

## An unusual presentation of a catecholamine producing tumour

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### Introduction

In patients with pheochromocytomas it is well known that different factors can precipitate an acute pheochromocytoma crisis. Our patient presented with a vesicular skin rash and respiratory distress suggestive of disseminated varicella zoster for which he was treated with steroids and acyclovir. Two days later hypertension was noted for the first time.

### Case description

A 21-year old male patient was referred to our emergency department with dyspnoea, sweating, fever, headache, palpitations, non-productive coughing and a vesicular skin rash. The rash started first and the other symptoms five days later.

The patient was lucid, with a blood pressure of 140/89 mmHg, a pulse rate of 122 beats per minute, a temperature of 37.9°C and a respiratory rate of 32 per minute. On examination a few small cervical lymph nodes were noted. Examination of his cardiovascular system revealed a heaving apex but was otherwise not significant. He had bilateral crackles without any bronchial breathing. Respiratory distress was evident with nasal flaring, the use of accessory respiratory muscles and sub-costal recession. The skin rash was diffuse and vesicular in nature, involving his whole body.

A blood gas analysis revealed type 1 respiratory failure. Blood urea, creatinine, electrolytes, liver enzyme determinations as well as a clotting profile were within normal limits. A full blood count and blood platelets were within normal limits. The C-reactive protein was 61.1 mg/L. Examination of the urine showed mild proteinuria. A chest roentgen plate revealed an interstitial infiltrate. Treatment with aciclovir 600 mg 8 hourly IVI and prednisone 60 mg daily per os was empirically initiated for suspected disseminated varicella zoster infection.

Two days after admission to hospital the patient developed significant hypertension of 200/140 mmHg. On subsequent days it was noted that the hypertension followed a sinus wave pattern. Thus, workup for secondary causes of hypertension was commenced. Thyroid functions were normal and a Doppler investigation of the

renal arteries was within normal limits. No mass lesions could be demonstrated in the adrenal glands.

Three 24-hour urine samples were collected for measurement of metanephrine excretion. The results are shown in Table I.

Table I: 24-hour urine metanephrine results

Urine sample:	Metadrenaline	Metnoradrenaline
1	2946 nmol/24 h	107439 nmol/24 h
2	931 nmol/24 h	28771 nmol/24 h
3	1066 nmol/24 h	22644 nmol/24 h

A MRI scan was performed which confirmed an extra-adrenal mass localised in the left para-aortic area measuring 8.5 x 3.6 cm. This was in keeping with a possible pheochromocytoma.

This was followed by an F-18FDG (F-fluorodeoxy-glucose) PET/CT scan which was consistent with a pheochromocytoma. An area of intense FDG uptake was also noted in the right axillary lymph nodes, suspicious of metastatic disease.

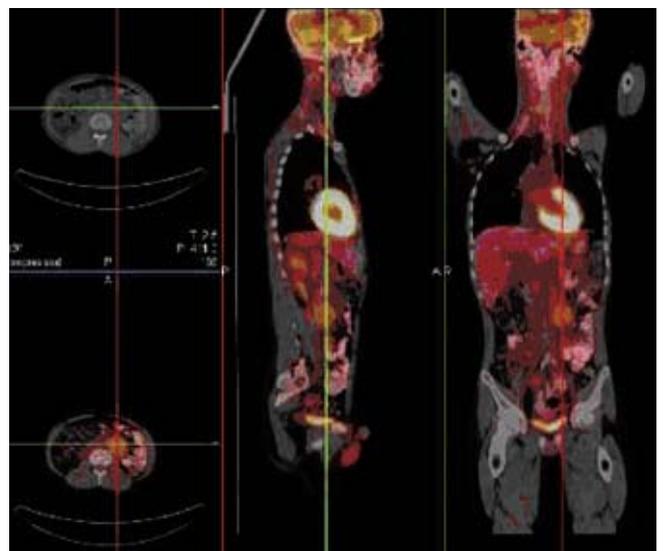


Figure 1: F-18FDG PET/CT scan indicating a pheochromocytoma (arrow)

We have reason to believe that the patient's blood pressure was elevated for a significant time prior to presentation as was confirmed by left ventricular hypertrophy on electrocardiogram and echocardiogram.

We also considered that the hypertensive crisis was precipitated by the use of glucocorticosteroids. This is based on a recently published article that reported four cases of pheochromocytoma crisis induced by glucocorticosteroids.<sup>1</sup>

The patient's blood pressure was well controlled with doxazosin controlled release, atenolol, nifedipine controlled release and perindopril prior to surgical removal of a left para-aortic extra-medullary tumour. Surgery and the post-operative period in the intensive care unit were uncomplicated.

