


Catecholamine-induced cardiomyopathy improvement after para-aortic paraganglioma resection: a case report

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Abstract

Phaeochromocytomas/paragangliomas (PPGL) are rare tumours that can cause cardiovascular complications following the secretion of catecholamines. We present a young female presented with heart failure with reduced ejection fraction as a result of norepinephrine secreting para-aortic paraganglioma and improvement of heart failure sign and symptoms and left ventricular ejection fraction following tumour resection.

Keywords Paraganglioma; Phaeochromocytoma; Catecholamine; Cardiomyopathy

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Introduction

Phaeochromocytomas/paragangliomas (PPGL) are rare neuroendocrine tumours that can secrete catecholamines and cause secondary hypertension. The prevalence is estimated around 1 per 100 000 persons per year.¹ Phaeochromocytomas originate from adrenal glands, while paragangliomas are typically extra-adrenal and can be anywhere else. Patients can be asymptomatic, present nonspecific symptoms, or have serious complications.² Although the most common cardiovascular manifestation is hypertension, patients can present with arrhythmia, hypotension, shock, myocardial ischemia and cardiomyopathy.³ Different types of PPGL-induced cardiomyopathies have been described, both chronic and acute. However, little is known about the clinical presentation, management and prognosis of such cardiomyopathies.⁴

Case presentation

A 37-year-old lady presented to our care unit with exertional dyspnoea (NYHA functional class 3) of 1 month duration. She had a history of poor-controlled hypertension for about 10 years, frequent episodes of palpitation with pallor and sweating, two episodes of loss of consciousness a year before (has not been further investigated), hyperthyroidism and significant weight loss since a year before.

Vital signs on presentation were blood pressure: 190/115 mmHg, heart rate: 90, respiratory rate: 16, O₂ saturation: 95% on room air and temperature: 36.4°C. On physical examination, jugular venous pulsation was elevated (estimated central venous pressure of 18 cmH₂O), S4 gallop was present, lungs were clear to auscultations and there was no extremity oedema. Thyroid exam was normal. Superficial flame-shape haemorrhages were seen in retinal exam.

Electrocardiogram showed normal sinus rhythm, normal QRS axis, T wave inversion in I, aVL and inferior leads, ST segment elevation in V1–V3 with deep T wave inversion in V2–V6 and prolonged QT interval (QTc: 545 ms) (*Figure 1*).

Echocardiography showed normal left ventricular (LV) size with moderate systolic dysfunction (LVEF: 35%) and Grade 2 diastolic dysfunction, global left ventricular hypokinesia with mild concentric left ventricular hypertrophy (LVH), normal right ventricular size, mild systolic dysfunction, normal bi-atrial sizes, no significant valvular heart disease, mild pulmonary regurgitation, mean pulmonary artery pressure by pulmonary valve acceleration time (PVACT): 40 mmHg and no pericardial effusion (*Figure 1*).

Lab data were remarkable for highly elevated NT-pro BNP and azotaemia *Table 1* shows first routine laboratory data.

Considering a long-standing poor controlled hypertension with end organ damage (heart and kidney), a survey for secondary hypertension was planned. A 46 × 65 mm, hypo-echo density mass-like lesion was found in abdominal ultrasound, located to the left side of aorta compressing the left renal artery and resulting in significant renal artery stenosis. Despite showing normal cortical and pyramidal echogenicity and normal corticomedullary difference, left kidney was smaller in size (95 mm in diameter with 13 mm parenchymal thickness) compared with right kidney (106 mm and 16 mm thickness).

Figure 1 Cardiac involvement in paraganglioma. (A) Twelve lead standard electrocardiography shows repolarization abnormalities with prolong QTc. (B) 2D echocardiography shows left ventricular hypertrophy. (C) CT angiography shows left ventricular hypertrophy and mild left-sided pleural effusion with passive atelectasia in left lower lobe.

