Endocrinology, Diabetes & Metabolism CASE REPORTS

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Two cases of cardiomyopathy associated with phaeochromocytoma successfully managed with veno-arterial extracorporeal membrane oxygenation (V-A ECMO)

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Summary

Phaeochromocytoma, a rare neuroendocrine tumour of chromaffin cell origin, is characterised by catecholamine excess. Clinical presentation ranges from asymptomatic disease to life-threatening multiorgan dysfunction. Catecholamine-induced cardiomyopathy is a dreaded complication with high lethality. While there is lack of evidence-based guidelines for use of veno-arterial extracorporeal membrane oxygenation (V-A ECMO) in the management of this condition, limited to case reports and small case series, V-A ECMO has been reported as 'bridge to recovery' therapy, providing circulatory support in the initial period of stabilisation prior to surgery. We report on two patients presenting with catecholamine-induced cardiomyopathy and circulatory collapse who were successfully treated with V-A ECMO for 5 and 6 days, respectively, providing initial haemodynamic support. After stabilisation and introduction of alpha-blockade, both cases had favourable outcomes, with successful laparoscopic adrenalectomies on days 62 and 83 of admission, respectively. Our case reports provide further support for the use of V-A ECMO in the treatment of such gravely ill patients.

Learning points

- Phaeochromocytoma should be considered in the diagnosis of patients presenting with acute cardiomyopathy.
- Management of catecholamine-induced cardiomyopathy is complex and requires multidisciplinary specialist input.
- Pre-operative management of phaeochromocytoma involves alpha-blockade; however, haemodynamic instability in the setting of cardiogenic shock can preclude alpha-blockade use.
- Veno-arterial extracorporeal membrane oxygenation is a life-saving intervention which may be considered in cases of acute catecholamine-induced cardiomyopathy and cardiogenic shock in order to provide the required haemodynamic support in the initial phase of treatment, enabling the administration of traditional pharmacological agents, including alpha-blockade.

Background

Symptoms of phaeochromocytoma typically include paroxysmal hypertension, headache, palpitations, diaphoresis and/or anxiety. However, recent data suggest that >60% of phaeochromocytomas are diagnosed incidentally on cross-sectional imaging (1). Catecholamine crisis is rare, occurring in approximately 11% of phaeochromocytoma presentations (2). Stress (Takotsubo) cardiomyopathy and cardiogenic shock,

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pulmonary oedema and/or multiorgan failure are all associated with catecholamine crisis (3). Often fatal, mortality is estimated at 15% (4). Cardiomyopathy is due to coronary artery vasoconstriction and vasospasm, leading to myocardial ischaemia, in addition to a direct toxic effect of catecholamines on the cardiac myocytes (4).

Medical stabilisation for phaeochromocytoma crisis, with alpha-blockade prior to surgery, results in reduced post-operative complications and mortality when compared with emergent surgery (5). However, adequate alpha-blockade can prove challenging due to the potential for significant hypotension in patients with phaeochromocytoma crisis.

Extracorporeal membrane oxygenation (ECMO) is an intervention designed to support lung/heart function in the setting of severe potentially reversible respiratory and/or cardiac failure refractory to conventional supports. Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) is a form of mechanical circulatory support. Hekimian et al. (2016) reported on the use of V-A ECMO in nine patients with phaeochromocytoma-induced cardiogenic shock, detailing its use as a life-saving intervention in six of the cases (6). Reversibility of cardiac dysfunction was demonstrated in all survivors, and ECMO was weaned within 1 week. ECMO may therefore be seen as an effective rescue therapy for cardiogenic shock, and we provide details of its successful use in our cases.

