Basal dyskineses has been more commonly described in pheochromocytoma-related Takotsubo's cardiomyopathy. We present two cases of severe cardiogenic shock requiring Extra-Corporeal Membrane Support (ECMO) with Takotsubo's cardiomyopathy secondary to pheochromocytoma at University Health Network, Toronto. In both cases, the pheochromocytoma was incidentally discovered on imaging. Both patients responded favourably to ECMO and alpha-adrenergic blockade with recovery of ejection fraction. Both received adrenalectomy as an outpatient with successful recovery. Although rare, PPGL should be considered in younger patients presenting with severe unexplained cardiogenic shock and Takotsubo's cardiomyopathy.

Keywords: Pheochromocytoma; Takotsubo's cardiomyopathy; Adrenal tumours; Cardiovascular; ECMO

Introduction

Pheochromocytoma is a rare neuroendocrine catecholamine-secreting tumor that arises from the sympathetic paraganglia in the adrenal known as adrenal medulla. Tumors arising from extra-adrenal sympathetic and parasympathetic paraganglia are called paragangliomas. The incidence of Pheochromocytomas and Paragangliomas (PPGL) is approximately 2 cases per million people annually [1,2] and occur equally among males and females [3,4]. Although a classic triad of headaches, sweating, and tachycardia has been described in patients with pheochromocytoma, many patients do not have all of these symptoms [5]. In fact, the clinical presentation of pheochromocytoma may be highly variable, thus posing challenges to diagnosis. Tumours arising in the setting of germline mutations in one susceptibility gene including RET, VHL, NF1, SDHA, SDHB, SDHC, SDHD, SDHAF2, MAX, TMEM12, FH, MDH2, EGLN1, SLC25A11, DNMT3A, EPAS 1, GOT2 account for approximately 40% of the clinical cases of pheochromocytoma/paraganglioma, while remaining cases are attributed to sporadic tumour development. The prevalence of pheochromocytoma-related cardiomyopathy ranges from 11-17% depending on the case series [6-8]. Takotsubo's cardiomyopathy is characterized by reversible left ventricular wall dyskinesis that mimics myocardial infarction, but occurs in the absence of coronary artery disease on angiography. The complication rate in Takotsubo's cardiomyopathy associated with pheochromocytoma has been reported to be higher compared to patients who have Takotsubo's cardiomyopathy without pheochromocytoma.

A retrospective analysis from Cedars-Sinai Medical Centre (Los Angeles) previously showed that 12% of PPGL patients initially presented with cardiac complications of heart failure, left ventricular thrombus, myocardial infarction, and severe arrhythmia [9]. Cardiovascular collapse associated with PPGL crisis requiring Extra-Corporeal Membrane Support (ECMO) has been well described in the literature [10]. A meta-analysis of 62 patients with pheochromocytoma crisis on ECMO revealed important characteristics: median duration of required ECMO support was 5 days and most patients had complete recovery of myocardial function (LVEF >50%) [11]. Survival rate post ECMO was 87% and the most common in-hospital complications were limb ischemia and ischemic stroke. Another systematic review of 40 patients with pheochromocytoma-related cardiogenic shock noted a 7% mortality [12]. A previous case report from University Health Network (UHN) described a germline mutation in the TMEM127 gene of a 47 year old female patient with clear cell renal cell carcinoma presenting with Takotsubo's cardiomyopathy secondary to pheochromocytoma and requiring extracorporeal support [13]. Undoubtedly, PPGL should be considered a possibility in patients presenting with Takotsubo's and sudden severe cardiogenic shock.

Only 7.5% of patients presenting with Takotsubo's cardiomyopathy are diagnosed with pheochromocytoma or paraganglioma, which might be an underrepresentation due to selection bias and not

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looking for the neuroendocrine tumour [14]. The majority of patients presenting with PPGL and Takotsubo's are female and less than 50 years of age [15]. Patients with pheochromocytoma associated Takotsubo's tend to be younger (average 19.87 years younger) than the general population of patients with Takotsubo's without pheochromocytoma. A review of 80 published cases of pheochromocytoma-induced Takotsubo's cardiomyopathy revealed that extracorporeal life support was used in 18.2% of cases. Risk of recurrence and severe complications were higher in cases of pheochromocytoma-induced Takotsubo's compared to general Takotsubo's cases [15]. In this case, we describe two clinical cases of severe Takotsubo's cardiomyopathy requiring ECMO in the setting of pheochromocytoma. In both cases, the adrenal mass was discovered incidentally when evaluating the patient for comorbidities in preparation for a possible cardiac transplant given their young age, overall health, and sudden presentation.

Case Presentation

Clinical Case 1

A 58-year old woman with no previous comorbidities presented with pulmonary edema and severe cardiogenic shock. She required rapid escalation of vasopressor and inotrope therapy, then started on intra-aortic balloon pump and transitioned to veno-arterial extracorporeal support with consideration of cardiac transplant. Initial echocardiogram showed a left ventricular ejection fraction of 17% with basal segments contrasting best and apical akinesis. Coronary angiography showed no coronary artery disease. Abdominal ultrasound was done in workup for possible cardiac transplant and showed a 4.6cm abdominal mass. Computed tomography confirmed a 4.6cm mass with classic radiologic features of pheochromocytoma. Plasma metanephrines and normetanephrines were significantly elevated with both greater than 6.25nmol/L (normal normetanephrine <0.89nmol/L and normal metanephrine <0.49nmol/L). Doxazosin 1mg daily was initiated, and she was weaned off ECMO. Her ejection fraction improved to 55% on transthoracic echocardiogram within the following day. She had elective retroperitoneoscopic adrenalectomy two months later. Genetic testing did not reveal any pathogenic germline mutations in MAX, MEN1, NF1, RET, SDH, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127 or VHL. Her post-operative normetanephrine and metanephrine were normal four months after the operation. She is undergoing close monitoring with serial plasma metanephrines to assess for recurrence.

