Unusual association of diseases/symptoms

Pheochromocytoma presenting as acute decompensated heart failure reversed with medical therapy

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Summary

A 26-year-old woman presented to hospital with acute chest pain, hypertension, tachycardia and an elevated serum creatinine. She developed respiratory distress requiring endotracheal intubation and mechanical ventilation. She progressed to multiorgan failure due to decompensated congestive heart failure. Echocardiography demonstrated global hypokinesis and an ejection fraction of <10%. Her cardiac function improved with fluid resuscitation and β blockade, and she was eventually discharged home. She was readmitted a few days later with pancreatitis after presenting with nausea, abdominal pain and hypertension. During hospitalisation she had paroxysms of headache, nausea and diaphoresis associated with hypertension and tachycardia. A CT scan of her abdomen revealed an adrenal mass and serum metanephrine studies confirmed the diagnosis of pheochromocytoma. After fluid resuscitation and sympathetic blockade her ejection fraction improved to 55%. The patient underwent an uneventful adrenalectomy and made a complete recovery.

BACKGROUND

Pheochromocytoma is a neoplasm of neuroectodermal chromaffin tissue derived from neural crest cells with associated catecholamine secretion. Known as the ‘Great Masquerader’ these tumours have a prevalence of 4–8 per million patients and can have varied clinical manifestations ranging from asymptomatic to hypertension with headaches and palpitations or in rare cases, multiorgan failure.^{1–3} These varied symptoms are thought to be due to wide-ranging responses to excess catecholamines. Our patient presented with severe congestive heart failure that improved with blockade of catecholamine signalling.

CASE PRESENTATION

A 26-year-old woman was seen in the emergency department (ED) for chest pain and hypertension. She was found to have a urinary tract infection and was sent home with an antibiotic and thiazide diuretic. Two days later, she returned with epigastric pain, nausea, emesis and myalgias. The patient had no significant medical history and denied cardio-respiratory symptoms; however, she complained of a low exercise tolerance for the last year. There was no family history of cardiac or pulmonary disease or of sudden cardiac death. She was born in the USA and had neither travelled recently nor had any sick contacts.

On examination, she was hypertensive (170/105 mm Hg), tachycardic (125 bpm), had dry mucous membranes and appeared ill looking. She was found to have an elevated serum creatinine of 160 μ mol/l (normal 60–110 μ mol/l). After receiving 1.5 l of intravenous fluids for presumed volume depletion and prerenal azotaemia she became short of breath. Crackles were noted on auscultation of her chest and a portable chest film demonstrated hazy infiltrates that likely represented pulmonary oedema. She then developed hypotension with systolic

pressures in the 90s. Non-invasive positive pressure ventilation was initiated. An ECG demonstrated sinus tachycardia with a rate of 130 bpm and minimal ST depression on the precordial leads. In consultation with a cardiologist, the patient received 40 mg of intravenous furosemide. An echocardiogram demonstrated global hypokinesis with a left-ventricular ejection fraction <10% (see figure 1).

The patient was transferred to the intensive care unit where she became more anxious and tachycardic to 170 bpm. She was intubated and sedated. Despite the placement of a Foley catheter and administration of intravenous loop diuretics, she remained anuric for the first 12 h of hospitalisation. She developed signs of acute kidney injury with a creatinine that increased to 350 μ mol/l within the first 24 h of hospitalisation. She received nor-epinephrine and milrinone to improve cardiac output. On the second day of hospitalisation, she was evaluated by a cardiologist and cardiothoracic surgeon for emergent circulatory support as she had developed signs of poor tissue perfusion with a lactic acidosis (8.4 mmol/l; normal <2.2 mmol/l) and transaminitis with aspartate aminotransferase/alanine transaminase >150 IU/l (normal <40 U/l). She was taken to the cardiac catheterisation laboratory for emergent right heart catheterisation and biopsy to exclude acute myocarditis. Over the next few days, she was gently fluid resuscitated (guided by bioreactance non-invasive cardiac output), the pressors were gradually weaned off and she became non-oliguric. She slowly regained renal function and organ perfusion improved with resolution of the lactic acidosis and a decrease in liver transaminases. On hospital day 5 she was transferred to the medical ward and was eventually discharged home on non-selective β blockade, an ACE inhibitor and nitrate with planned follow-up at the heart-failure clinic.

