CASE REPORT

Reversible catecholamine-induced cardiomyopathy due to pheochromocytoma: Case report

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Abstract
Pheochromocytoma is a tumor originating from chromaffin tissue. It commonly presents with symptoms and signs of catecholamine excess, such as hypertension, tachycardia, headache and sweating. Cardiovascular manifestations include catecholamine-induced cardiomyopathy, which may present as severe left ventricular dysfunction and congestive heart failure. We report a case of pheochromocytoma which was diagnosed following investigation of dilated cardiomyopathy. We highlight the dramatic symptomatic improvement and reversal of cardiomyopathy, with recovery of left ventricular function after treatment.

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Case report

A 40-year-old man, apparently healthy until three months previously, had begun to suffer non-productive cough at night, weight loss (10–15 kg over three months), anorexia and dyspnea on progressively less exertion. The only relevant history was sporadic mild hypertension for several years for which he did not seek treatment, excessive sweating and persistently high heart rate (HR).

He consulted his family physician, who referred him to the pulmonary diagnostic center in his area of residence for suspected lung disease, including tuberculosis or atypical pneumonia. Diagnostic exams were inconclusive and various antibiotics were prescribed (amoxicillin/clavulanic acid, clarithromycin and levofloxacin) but he did not respond; one episode of fever (axillary temperature 39.0°C) was documented under antibiotic therapy. The patient’s symptoms persisted and he began to suffer paroxysmal nocturnal dyspnea, orthopnea, pallor, constricting chest pain and profuse sweating, which prompted him to go to the emergency department (ED) and he was subsequently hospitalized.

On physical examination, the patient was anxious, apyretic but sweating, pallid, hydrated and not jaundiced. His blood pressure (BP) was 178/119 mmHg, HR 113 bpm, respiratory rate 20 cpm, peripheral oxygen saturation 92% with oxygen therapy through a nasal cannula at 2 l/min, with no jugular venous distension. Cardiopulmonary auscultation revealed tachycardia, no audible heart murmurs, and pulmonary rales in the lower half of both hemithoraces. Abdominal palpation showed no abnormalities and there were no signs of lower limb edema or deep vein thrombosis.

The electrocardiogram (ECG) showed sinus tachycardia, HR 104 bpm, and long QT interval (QTc 488 ms). The chest X-ray revealed bilateral interstitial infiltrate with obliteration of the right costophrenic angle.

Transthoracic echocardiography showed left ventricular (LV) dilatation and global hypokinesia, with ejection fraction of 37%, and mild left atrial dilatation (Table 1 and Figure 1). NT-proBNP at admission was 7678 pg/ml.

Following heart failure therapy with angiotensin-converting enzyme inhibitors, diuretics and intravenous nitrates, there was a slight clinical improvement, particularly in dyspnea, orthopnea and paroxysmal nocturnal dyspnea. However, it did not result in control of BP or HR, and the patient remained hypertensive with sinus tachycardia.

Thoracic-abdominal computed tomography (CT) showed mild apical fibrosclerosis, diffuse ground-glass infiltrates, with interlobular septal thickening, subcarinal adenopathy 1.5 cm in diameter, bilateral hilar enlargement, bilateral pleural effusion and a solid hypodense mass on the left side of the abdomen.

Table 1 Echocardiographic parameters before treatment and two months after surgery.

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>Two months after surgery</th>
</tr>
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<tbody>
<tr>
<td>LVDD/BSA (cm/m²²)</td>
<td>3.3</td>
<td>2.8</td>
</tr>
<tr>
<td>LVSD/BSA (cm/m²²)</td>
<td>2.7</td>
<td>2.0</td>
</tr>
<tr>
<td>LVEDV/BSA (ml/m²²)</td>
<td>84</td>
<td>39</td>
</tr>
<tr>
<td>LVESV/BSA (ml/m²²)</td>
<td>53</td>
<td>16</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>37</td>
<td>58</td>
</tr>
</tbody>
</table>

LVDD/BSA: left ventricular diastolic diameter indexed to body surface area; LVEDV/BSA: left ventricular end-diastolic volume indexed to body surface area; LVEF: left ventricular ejection fraction; LVESV/BSA: left ventricular end-systolic volume indexed to body surface area; LVSD/BSA: left ventricular systolic diameter indexed to body surface area.