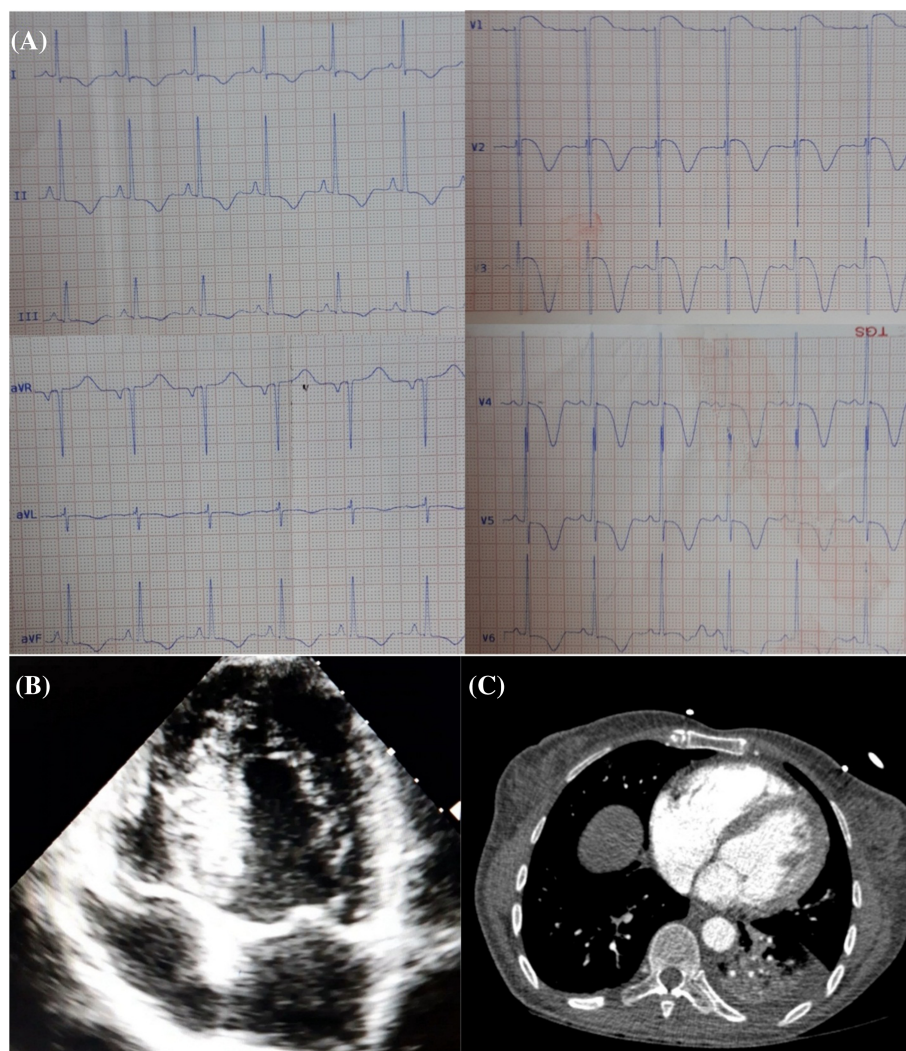


Table 1 Laboratory data

Test	Result	Unit	Reference value
Haemoglobin	16.4	g/dL	12–15.6
White blood cell	13 110	cells/mm ³	4500–11 000
Platelet	439 000	cells/mm ³	150 000–450 000
BUN	18	mg/dL	7–20
Creatinine	2	mg/dL	0.6–1.4
Na	139	mEq/L	136–146
K	4.2	mEq/L	3.8–5.6
Ca	10.9	mg/dL	8.5–10.5
Phosphorus	6	mg/dL	2.5–5
Mg	2.2	mg/dL	1.9–2.5
Fasting blood sugar	105	mg/dL	70–115
NT-proBNP	35 000	pg/mL	< 125
Erythrocyte sedimentation rate (ESR)	15	mm/h	< 20
C-reactive protein	3	mg/L	Negative: <6
Cholesterol	293	mg/dL	Up to 200
Triglyceride	183	mg/dL	Up to 200
High-density lipoprotein (HDL)	46	mg/dL	≥35
Low-density lipoprotein (LDL)	182	mg/dL	Up to 130
AST	20	IU/L	5–40
ALT	19	IU/L	5–40
ALK. phosphatase	302	IU/L	64–306
Total bilirubin	0.6	mg/dL	0.4–1.5
Uric acid	8.1	mg/dL	2.3–7.9
Albumin	50	g/L	34–53
Total protein	83	g/L	60–83
TSH	1.2	IU/L	0.5–5
PTH-CLA	151	pg/mL	15–68.3
Serum iron	86	ug/dL	40–155
TIBC (total iron binding capacity)	374	mg/dL	260–460
Ferritin	19	ng/dL	20–210