The patient returned to the ED 4 days later with an elevated blood pressure, nausea and abdominal pain. A

Figure 1 (A) Baseline ECG: severely reduced left ventricle systolic function with an estimated ejection fraction of less than 10%. Reduced right ventricle cavity size, appearing under filled. (B) Preoperative ECG: normal global left ventricular systolic function with an estimated ejection fraction of 55%. Normal right ventricular size.

contrast scan of her abdomen revealed pancreatitis and an adrenal mass. During her treatment for pancreatitis she began to have paroxysms of headaches, nausea, emesis and abdominal pain with corresponding hypertension to the 220s systolic and tachycardia to 120s with a baseline systolic pressure of 90–110 mm Hg (see figure 2). Her urinary and plasma catecholamines were elevated and confirmed on repeat testing. She was given aggressive fluid rehydration and α and β blockade for a planned adrenalectomy. Prior to surgery her left-ventricular ejection fraction had improved to 55% on medical management (see figure 1). Pathology of her adrenal gland was consistent with a non-malignant pheochromocytoma (see figure 3).

INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

The differential diagnosis for a 26-year-old African American woman with new onset heart failure and no significant medical history includes viral myocarditis, hypothyroidism, giant cell myocarditis, ischaemic cardiomyopathy, sarcoidosis, holiday heart syndrome and cocaine-induced cardiomyopathy. Right heart catheterisation and biopsy in our patient demonstrated normal myocardium with no signs of inflammation, giant cell myocarditis or viral myocarditis. In addition, serology for coxsackie B1–B6 antibodies though positive (IgG) did not change significantly over the 2 weeks from her initial presentation, making viral myocarditis unlikely. The absence of granulomas on myocardial biopsy together with a

Figure 2 Paroxysm of hypertension and tachycardia.

normal angiotensin level of 24 U/l (normal: 12–68 U/l) made cardiac sarcoidosis less likely. She had no history of alcohol or cocaine abuse and her urine drug screen on admission was negative for drug metabolites making cocaine-induced or holiday heart cardiomyopathy unlikely. Echocardiograms demonstrated no focal wall motion abnormalities, cardiac enzymes remained normal, and electrokymogram showed no acute significant ST changes indicating that ischaemic cardiomyopathy was unlikely.

During her second hospital admission the patient began having paroxysms of tachycardia, hypertension, tachypnoea and diaphoresis (see figure 2). These symptoms triggered a more focused approach to the diagnosis. The plasma metanephrine level from her initial hospitalisation was 246 pg/ml (normal: 0–62 pg/ml) and 80 pg/ml from her second hospitalisation. Similarly, plasma normetanephrines levels were 11 796 pg/ml (normal: 0–145 pg/ml) and 5603 pg/ml, respectively. During her second hospitalisation, the plasma norepinephrine level was 8 196 pg/ml (normal: 0–874 pg/ml) and the epinephrine level was 1 391 pg/ml (normal: 0–62 pg/ml). Plasma Chromagranin A level was elevated to 17 nmol/l (normal: 0–5 nmol/l).

TREATMENT

The patients' blood pressure was initially stabilised with labetalol and prazosin (to achieve both α and β adrenergic blockade). This was then changed to carvedilol and phenoxybenzamine as per current recommendations.⁴ She was slowly hydrated with intravenous fluids. Her pre-operative ejection fraction 1 week later had increased to 55% (see figure 1). She underwent a laparoscopic left adrenalectomy removing a 5×3×3 cm tumour. Her

postoperative course was unremarkable. She was discharged home on low-dose β blocker and ACE inhibitor.

OUTCOME AND FOLLOW-UP

The patient underwent an uneventful adrenalectomy and made a complete recovery. She has remained symptom free.

