Paraganglioma presenting as stress cardiomyopathy: case report and literature review

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Summary

Pheochromocytoma/paraganglioma (PPGL) are neuroendocrine tumors that can secrete catecholamines. The authors describe a challenging case who presented as stress cardiomyopathy and myocardial infarction (MI). A 76-year-old man, with a medical history of Parkinson's disease, type 2 diabetes mellitus, hypertension, dyslipidaemia and a previous inferior MI in 2001, presented to the emergency department due to chest pain, headaches and vomiting. He also reported worsening blood glucose levels and increasing constipation over the preceding weeks. BP was 185/89 mmHg (no other relevant findings). EKG had ST segment depression in leads V2-V6, T troponin was 600 ng/L (<14) and the echocardiogram showed left ventricular hypokinesia with mildly compromised systolic function. Nevertheless, he rapidly progressed to severe biventricular dysfunction. Coronary angiogram showed a 90% anterior descendent coronary artery occlusion (already present in 2001), which was treated with angioplasty/stenting. In the following days, a very labile BP profile and unexplained sinus tachycardia episodes were observed. Because of sustained severe constipation, the patient underwent an abdominal CT that revealed a retroperitoneal, heterogeneous, hypervascular mass on the right (62 × 35 mm), most likely a paraganglioma. Urinary metanephrines were increased several fold. 68Ga-DOTANOC PET-CT scan showed increased uptake in the abdominal mass (no evidence of disease elsewhere). He was started on a calcium-channel blocker and alpha blockade and underwent surgery with no major complications. Eight months after surgery, the patient has no evidence of disease. Genetic testing was negative for known germline mutations. This was a challenging diagnosis, but it was essential for adequate cardiovascular stabilization and to reduce further morbidity.

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Learning points:

- PPGL frequently produces catecholamines and can manifest with several cardiovascular syndromes, including stress cardiomyopathy and myocardial infarction.
- Even in the presence of coronary artery disease (CAD), PPGL should be suspected if signs or symptoms attributed to catecholamine excess are present (in this case, high blood pressure, worsening hyperglycaemia and constipation).
- Establishing the correct diagnosis is important for adequate treatment choice.
- Inodilators and mechanical support might be preferable options (if available) for cardiovascular stabilization prior to alpha blockade and surgery.
- Laboratory interference should be suspected irrespective of metanephrine levels, especially in the context of treated Parkinson's disease.
Background

PPGLs are rare neuroendocrine tumors that usually produce and secrete catecholamines. Presentation can be extremely variable (1). Cardiovascular manifestations include chronic hypertension and hypertensive crisis associated with headaches, diaphoresis, pallor, tremor, palpitations and anxiety. Less commonly, PPGL can present as acute or chronic cardiomyopathy, MI even in the absence of CAD, heart failure, cardiogenic shock, tachyarrhythmia and aortic dissection (1). The authors describe a challenging case that presented as MI and stress cardiomyopathy in a patient with established CAD, whose clinical picture could not be explained by the coronary artery findings.

Case presentation

We present a 76-year-old man, with a past medical history of Parkinson’s disease, type 2 diabetes mellitus, hypertension, dyslipidemia and a previous inferior ST segment elevation MI (STEMI) in 2001 with right coronary artery angioplasty (the coronary angiogram also showed a 90% proximal left anterior descending (LAD) artery occlusion that was not treated invasively). Patient’s medication included metformin 500 mg bid, olmesartan 20 mg/day, acetylsalicylic acid 150 mg/day, rosuvastatin 10 mg/day, sublingual nitroglycerin (SOS), levodopa 300 mg/day with benserazide 75 mg/day and rasigiline 1 mg/day. There was no history of smoking/illicit drugs/alcohol abuse. There was no relevant family history. He presented to the emergency department in November 2017 with chest pain, headaches and vomiting. The patient also reported worsening of his blood glucose levels and increasing constipation over the preceding weeks. At presentation, high blood pressure was noted (BP 185/89 mmHg) and the patient was found to be euvolemic. Cardiovascular and respiratory examination did not identify an abnormality. No other relevant findings.