Clinical Case 2

A 21-year-old woman with no known medical comorbidities presented to the hospital with headache, hypertensive emergency, pulmonary edema and cardiogenic shock. She was treated with diuresis and inotropes, but eventually required ECMO. Abdominal ultrasound in the context of her hypertension revealed a 5.3cm right adrenal mass. Magnetic resonance imaging revealed a right adrenal mass measuring 5.3 x 4.7 x 4.9 cm and an unremarkable left adrenal gland with no evidence of metastatic lesions. Plasma normetanephrines and metanephrines were markedly elevated at 13.32nmol/L (normal <0.89nmol/L) and at 20.04nmol/L (normal <0.49nmol/L), respectively. Transthoracic echocardiogram showed an ejection fraction of 35% with basal hypokinesis and coronary angiogram showed no evidence of coronary artery disease. She was started on doxazosin once ECMO was discontinued and her hemodynamic status improved. After stabilization of her blood pressure and heart rate, she was discharged home on doxazocin and metoprolol. She had an elective laparoscopic adrenalectomy three weeks later with full recovery. Postoperatively, she had normalization of her plasma metanephrines and normetanephrines. She also had complete resolution of her hypertension and her ejection fraction recovered to 59%. Genetic screening was negative for a pathogenic germline mutation in MAX, MEN1, NF1, RET, SDH, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127 or VHL.

Discussion

Takotsubo's cardiomyopathy subtypes

We describe two cases seen at UHN presenting with severe pheochromocytoma-induced Takotsubo's cardiomyopathy requiring extracorporeal support for survival. Both cases involved wall motion abnormalities seen on echocardiogram, one predominantly basal hypokinesis with apical sparing and the second predominantly apical with basal sparing. Pheochromocytoma-induced Takotsubo's most commonly involves three subtypes: 1) Basal dyskinesis (inverted subtype); 2) Apical dyskinesis (classic subtype); and 3) Global dyskinesis.15 The inverted variant is most commonly reported in pheochromocytoma cases and is apical sparing [15]. The inverted variant occurs primarily in the basal or mid-ventricular segments of the myocardial wall. Previous case series of pheochromocytoma-induced Takotsubo's cardiomyopathy describes 30% of cases with basal (inverted) dyskinesis [5]. The underlying mechanisms for presenting with inverted versus classic forms of Takotsubo's are unclear. Previous research suggests that regional differences in the myocardium's response to adrenergic stimulation, beta-receptor density, and sympathetic innervation may account for these subtype differences [16]. Previous animal studies in dogs have shown that the apical myocardium is the most responsive to sympathetic stimulation [17]. Thus, it is not clear why one subtype may present over another in pheochromocytoma-related Takotsubo's compared to general Takotsubo's. In addition, there is no clear literature supporting the prevalence of one catecholamine subtype over another in these described Takotsubo's subtypes. One report showed mixed catecholamine phenotypes with similar elevations in plasma normetanephrines, metanephrines, epinephrine, and norepinephrine in 18 cases of pheochromocytoma-related cardiomyopathy [6]. Evidence in this area is limited.

In this clinical report, both patients displayed improvement in Left Ventricular (LV) function following ECMO and alpha-adrenergic antagonist treatment. Recovery of ejection fraction after adrenalectomy occurs in 96% of cases [5]. Delayed outpatient elective surgery is preferred to urgent surgery due to lower risk of intraoperative and postoperative complications and mortality [18]. Although phenoxybenzamine is most widely used, selective alpha-receptor blockers such as doxazosin are more readily available, have shorter half-lives allowing for easy titration, and not associated with reflex tachycardia [19]. Blood pressure and heart rate monitoring alongside intravascular volume repletion are key aspects of perioperative treatment.

Conclusion

We describe two presentations of pheochromocytoma-related

Takotsubo's cardiomyopathy with cardiogenic shock requiring ECMO for survival. Both cases differed in terms of the level of myocardium that was affected with Case 1 involving the apex and Case 2 involving basal segments. Clinical improvement occurred rapidly in both cases with ECMO and alpha blockade. Both patients remain well one year after unilateral adrenalectomy with no recurrence. Although rare, it is imperative that pheochromocytoma/sympathetic paraganglioma remain on the differential for causes of severe unexplained cardiogenic shock and Takotsubo's cardiomyopathy, particularly in young patients, even in the absence of classic PPGL symptoms, as clinical presentation varies widely.

Informed Consent: Both patients from the two cases described were contacted over telephone and provided details of the case report verbally, including intent for publication in the Canadian Journal of General Internal Medicine. Both patients consented to submission to this journal and publication of the case report containing no patient identifiers beyond age and gender.

Authors' Contribution

All authors contributed to conception and design, procurement of data, drafting of the original manuscript, and critical review of the original manuscript.

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