Figure 1 Transthoracic echocardiography in apical 4-chamber view at end-diastole, showing reduction in left ventricular end-diastolic volume: (A) before treatment; (B) two months after surgery.
Adrenal gland, calcified in its interior and measuring 4.5×5.5 cm, with relatively well-defined borders and slight streaky densification of the adjacent fat (Figure 2).

Given the suspicion of pheochromocytoma, laboratory tests of plasma and urine catecholamines and their metabolites were performed, which showed elevation of all plasma catecholamines; 24-hour urine showed increased normetanephrine and adrenaline, but normal metanephrine (Table 2).

Whole-body 123I-metaiodobenzylguanidine (MIBG) scintigraphy revealed a nodular mass 3–4 cm in diameter at the same site on the adrenal gland as observed on abdominal CT, consistent with a diagnosis of pheochromocytoma. No other areas of abnormal uptake were detected (Figure 3).

Table 2 Initial assessment of plasma and urine catecholamines and their metabolites.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Plasma catecholamines</strong></td>
<td></td>
</tr>
<tr>
<td>Adrenaline (pg/ml)</td>
<td>160.2 &lt;100</td>
</tr>
<tr>
<td>Noradrenaline (pg/ml)</td>
<td>10 058.0 &lt;600</td>
</tr>
<tr>
<td>Dopamine (pg/ml)</td>
<td>827.7 &lt;100</td>
</tr>
<tr>
<td>Total catecholamines</td>
<td>11 045.9 &lt;800</td>
</tr>
<tr>
<td><strong>Urine catecholamines</strong></td>
<td></td>
</tr>
<tr>
<td>Adrenaline (µg/24 h)</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Noradrenaline (µg/24 h)</td>
<td>1943.9 12.1–85.5</td>
</tr>
<tr>
<td>Dopamine (µg/24 h)</td>
<td>187.8 0–498</td>
</tr>
<tr>
<td>Normetanephrine (µg/24 h)</td>
<td>6002.9 105–354</td>
</tr>
<tr>
<td>Metanephrine (µg/24 h)</td>
<td>180.6 74–297</td>
</tr>
<tr>
<td>Vanillylmandelic acid (mg/24 h)</td>
<td>24.9 1.8–6.7</td>
</tr>
</tbody>
</table>

Figure 2 Abdominal computed tomography, showing hypo- dense solid mass on the left adrenal gland (arrows).

Figure 3 Whole-body 123I-metaiodobenzylguanidine scintigraphy in posteroanterior view, showing nodular mass on the left adrenal gland (arrows).

Twenty-four-hour Holter ECG monitoring (Figure 4) showed sinus rhythm, mean HR 103 bpm (74–123 bpm), with significantly diminished variability (standard deviation of R-R intervals [SDNN] 39 ms). Frequency analysis of HR variability showed that both high- (HF) (15 ms²) and low-frequency (LF) (43 ms²) components were virtually abolished.

Ambulatory BP monitoring revealed elevated 24-hour mean systolic and diastolic BP (systolic: 143 mmHg; diastolic: 92 mmHg), with a non-dipper pattern (nighttime fall 7%).

Preoperative management was begun with fluids and alpha- and beta-adrenergic receptor blockers, phenoxybenzamine being titrated up to 90 mg/day and bisoprolol (5 mg) added subsequently, resulting in BP control and a marked reduction in diaphoresis.

The patient underwent left laparoscopic adrenalectomy, with no significant hemodynamic alterations during the procedure. A 7 cm×4 cm×3.7 cm nodular mass, covered with adipose tissue 0.4–1.3 cm thick, was removed. Anatomopathological study of the specimen confirmed it to be a pheochromocytoma. Although the surgical procedure had been uneventful, the patient developed hypotension in the postoperative period, which was reversed with intravenous crystalloids. He was discharged medicated with furosemide 40 mg/day, spironolactone 25 mg/day, carvedilol 18.75 mg/day and enalapril 2.5 mg/day.
There was no biochemical or radiological evidence of pheochromocytoma during follow-up. Laboratory tests showed normalization of serum NT-proBNP to <20 pg/ml; 24-hour Holter ECG monitoring two weeks after surgery (Figure 4) showed sinus rhythm, significantly lower mean HR (73 bpm) than the previous exam and increased HR variability (SDNN 97 ms). Frequency analysis of HR variability revealed recovery of HF (139 ms²) and LF (376 ms²) components. Transthoracic echocardiography two months after surgery showed normalization of LV dimensions and recovery of LV systolic function (Table 1 and Figure 3). In view of the reversibility of the cardiomyopathy and the fact that the patient was asymptomatic, all medication was discontinued during follow-up.