Investigation

EKG showed ST segment depression (leads V2-V6). Troponin level was 600 ng/L (<14). The first transthoracic echocardiogram (TTE) showed left ventricular hypokinesia with mildly compromised systolic function. He was diagnosed a NSTEMI (Killip-Kimball class I). In the following hours, he became hypotensive with signs of systemic hypoperfusion and performed another TTE that now documented severe biventricular dysfunction. In this setting, an emergency coronary angiography was performed and revealed the already known 90% LAD artery occlusion that was not treated in 2001 and now treated with angioplasty/stenting. After the procedure, he became more hypotensive (BP 90/64 mmHg) and tachycardic (HR: 122 bpm) with progression to pulmonary edema and cardiogenic shock. He was started on norepinephrine and admitted to the coronary intensive care unit (ICU). In the following days, his BP profile was labile, with hypertensive crisis associated with vomiting and headaches that led to norepinephrine suspension alternating with severe hypotension and restarting of vasoactive amines. He also had unexplained sinus tachycardia episodes even without norepinephrine. Due to prolonged and severe constipation, present before and during hospital stay, the patient underwent an abdominal CT, which revealed a retroperitoneal, heterogeneous, hypervascular mass on the right (62 × 35 mm) (Fig. 1). At this point, the patient was observed by an endocrinologist. Urinary metanephrines estimated 12 days after the last vasoactive amine administration were significantly increased (Table 1). Due to markedly elevated plasma 3-methoxytyramine levels, there was a significant concern for malignant disease, so a staging 68Ga-DOTANOC PET-CT scan was performed. It showed increased uptake in the abdominal mass only, with no evidence of disease elsewhere (Fig. 1).

Treatment

While in the ICU, blood pressure was still elevated, so the patient was started on amlodipine 10 mg/day and alpha blockade. Alfuzosin was the only alpha-blocker available at the hospital, so he was started on 0.4 mg twice daily. Subsequent 24-h BP monitoring revealed high systolic BP, with a concomitant high diastolic BP, especially at night (average 24-h BP of 155/81 mmHg and nocturnal of 167/83 mmHg), so amlodipine was switched to nifedipine 30 mg/day, with improved BP control. As blood glucose levels had also deteriorated, metformin 500 mg bid was uptitrated to 1000 mg bid and vildagliptin 50 mg bid was added, improving diabetes control. He underwent laparoscopic surgery while under treatment with alfuzosin 0.4 mg twice daily and nifedipine 30 mg daily, with no major anesthetic complications. No hypertensive crisis occurred during surgery, so no extra medication was necessary for blood pressure control during the procedure.
Outcome and follow-up

Histopathology confirmed the diagnosis of paraganglioma, with no aggressive features or lymph node involvement. Genetic testing was negative for known germline mutations (next-generation sequencing panel –TruSight Cancer Gene Set, Illumina). The genes evaluated include RET, VHL, SDHAF 2, SDHB, SDHC, SDHD, TMEM127 and MAX.

After surgery, BP normalized (with nifedipine 30 mg/day only) and blood glucose control improved (which allowed returning to previous medical therapy). The only abnormality that persisted in the TTE was left ventricle posterior/inferior wall hypokinesia, most likely related to previous inferior MI. Constipation disappeared. This was accompanied by a significant decrease in urinary metanephrines 2 months post-operatively, with normalization of metanephrine, a significant decrease in normetanephrine and no change in 3-methoxytyramine (Table 1). An abdominal MRI and 68Ga-DOTANOC PET-CT scan were performed, with no evidence of recurrent or metastatic disease. After careful down-titration of his anti-Parkinsonic interfering medication for 23 days (including 7 days with no treatment), 3-methoxytyramine was 437 µg/24 h (reference range: 103–434 µg/24 h), confirming pharmacological interference.