Table 2 Urine biochemical before and after surgery

Parameter	Before surgery	After resection	Normal value
Vanillylmandelic acid (mg/24 h)	7	—	0–13.6
Metanephrine (μg/24 h)	87	136	<350
Normetanephrine (μg/24 h)	1,472	578	<600
Epinephrine (adrenaline) (μg/24 h)	1.8	2.5	<20
Norepinephrine (noradrenaline) (μg/24 h)	123	37.2	<90

Further laboratory work ups revealed a high serum renin level: 253 μIU/mL (4.2–59) and elevated normetanephrine in the 24 h urine sample (*Table 2*).

Metaiodobenzylguanidine (MIBG) scintigraphy with single-photon emission computed tomography technique (SPECT) showed an intense uptake in the left para-aortic mass with a diameter of 46 mm without any other uptake elsewhere, confirming the clinical diagnosis of paraganglioma and related heart and kidney damage (*Figure 2*).

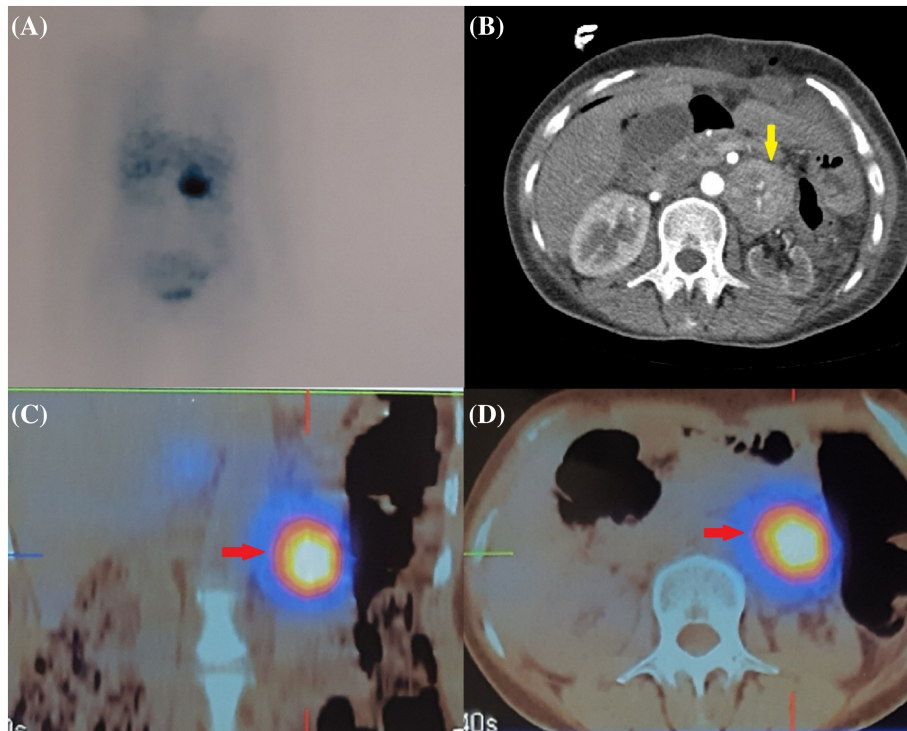
CT angiography of abdominal aorta showed a large mass encasing proximal and mid part of left main renal artery with at least moderate stenosis and displacement of left renal vein. Small arterial feeders originating from aorta at a level below the left main renal artery were also depicted (*Figure 2*).

The patient was scheduled for surgical removal of the paraganglioma after optimization of heart failure and hypertension treatment. She was started on hydralazine, lisinopril, spironolactone, furosemide and phenoxybenzamine for 2 weeks until the day of surgery. Dyspnoea and congestion symptoms improved before surgery.