Case presentation

Case 1

A 30-year-old female, with background of neurofibromatosis type 1 (NF1), presented to the emergency department (ED) with acute, severe right–sided abdominal pain. She was not prescribed regular medications, and family history was negative. Blood pressure (BP) was 118/70mmHg, pulse rate was 152bpm, SpO_2 was 98% (room air), temperature was 36.4°C and respiratory rate was 24/min. Clinical examination revealed pallor, diaphoresis, bilateral lung crepitations and right upper quadrant abdominal tenderness. She was initially treated with intravenous (IV) fluid resuscitation.

Case 2

A 58-year-old female healthcare worker presented with sudden-onset severe chest pain and dizziness whilst at work. Background included hypertension and a previously diagnosed adrenal mass in an overseas institution. She was not prescribed regular medications. Following symptom onset, she was emergently transferred to ED. Initial observations showed significant hypertension (231/169 mmHg), tachycardia (150–160 bpm) and hypoxia, with SpO_2 75% on 15 L O_2 via a non-rebreather mask. Clinical examination showed pulmonary oedema.

Investigation

Case 1

For laboratory findings, see Table 1. ECG showed sinus tachycardia with right bundle branch block. Computed tomography (CT) pulmonary angiogram revealed no pulmonary embolus, bilateral multifocal patchy consolidation and pulmonary ground-glass opacification. CT abdomen/pelvis illustrated a 6.3 × 5.6 × 5.4 cm right-sided adrenal mass with evidence of haemorrhagic transformation and rupture, with associated moderate right-sided retroperitoneal haematoma, concerning for phaeochromocytoma (Fig. 1).

Case 2

ECG showed sinus tachycardia with widespread ST depression. Blood gases revealed type 2 respiratory failure

Table 1 Initial laboratory investigations from cases 1 and 2.

Laboratory	Case 1	Case 2	Reference values
White cell count, × 10^9/L	19.99	11.16	3.5–11
Haemoglobin, g/dL	13.4	15.5	11.5–16.5
Platelets, × 10^9/L	388	277	150–400
D-Dimer, mg/L	>20.00	1.82	0.00–0.50
Sodium, mmol/L	139	144	133–146
Potassium, mmol/L	3.9	4.2	3.3–5.0
Urea, mmol/l	6.1	7.8	2.8–8.6
Creatinine, µmol/L	138	66	46–86
Troponin, ng/L	7460	7	<16
C-reactive protein, mg/L	11	<1	<7
Free T4, pmol/L	10.4	10.9	9.00–20.0
TSH, mIU/L	2.79	1.03	0.35–4.94
Creatine kinase, IU/L	297	245	33–208
Lactate, mmol/L	9.4	11.4	0.5–2.0
pH	7.18	7.07	7.35–7.45
Bicarbonate, mmol/L	15.1	12.3	22.4–25.8
Random cortisol, nmol/L	907	592	150 – 455
Plasma normetanephrine, pmol/L	>12 600	>12 600	182–867
Plasma metanephrine, pmol/L	>11 578	>11 578	61–377
3-Methoxytyramine, pmol/L	2225		<185

TSH, thyroid-stimulating hormone.

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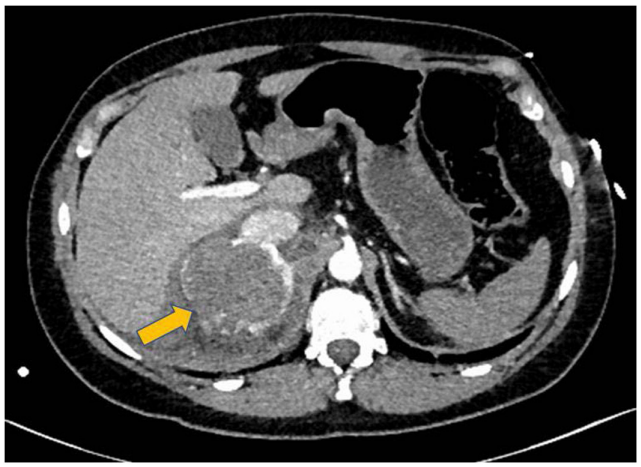