Discussion

Pheochromocytomas are catecholamine-secreting neuroectodermal tumors, most commonly arising from the adrenal medulla; extra-adrenal pheochromocytomas are known as paragangliomas. The incidence of pheochromocytoma is approximately 1–8/million in the general population, 0.1% in the elderly and 0.1–0.6% in hypertensive patients; 4–6.5% of adrenal ‘incidentalomas’ are pheochromocytomas. Pheochromocytomas can be sporadic or familial; sporadic forms are usually diagnosed between the ages of 40 and 50, whereas the hereditary forms, including those associated with multiple endocrine neoplasia type 2, neurofibromatosis type 1 and von Hippel-Lindau syndrome, present in childhood or early adulthood; most cases require genetic testing. Pheochromocytomas can be isolated or multiple and are usually benign, although there are malignant forms.1,2

Hypertension, tachycardia, pallor, headache and anxiety usually dominate the clinical presentation, although some patients are asymptomatic. It has been suggested that the absence of hypertension in some patients with pheochromocytoma is due to predominant secretion of adrenaline, inactivation of noradrenaline inside the tumor, or tolerance of tissue receptors to circulating catecholamines.1 Both types of plasma catecholamines were elevated in our patient, but noradrenaline more markedly so.

Pheochromocytomas are associated with various cardiovascular complications, including LV hypertrophy, ischemic heart disease, myocardial infarction, cardiac arrhythmias, takotsubo cardiomyopathy, heart failure due to dilated cardiomyopathy and shock. The serious and potentially fatal cardiovascular complications of these tumors are due to the potent effects of catecholamines, especially noradrenaline, the main transmitter released from sympathetic nerve terminals.6

Patients with pheochromocytoma may present various disturbances in rhythm, conduction and ventricular repolarization on the ECG. Our patient had sinus tachycardia and long QT interval. Paroxysmal ventricular repolarization alterations, consisting of marked QT interval prolongation and inverted T waves, are frequently observed in patients with pheochromocytoma and can cause malignant ventricular arrhythmias.4,5

Assessment of HR variability is a noninvasive way of obtaining information on autonomic nervous system function in patients with pheochromocytoma. SDNN is one parameter that reflects autonomic activity. The low SDNN and the fact that the HF and LF components were virtually abolished in our patient are explained by inhibition of the central sympathetic nervous system by prolonged elevation of plasma catecholamines.6

Patients with pheochromocytoma usually have normal or increased ventricular systolic function on echocardiography, with only around 10% presenting catecholamine-induced cardiomyopathy,7 the echocardiographic features of which

Figure 4 (A) Histogram of RR intervals on 24-hour Holter ECG: (A1) initial and (A2) after surgery; (B) frequency analysis of heart rate variability: (B1) initial and (B2) after surgery. HF: high frequency; HR: heart rate; LF: low frequency; SDNN: standard deviation of R-R intervals; T: total; VLF: very low frequency. SDNN rose from 39 ms to 97 ms between the two exams. The HF (15 ms²) and LF (43 ms²) components were virtually abolished on initial assessment, and recovered after surgery (HF: 139 ms², LF: 376 ms²).
were first described in the late 1980s. Among the mecha-
nisms suggested for transient LV ballooning are microvascu-
lar dysfunction of the coronary arteries, multivessel epicard-
dial spasm, impaired fatty acid metabolism, myocarditis and
catecholamine-mediated myocardial dysfunction. Various
cases have been reported in which the first manifesta-
tion of pheochromocytoma was Takotsubo syndrome, the
wall motion abnormalities being reversed after resection
of the tumor; it is therefore recommended that pheochro-
mocytoma should be ruled out in patients presenting with
Takotsubo cardiomyopathy.

The prognosis of catecholamine-induced cardiomyopa-
thy associated with pheochromocytoma depends on early
diagnosis and prompt medical and surgical treatment.
Diagnosis in suspected pheochromocytoma includes mea-
surement of urine and plasma catecholamines and urine
metanephrines (normetanephrine and metanephrine). How-
ever, since catecholamine release is often paroxysmal, a
single measurement may not be sufficient to give a true
picture; sensitivity can be improved by repeating the anal-
ysis two or more times, especially following a paroxysmal
episode.