DISCUSSION

Pheochromocytomas are rare tumours of chromaffin cells which produce excess catecholamines. They have a prevalence of 0.05–0.1% in patients with sustained hypertension.^{1–4} While excess catecholamines often cause episodic sweating, headaches, nausea, anxiety, hyperglycaemia, tachycardia and hypertension, these signs alone are non-specific for the diagnosis.^{1–4} Chronic hypertension is present in about 50% of patients with pheochromocytoma, 30% have episodic hypertension while 20% are normotensive. Paroxysmal symptoms usually last minutes to less than an hour; however, two documented episodes in our patient lasted greater than 4 h (see figure 1). Rarely, failure to diagnose and treat this condition can lead to congestive heart failure.^{5 6} The cause of the heart failure is unclear; however, catecholamine-induced cardiomyopathy or the abrupt withdrawal of catecholamine signalling in a patient with desensitised adrenoceptors and a reduced circulatory volume may play a role. Nearly 50% of cases are discovered at autopsy.^{1 5 7}

The challenge in diagnosing this condition lies in the availability and timing of biochemical assays. There are multiple assays available for both plasma and urinary catecholamines and their metabolites (metanephrines).

Figure 3 Tumour pathology. (A) Gross specimen of tumour: gross specimen of left adrenal containing tumour weighing 28 g and measuring 5.2×3.2×3.0 cm. (B) Histology of tumour: solid tumour and nesting cellular pattern with finely granular eosinophilic cytoplasm and no evidence of necrosis, capsular invasion or vascular invasion.

One multicentre study of 758 patients suspected of having a pheochromocytoma reported plasma-free metanephrines to be the best diagnostic test with a sensitivity of 97–99% and a specificity of 89%.⁸

The majority of cases of heart failure in patients with pheochromocytomas demonstrate a stress-induced cardiomyopathy called Takotsubo cardiomyopathy or broken-heart syndrome.^{4 9–11} In these patients echocardiograms demonstrate transient left ventricular apical ballooning with midventricular dyskinesia that extends beyond the distribution of any single coronary artery.^{9 11} Our patient had global hypokinesia that has rarely been observed in patients with pheochromocytoma.^{11 12} Autopsy findings in patients with pheochromocytoma and cardiomyopathy demonstrate multifocal myocarditis and replacement fibrosis with mixed inflammatory cells and contraction band necrosis.^{4 13 14} The interstitial mononuclear

inflammation seen on autopsy is distinct from the polymononuclear inflammation seen in ischaemic cardiomyopathy. The normal biopsy in our patient may be explained by sampling error and the patchy multifocal nature of the myocardial injury.

The cause of the cardiomyopathy in patients with pheochromocytoma is unclear. Exogenous epinephrine and norepinephrine has a dose-dependent cardiotoxic effect.¹⁵ Excess catecholamines, specifically norepinephrine signalling through β -adrenergic receptors, causes an increase in cyclic-AMP mediated calcium release into myocytes leading to decreased myocyte viability.^{9 15} However, it is likely that other factors play a role in the cardiac dysfunction in patients with pheochromocytoma other than catecholamines. In an experimental model, Mobine *et al*¹⁵ demonstrated worse cardiac function in rats implanted with pheochromocytoma cells than those given

equivalent doses of norepinephrine alone. Cardiac dysfunction may be associated with an increase in oxygen-derived free radicals caused by increased catecholamines which interfere with sodium and calcium transporters leading to myocyte calcium overload.⁹ Finally, cardiogenic shock could be related to changes in circulating hormones in a patient with constricted circulatory volume and desensitised adrenoreceptors. Cardiovascular collapse is postulated to occur after a prolonged episode of catecholamine-induced hypertension followed by an abrupt drop in circulating hormones.¹² This last theory seems most consistent with our patient's history. In addition to a decreased myocardial contractility these patients are frequently volume depleted due to pressure natriuresis.¹⁶ Our patient's echocardiogram and heart catheterisation revealed an underfilled right atrium and right ventricle.

While surgical removal of the tumour is the definitive therapy, patients must first be stabilised on adequate α and β blockade. Previous case reports demonstrated that the cardiomyopathy can be reversed with surgical removal of pheochromocytoma.^{6, 17} Our patient's ejection fraction increased from 10% on presentation to 55% prior to surgery after approximately 10 days of α and β blockade. This case demonstrates that pheochromocytoma-induced heart failure can be reversed with medical therapy.

Learning points

- Pheochromocytoma should be considered in the differential diagnosis in patients with sudden and unexplained onset of cardiac failure.
- Plasma metanephrines are the test of choice to confirm or exclude the diagnosis of pheochromocytoma.
- Myocardial dysfunction associated with pheochromocytoma can be reversible with α and β blockade.

Competing interests None.

Patient consent Obtained.

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