Figure 1
Case 1. Axial CT image showing haemorrhagic right adrenal mass (arrow).

with profound metabolic acidosis. Laboratory findings are shown in Table 1. CT head, thorax, abdomen, and pelvis revealed an 8.4 × 6.7 × 8.0 cm haemorrhagic mass in the right upper quadrant, arising from the right adrenal gland, with right retroperitoneum extension (Fig. 2) and pulmonary oedema. Transthoracic echocardiogram (TTE) showed apical hypokinesis, concerning for Takotsubo cardiomyopathy. Working diagnosis was catecholamine crisis secondary to ruptured phaeochromocytoma with resultant severe hypertension and cardiomyopathy.

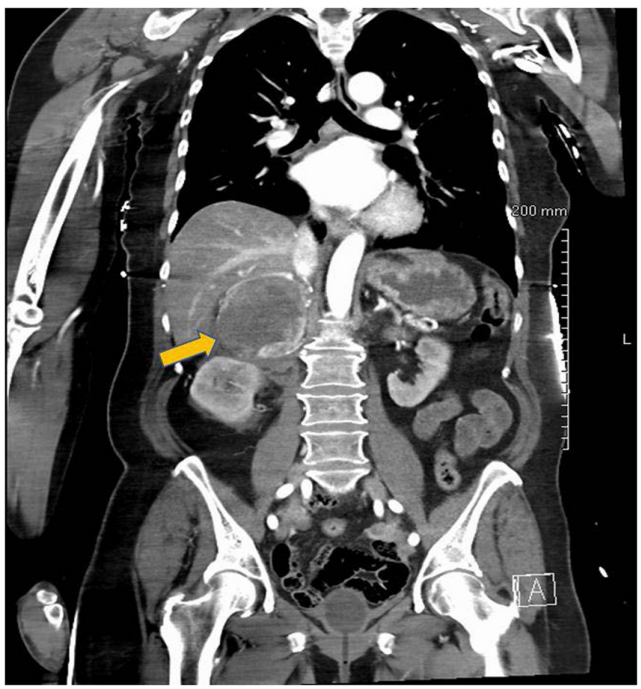

Figure 2
Case 2. Coronal CT image showing haemorrhagic mass in right adrenal (arrow).

Treatment

Case 1

The patient deteriorated, requiring intubation. Administration of 3 mg IV metoprolol and 0.5 mg IV phentolamine resulted in profound hypotension and subsequent pulseless electrical activity cardiac arrest. Two minutes of cardiopulmonary resuscitation achieved successful return of spontaneous circulation. Adrenaline, blood transfusion and further volume resuscitation were administered. TTE performed immediately post-arrest showed left ventricular ejection fraction (LVEF) of 40–45%, a hypercontractile apex and circumferential basal hypokinesis, with impression of reverse Takotsubo cardiomyopathy. Repeat TTE on day 2 of admission showed LVEF 10–20%. She was transferred to the intensive care unit (ICU) for V-A ECMO. Magnesium sulphate infusion and regular phentolamine were commenced. Working diagnosis was a catecholamine crisis precipitated by haemorrhage into the phaeochromocytoma capsule with resultant catecholamine-induced cardiomyopathy and circulatory collapse.

In ICU, V-A ECMO was employed, alongside vasopressor support during the initial phase of alpha-blockade with IV phentolamine. Cautious doses of phentolamine were given with crystalloid volume expansion pre- and post- medication adminstration to minimise hypotension. V-A ECMO use, continued for 5 days, provided circulatory support allowing the administration of alpha-blockade, with gradual uptitration over several days to 5 mg daily. Plasma metanephrines were markedly elevated (Table 1), supporting the diagnosis of catecholamine-induced circulatory crisis and cardiomyopathy. Enteral phenoxybenzamine (10 mg BD) was introduced on day 6 of admission, with gradual increase to a total dose of 300 mg daily in divided doses. On day 12 of admission, she was extubated and phentolamine was stopped. Propranolol was added on day 13 of admission, and dose was gradually titrated to 180 mg daily in divided doses. Anuric renal failure was managed with continuous veno-veno haemodiafiltration (CVVHDF) for 17 days and subsequently with intermittent haemodialysis for 3 days, with full recovery of renal function.