Surgery was performed via subcostal approach under general anaesthesia. Blood pressure was controlled during surgery by sodium nitroprusside and labetalol and deep sedation. An ovaloid 4.5 × 4 × 2.5 cm encapsulated mass was released from the aorta and left renal vein with abundant adhesions and many collaterals (*Figure 3*).

Histologic study showed neoplastic tissues with diffuse and nested pattern (zellballen) of large polygonal cells with vesic-

Figure 2 Noninvasive imagings of para-aortic paraganglioma. (A) Whole body scan shows intensely increased ^{131}I -MIBG uptake in the left para-aortic region. (B) CT angiography shows $4 \times 3.9 \times 4$ cm encapsulated para-aortic mass (at renal level) with smaller left kidney C&D. increased ^{131}I MIBG uptake (red arrow) in coronal (C) and axial (D) plane CT, computed tomography; MIBG, metaiodobenzylguanidine.



ular round or ovaloid shaped nuclei, abundant eosinophilic to clear cytoplasm with vascular hyalinized stroma. Foci of giant multinucleated cells and bizarre cells were also seen. Mitotic count was 1/20 HPF. There were no atypical mitoses, necrosis or capsular invasion.

Immunohistochemistry (IHC) study on neoplastic cells showed diffused and strong immunoreaction with synaptophysin and chromogranin A and negative immunostaining with pan CK markers. S100 immunostaining highlighted the 'sustentacular' cells around the neoplastic cell nests. All findings were in support of paraganglioma (Figure 3).

Patient had an uneventful recovery. She was discharged on low dose of lisinopril, spironolactone and carvedilol.

On an outpatient follow-up 2 weeks later, she was stable with no symptoms of heart failure, improvement in LV function (LVEF: 50%) and reduction in 24 h urine normetanephrine and norepinephrine, as well as NT pro-BNP.

Discussion

Paragangliomas, also referred to as extra-adrenal pheochromocytomas, are developed from chromaffin cells which synthesize catecholamine. These tumours are ex-

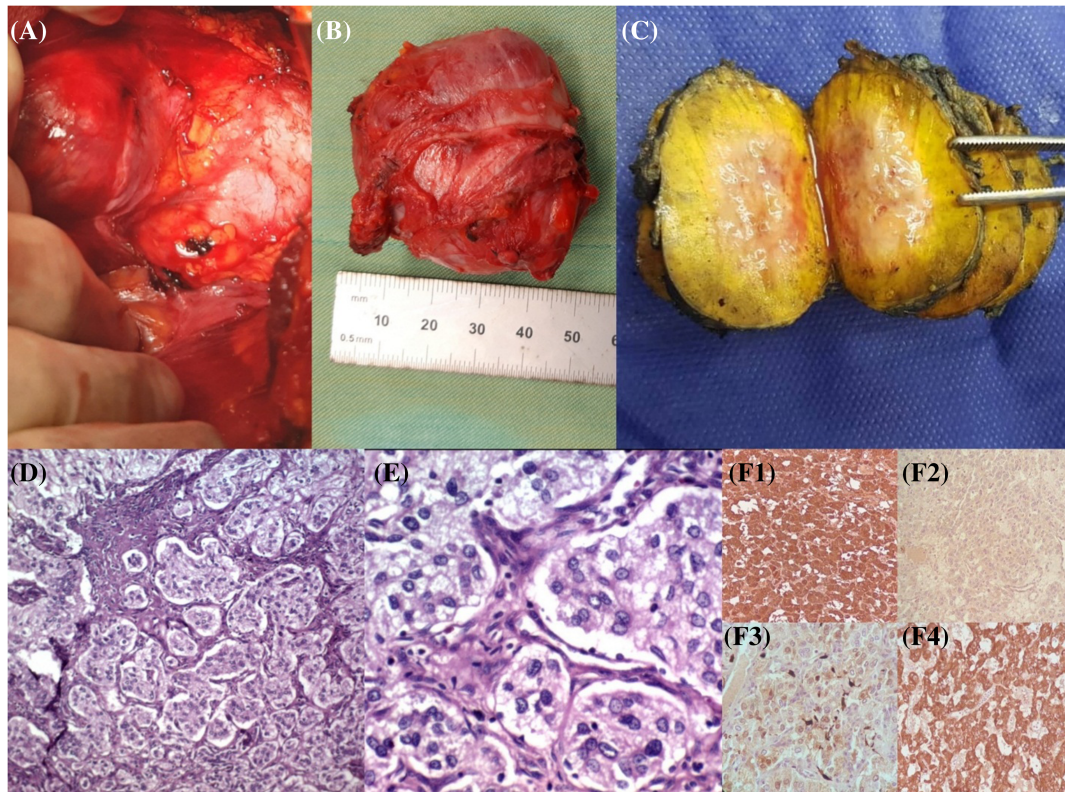
tremely rare, and about 5–10% of these comprise paragangliomas, located in the para-aortic sympathetic chains or the urinary bladder; least commonly, paragangliomas are found in the thoracic or head and neck regions.⁵