Discussion

The patient described had an unusual cardiovascular presentation of catecholamine excess. There are 2 types of PPGL-related cardiomyopathy – acute and chronic (2). Both are rare forms of presentation. Most cases of the acute form refer to a Takotsubo-like phenotype (with LV ballooning), unlike our patient, who had diffuse biventricular hypokinesia. Data about its prevalence in PPGL are scarce, but there have been a few series addressing this issue. In 2011, Park et al. (3) reported three cases of acute cardiomyopathy, two with Takotsubo-like features (and one with diffuse hypokinesia) among 36 patients with pheochromocytoma. Zelinka et al. (4) reported, in 2012, 2 cases of Takotsubo-like cardiomyopathy in a cohort of 145 pheochromocytoma patients (1.4%). More recently, Giavarini et al. (5) found a prevalence of 4.3% in 140 PPGL (n=6). Riester et al. (6) in a multicentre retrospective study found a prevalence of 3% (n=4) in a cohort of 135 PPGL (mostly pheochromocytoma) and

Table 1 Pre and post-operative 24-h urinary metanephrines.

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Pre-operative result</th>
<th>Post-operative result (8 weeks)</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total metanephrines, µg/24 h</td>
<td>23,180</td>
<td>10,163</td>
<td>329–1263</td>
</tr>
<tr>
<td>Metanephrine, µg/24 h</td>
<td>10,094</td>
<td>214</td>
<td>64–302</td>
</tr>
<tr>
<td>Normetanephrine, µg/24 h</td>
<td>4496</td>
<td>1179</td>
<td>162–527</td>
</tr>
<tr>
<td>3-Methoxytyramine, µg/24 h</td>
<td>8590</td>
<td>8770</td>
<td>103–434</td>
</tr>
<tr>
<td>24-h urinary volume, mL</td>
<td>2330</td>
<td>2000</td>
<td>–</td>
</tr>
</tbody>
</table>

https://edm.bioscientifica.com/
Gagnon et al. (7) found a prevalence of 2.6% (n=4) in 152 secretory PPGLs.

Underlying mechanisms causing catecholamine-related cardiomyopathy are not fully understood but include direct myocardial damage (calcium-mediated and associated with free radicals), coronary artery vasospasm, tachycardia with increased oxygen demand, increased afterload, alpha and beta receptor downregulation (after chronic exposure to high levels of catecholamines) with decreased number of myocardial contracting units (8, 9).

In our case, the diagnosis was particularly challenging because the patient already had established CAD and presented with a NSTEMI, which could be secondary to his atherosclerotic disease. However, sudden progression to biventricular failure not explained by the coronary angiogram raised the suspicion that some non-atherosclerotic coronary mechanism could be causing the acute cardiac failure. His progression to cardiogenic shock and pulmonary edema after the procedure was also not explained by coronary artery findings. Moreover, while in the coronary ICU, the labile BP profile and sudden sinus tachycardia episodes were also not explained by the known cardiac disease nor by norepinephrine treatment. As after laparoscopic surgery, cardiac function returned to normal, the clinical picture was most likely related to catecholamine-induced cardiomyopathy. Constipation ended up being an important complaint to establish the diagnosis and can also be explained by catecholamine excess (as the initial report of a recent worsening of diabetes control). Both improved significantly after surgery, which makes this relationship much more likely.