With a protracted course of medical optimisation, the patient's haemodynamic parameters stabilised to a pre-operative BP ranging from 90/60 mmHg to

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110/70 mmHg, and heart rate ranging 80–100 bpm in sinus rhythm. TTE on day 27 of admission showed heart function normalisation (LVEF 55–60%) and no regional wall motion abnormalities. Pre-operative metaiodobenzylguanide (MIBG) scan showed intense tracer uptake in the right adrenal gland but not elsewhere. Uncomplicated laparoscopic right adrenalectomy occurred on day 62 of admission. Histology confirmed phaeochromocytoma with a haemorrhagic 5.1 cm lesion, positive for chromogranin and synaptophysin, and a proliferation index of <1%. Both phenoxybenzamine and propranolol were stopped in the immediate post-operative period and BP remained normal.

Case 2

The patient was emergently intubated in the ED. Sodium nitroprusside infusion was commenced and later switched to glycerol trinitrate due to pulmonary oedema. Magnesium sulphate infusion and IV furosemide 80 mg were administered. She was transferred to ICU for V-A ECMO. Initial treatment with IV phentolamine 1.25 mg was administered, with resultant hypotension requiring vasopressor support.

V-A ECMO was employed for 6 days with vasopressor support to facilitate the administration of IV phentolamine. BP was fluctuant in the initial stages. Plasma volume expansion was limited by pulmonary oedema. Gradual, slow uptitration of phentolamine was possible with the aid of circulatory support provided by V-A ECMO. Initial IV hydrocortisone, to treat any potential adrenal insufficiency, was subsequently weaned. Plasma metanephrines returned markedly elevated (Table 1). Phenoxybenzamine was introduced on day 10 of admission with gradual uptitration of the dose to a dose of 360 mg daily. On day 13 of admission, she was extubated and phentolamine was stopped. Propranolol was introduced on day 14 and uptitrated to 180 mg daily. Anuric renal failure was managed with CVVHDF for 18 days, followed by one session of haemodialysis until recovery of renal function. Inpatient course was complicated by *Escherichia coli* bacteraemia, managed with antibiotic therapy, and small bowel obstruction that was conservatively managed. BP control proved challenging, and additional oral agents were required to control hypertension (amlodipine 10 mg daily and doxazosin 8 mg daily). MIBG scanning showed uptake of tracer in the right adrenal gland only. Pre-operative coronary angiography showed moderate coronary artery disease for medical management. TTE on day 4 showed normal LVEF with resolution of apical hypokinesis. The patient underwent uncomplicated laparoscopic right adrenalectomy on day 83 of admission. Histology was positive for synaptophysin, chromogranin and CD56, confirming the diagnosis of phaeochromocytoma, with low mitotic figures and phaeochromocytoma of the adrenal gland scaled score (PASS) of 6. All antihypertensives were stopped post-operatively.

Outcome and follow-up

Case 1

The patient was discharged on day 91 to a rehabilitation facility. Post-operative plasma metanephrines normalised (metanephrine <40 pmol/L, normetanephrine 245 pmol/L, and 3- methoxytyramine (3-MT) <65 pmol/L). Follow-up is ongoing with endocrinology.

Case 2

The patient was discharged directly home 2 weeks later (day 97 of admission) following inpatient rehabilitation, with endocrinology outpatient follow-up. Subsequent plasma metanephrines were normal (metanephrine <40 pmol/L, normetanephrine 545 pmol/L, and 3-MT <65 pmol/L). Genetic testing is planned.