Preoperative evaluation to determine the location of
a pheochromocytoma can be performed by a variety of
imaging techniques, including CT, magnetic resonance imag-
ing (MRI) and 123I-MIBG scintigraphy. CT has sensitivity
and specificity of over 90% in locating adrenal pheochro-
mocytomas, but is less accurate in detecting tumors in other
locations. T2-weighted MRI images, with 91–100% sensitivity
and 50–97% specificity, provide excellent anatomical detail
and are better than CT at detecting paragangliomas. The
radiopharmaceutical 123I-MIBG is structurally similar to nor-
adrenaline and is thus selectively taken up and concentrated
d in chromaffin tissue. Its sensitivity of 77–91% and specificity
of 96–100% makes it the method of choice to locate extra-
adrenal tumors that are not detected on CT or MRI.

Elective surgery is the treatment of choice for pheochro-
mocytoma, and should be preceded by appropriate medical
therapy for 10–14 days. However, in extreme conditions
(e.g. shock due to hemorrhagic necrosis or rupture of a
pheochromocytoma), when hemodynamic stabilization and
adequate medical pretreatment are not possible, emer-
gency tumor resection may be the only option.

Preoperative drug therapy and appropriate intravascular
volume expansion are key factors in improving progno-
sis in pheochromocytoma, and have reduced perioperative
mortality to less than 2%. The usual strategy includes
initial blockade of alpha-adrenergic receptors, for which
phenoxybenzamine is most commonly used since it noncom-
petitively blocks alpha-adrenergic receptors. Beta-blockers
are added after the first few days; these are particularly
important in catecholamine-induced tachyarrhythmias, but
should never be administered in the absence of effec-
tive alpha-adrenergic blockade since they can worsen
hypertensive episodes by exacerbating vasoconstriction
through inhibition of vasodilation mediated by beta-2 adren-
ergic receptors. Cardioselective beta-blockers are now
preferred, since they act mainly on beta-1 adrenergic
receptors.

Laparoscopic adrenalectomy has become the standard
approach for benign adrenal tumors, since it is associated
with lower postoperative mortality, shorter hospital stay
and lower cost than laparotomy. A recent study demon-
strated that laparoscopic resection of pheochromocytomas
measuring ≥6 cm in patients with no radiological evidence of
malignancy is feasible and safe, with comparable results to
resection of smaller tumors. There were no significant dif-
f erences in intraoperative complications, estimated blood
loss, cancer diagnosis, or recurrence; length of hospital stay
was comparable and there were no incidents of capsular
invasion or adverse cardiovascular events.

Patients need to be monitored closely in the first 24 hours
after surgery. The two main postoperative complications
are hypotension and hypoglycemia. The first is due to a
sudden drop in circulating catecholamines following tumor
resection in the presence of continued alpha-adrenergic
receptor blockade, as occurred in the case presented. The
risk of hypoglycemia is related to hyperinsulinemia follow-
ing recovery of insulin release after removal of the tumor.

Patients who present with acute heart failure may have
worse prognosis as a result of extensive focal myocardial
lesions. Nevertheless, catecholamine-induced cardiomyopa-
thy due to pheochromocytoma has been shown to be
reversible after surgical resection of the tumor.

Conclusions

The need for rapid differential diagnosis in a young patient
presenting with congestive heart failure due to severe
dilated cardiomyopathy prompted laboratory and imaging
exams that revealed a pheochromocytoma.

Preoperative medical management and laparoscopic
tumor resection were successful in achieving complete
reversal of the clinical setting within a few weeks, with pro-
gressive normalization of LV and autonomic nervous system
function, as shown by recovery of HR variability on assess-
ment by 24-hour Holter ECG. We highlight the importance
of including pheochromocytoma in differential diagnosis of
unexplained cardiomyopathy in a young patient with signs
and symptoms of catecholamine excess.

Ethical disclosures

Protection of human and animal subjects. The authors
declare that the procedures followed were in accordance
with the regulations of the relevant clinical research ethics
committee and with those of the Code of Ethics of the World
Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have
followed the protocols of their work center on the publica-
tion of patient data and that all the patients included in the
study received sufficient information and gave their written
informed consent to participate in the study.

Right to privacy and informed consent. The authors have
obtained the written informed consent of the patients or
subjects mentioned in the article. The corresponding author
is in possession of this document.

Conflicts of interest

The authors have no conflicts of interest to declare.
References