One of the rare manifestations of PPGL is cardiomyopathy, which can be acute or chronic.^{1,6} Catecholamine intoxication may lead to structural myocardial alteration and results in different types of cardiomyopathy, from an acute type like Takotsubo syndrome to an unexplained dilated cardiomyopathy or hypertrophic cardiomyopathy.⁷ Management of catecholamine exposure with surgical resection is associated with enhanced LV systolic function, depending on chronicity of catecholamine exposure and fibrosis burden.⁴

In addition to hypertension, several mechanisms for cardiac involvement in PPGLs are recognized. Catecholamine-induced myocarditis is one of them. In fact, myocarditis is a secondary process and occurs in response to contraction band necrosis.⁸ Another mechanism is cardiac overstimulation by epinephrine resulting in decreased myocardial contractility.⁹ Inadequate coronary perfusion caused by increased myocardial demand should also be considered in such cases.

PPGL may produce either norepinephrine or epinephrine. Norepinephrine-mediated alpha receptor stimulation results in vasoconstriction and hypertension; on the other hand, epinephrine beta 2 receptor stimulation results in skeletal mus-

Figure 3 Paraganglioma. (A) Paraganglioma next to the left kidney. (B) Gross examination shows encapsulated ovaloid shape solid mass with firm consistency measuring 4.5 × 4 × 2.5 cm. (C) On opening creamy yellowish homogenous cut surfaces without necrosis are seen. (D) H&E stained sections show diffuse and nesting (zellballen) pattern of neoplastic polygonal cells that separated by vascularized fibrous septa. (E) Higher magnification shows polygonal cells with round to oval shape vesicular nuclei and abundant granular eosinophilic to clear cytoplasm F1. Chromogranin; A diffuse strong in tumour cells F2. Negative PanCK F3. S100; Negative in tumour cells, positive in sustentacular cells F4. Synaptophysin; strong and diffuse in tumour cells.



cle vasodilatation and hypotension.¹⁰ Furthermore, similar to our patient experiencing episodes of bradycardia and heart block, the presentation of PPGLs can be vague, making it difficult to interpret symptoms and signs.¹¹

Paraganglioma is almost a benign tumour, but metastases are expected to be present at the time of diagnosis in more than 10% of these patients.¹² Our patient had a large norepinephrine-producing extra-adrenal functional tumour. Although no evidence of metastasis was found on the MIBG scan, the patient should be closely monitored for recurrence. This recurrence can appear years or decades after the resection of the primary tumour, and long-term follow-up is therefore necessary.¹³ Postoperative urinary catecholamine levels were assessed once for the follow-up, and urinary catecholamine levels (which has a sensitivity of 89.9% and specificity of 99%),⁹ blood pressure, and echocardiogram will be evaluated annually for the long-term follow-up.¹⁴ Given the importance and effectiveness of medical treatment in this patient, we will continue anti-failure therapy.

Limitation

We were unable to perform cardiac MRI study due to concerns for kidney failure. Cardiac MRI would have been helpful in better understanding of the cardiomyopathy process.

Take home message

Secondary causes of hypertension such as pheochromocytoma should be considered in patients with severe heart failure and uncontrolled hypertension.

Conflict of interest

None declared.

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