Discussion

These cases highlight the importance of multidisciplinary management in a catecholamine crisis, requiring input from critical care medicine, cardiology, endocrinology, and surgery. Our first case had a background of NF1, one of the ever-growing number of hereditary causes of phaeochromocytoma, occurring in 0.1–5.7% of patients with NF1. Currently, germline mutations are estimated in approximately 35% of patients with phaeochromocytoma (7). Genetic studies are awaited on our second case.

Evidence-based guidelines are lacking for the medical management of phaeochromocytoma crisis (8). Pharmacological stabilisation, with control of hypertension, is the main goal of treatment in the initial crisis, often requiring multiple antihypertensives. Phentolamine, a competitive α1- and α2-adrenergic receptor antagonist, indicated for the control of hypertension in phaeochromocytoma, has a rapid onset and short duration of action. Other medications used include calcium-channel blockers (e.g. nicardipine) and nitric oxide donors, such as sodium nitroprusside

and glyceryl trinitrate. Magnesium sulphate acts as a vasodilator, inhibiting catecholamine release from the adrenal medulla (9).

Phenoxybenzamine is a nonselective, non-competitive α1- and α2-adrenergic receptor blocker, used most commonly in the pre-operative alpha-blockade of phaeochromocytoma. The usual starting dose is 10 mg twice daily, with gradual uptitration to target orthostatic hypotension. Typical effective dosage is 1 mg/kg (9). In both of our cases, much higher doses were required, likely a result of extremely high levels of circulating catecholamines. Both patients were closely monitored for adverse effects.

Given its limited therapeutic indication, phenoxybenzamine is not widely available. Reflex tachycardia is a relatively common side effect of phenoxybenzamine, due to its effects on the α2-receptor, which is undesirable in the setting of cardiomyopathy. Doxazosin, a competitive α1-adrenergic receptor blocker, is a suitable alternative. It is widely available and can effectively provide alpha-blockade, with a shorter half-life and less reflex tachycardia (9). A head-to-head randomised control trial looking at intraoperative blood pressure control showed that the overall time spent outside a pre-specified blood pressure range was not different between the two drugs and phenoxybenzamine was associated with less intraoperative haemodynamic instability than doxazosin (10).

In both cases, the issue of hypotension was challenging, prohibiting the administration of alpha-blockade. V-A ECMO was pivotal in their management: initially by stabilising circulatory collapse and restoring organ perfusion and then enabling alpha-blockade to gain control of the catecholamine crisis. A review of the use of V-A ECMO as an intervention for phaeochromocytoma-induced cardiomyopathy and circulatory collapse in 62 patients showed 87% survival rate across cases reviewed and normalisation of myocardial function in almost all cases. Major complications associated with V-A ECMO use included haemorrhage, infection, stroke, limb ischaemia and coagulopathy (11).

Had V-A ECMO not been available in our institution, both patients may not have survived. Cautious medication uptitration prepared both patients for surgery, allowing time to recover from the initial insult of the catecholamine crisis. Close contact between endocrinology, critical care medicine, anaesthesiology and surgical colleagues allowed for appropriate timing of surgery after medical optimisation, resulting in superior outcomes. Our cases highlight the life-saving intervention of V-A ECMO in patients with phaeochromocytoma crisis.

Declaration of interest
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 for publication of their clinical details was obtained from the patient.

Author contribution statement
DF is the primary author and was directly involved in the care of the patients, conducting the chart review and preparing the manuscript. CM and SL were both contributors to the final draft of the manuscript and endocrinology registrars involved in the patients' care. JC was the treating surgical consultant in both cases and reviewed the manuscript. SOB is the hospital ECMO coordinator, involved in care for both patients and review of the manuscript. ICM and JH are consultants in critical care medicine and provided care to the patients and contributed to the preparation of the manuscript. SEM is the primary treating physician, consultant endocrinologist, and senior supervising author involved in preparation and review of the manuscript. All authors reviewed and approved the manuscript.

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