Gagnon et al. (7) reviewed 59 acute cardiomyopathy cases related to PPGL reported in literature, added 4 patients of their own, and characterized the secretory pattern in 33 pheochromocytoma and 4 paraganglioma. They found that the tumors most frequently had mixed epinephrine and norepinephrine dominant secretion. Our case is less typical because it is a paraganglioma with much higher epinephrine secretion than norepinephrine (reported only in one of the paraganglioma cases reviewed by Gagnon et al. (7)). 3-methoxytyramine was also very elevated pre and post-operatively. At first, although we admitted it could be due to medication, we could not rule out the possibility that the tumor was also secreting dopamine because very high levels were found. This raised suspicion for a more undifferentiated phenotype and led us to perform a more extensive evaluation (with PET-CT) at diagnosis. Its level did not change significantly after surgery and 68Ga-DOTANOC PET-CT showed no evidence of disease, so the most likely explanation for this was Parkinson's medication, which we confirmed after interrupting this treatment for a few days, as described. This assumption is corroborated by the work of Eisenhofer et al. (10) and Davidson et al. (11) using different assays. The first authors found that 3-methoxytyramine was several fold elevated with levodopa treatment, measured by LC-MS/MS (56-fold for free and 22-fold for deconjugated 3-methoxytyramine), while the second authors found a 14-fold increase of homovanillic acid with levodopa measured by HPLC-ECD (as in the case described). Unlike Eisenhofer et al., these authors also found metanephrine and normetanephrine measurement to be raised with this method (2.2 and 4.8-fold, respectively, versus other patients with Parkinson's disease). Acute cardiomyopathy management might be challenging, especially when patients progress to cardiogenic shock. Alpha blockade is standard therapy in PPGL crisis but cannot be initiated in a patient in cardiogenic shock because it would aggravate hypotension. Some authors argue that mechanical support (intra-aortic balloon, ECMO, CPB) might be preferred in these patients (when available) and allow for alpha blockade sooner with better outcomes (12). Hemiken et al. (13) report nine patients with pheochromocytoma-induced adrenergic crisis with cardiogenic shock treated with ECMO, with a mortality rate of 33% (three patients). The authors also performed a systematic review of 40 cases and report a lower mortality rate – 7%. They assume that publication bias might explain the difference. Whitelaw et al. (12) review 21 cases of pheochromocytoma-induced cardiogenic shock treated with intra-aortic balloon, with only 2 deaths.

Vasoactive amines should be avoided in the management of these patients because they already have high catecholamine levels causing myocardial dysfunction and they might be relatively insensitive to their action due to long-term exposure (as previously explained). Some argue that inotilators such as levosimendan and milrinone could be good alternatives because they act through non-adrenergic pathways, providing inotropic support and relieving afterload (12, 14). Levosimendan has been used successfully with few adverse events in small studies (14, 15), none of them included patients with PPGL. There are two case reports of patients with PPGL who were treated with levosimendan with good results (one also with dobutamine and the other with vasopressin also) (16, 17). Most recent European Society of Cardiology guidelines (18) for the treatment of Takotsubo cardiomyopathy do not advise milrinone use for cardiogenic shock, but there are at least five cases of PPGL described with its successful use (one also with norepinephrine, one with mechanical support and...
the remaining with standard medical care for heart failure), including a pregnant woman (19, 20, 21, 22, 23).

Alpha blockade is standard of care after cardiovascular stabilization. There is not a single consensual approach to begin this treatment. Generally accepted rule is to start with low dose and titrate slowly (adding beta-blockade if necessary, afterwards). Casey et al. (24) describe a possible approach to test for tolerance, which is a 2.5 mg single dose of IV phentolamine (with previous fluid boluses of 250–500 mL of crystalloid to correct hypovolemia), with a cardiac team on standby prepared to perform emergent mechanical support if needed.

Surgical removal of the primary tumor is definite treatment for these patients. Ideally, it should be done after cardiovascular stabilization, although the perfect timing is still a matter of debate (12). Some argue that in extreme cases, when patients fail to achieve hemodynamic stabilization after adequate treatment (for example, in cases of tumor rupture or hemorrhage with a large catecholamine surge), emergent surgery might be an option (12, 25). Scholten et al. (25) in their review of 97 cases of patients with adrenergic crisis (between 1944 and 2011) found 33 emergent adrenalectomies, with an 18% mortality rate (6 patients). When considering only the most recent surgeries (to exclude technical-related complications), only 1 in 18 patients died (6%). There was no mortality in the elective surgery group.

Prognosis depends on how long the catecholamine exposure was and how extensive is the myocardial damage (2, 8). If minimal myocardial damage, partial or full recovery is predictable (in a few weeks or months) (8, 26). Long-standing exposure to excess catecholamines with chronic extensive myocardial damage, including dilated cardiomyopathy, has a lower recovery rate (2, 8). Establishing the correct diagnosis in due time is essential for cardiovascular stabilization and to reduce further morbidity and mortality.

Declaration of Interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent was obtained from the patient described in this article for publication of the submitted paper and images.

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