Histological examination confirmed the presence of paraganglioma, with no involvement of the draining blood vessels. The axillary lymph node appeared tumour free, with features of sinus histiocytosis.

## Discussion

Pheochromocytomas are tumours that synthesise, store and secrete catecholamines. They arise from chromaffin cells derived from the embryonic neural crest. Most are located in adrenal medulla (80–85%), but it may also develop in or around the sympathetic ganglia.<sup>2</sup> These extra adrenal pheochromocytomas or paragangliomas could occur in thoracic, mediastinal and abdominal or pelvic locations, but are predominantly found in the organ of Zuckerkandl (75%).<sup>3</sup> This organ is located between the aortic bifurcation and the inferior mesenteric artery.<sup>4</sup> Less than 10% of these tumours are malignant.

Pheochromocytomas arise sporadically or in approximately 25% of cases as part of a hereditary syndrome.<sup>5</sup> Familial syndromes associated with pheochromocytomas include multiple endocrine neoplasia type II (IIA and IIB), caused by mutations in the RET proto-oncogene. A second familial syndrome associated is the Von Hippel-Lindau (VHL) syndrome where the germ-line mutation involves the Von Hippel-Lindau tumour suppressor gene. Neurofibromatosis type I, with mutation of the NF 1 suppressor gene as well as the familial paraganglioma syndromes 1 and 4 (PGL1 and PGL4) are also associated with pheochromocytomas.<sup>4,6,7</sup> Recently, two novel germ-line mutations were identified resulting in these familial paraganglioma syndromes. These involve the gene encoding for succinate dehydrogenase (SDH).<sup>5,7,8</sup> Mutation of the SDH gene subunit D (SDHD) is responsible for PGL1, and in subunit B (SDHB) is responsible for PGL4.<sup>9</sup>

The availability of genetic testing has improved the detection of susceptible patients for the development of hereditary pheochromocytomas, but controversies for screening recommendations exist. Some authors are of the opinion that all patients with catecholamine secreting tumours should be offered genetic screening for familial disease.<sup>8,10</sup> Others feel that is not cost-effective to screen all patients, and recommend that screening should only be done in pheochromocytoma patients with a positive family history, those with multiple or multifocal tumours, or patients under the age of 20 years at time of first diagnosis.<sup>2,11</sup>

The clinical features are very non-specific which leads to a delay of about three years between the onset of the symptoms and the

diagnosis.<sup>12,13</sup> The majority of symptoms of a pheochromocytoma are due to the direct action of secreted catecholamines. This results in hypertension with the classic triad of episodic headaches, sweating and palpitations. Symptoms of anxiety or panic together with metabolic effects such as weight loss, hyperglycaemia and rarely, lactic acidosis, may also occur.<sup>2,12,14</sup>

Hypertension is the most common presenting feature.<sup>3,12</sup> This is usually sustained and resistant to conventional treatment, although it could be paroxysmal in nature. Paroxysms may present as a distinct crisis in patients with sustained hypertension. These episodes may be serious and can potentially be fatal due to cardiovascular complications. This is due to the episodic nature of catecholamine secretion, which could be precipitated by stimuli such as micturition, certain food and drugs (i.e. tricyclic anti-depressants) or exposure to radiographic contrast agents. In a recently published article<sup>1</sup> four cases of pheochromocytoma crisis were reported, which were most likely induced by glucocorticosteroids. Of the four cases reported, glucocorticosteroid therapy was associated with a fatal outcome in one case, a multisystem crisis in another case, and serious hypertensive crisis in the other two. Several isolated cases of pheochromocytoma crisis after administration of glucocorticosteroids previously reported are mentioned,<sup>1</sup> but evidence for this is anecdotal.

Pheochromocytomas are confirmed by biochemical evidence of excessive catecholamine production. Catecholamines or their metabolites can be measured in either plasma or urine. There is still no consensus regarding which biochemical investigation is preferred in order to establish a diagnosis.<sup>6,15</sup> Measurement of plasma metanephrins has a high sensitivity (97–99%), and has been recommended as the biochemical test of choice.<sup>6,15</sup> Another study has concluded that measurement of plasma metanephrins lack specificity to be used as a screening test.<sup>16</sup> It was recommended that this test is the test of choice in high-risk patients with a familial syndrome, but measurement of 24-hour metanephrins and catecholamines is more specific, making it preferable as a screening test.<sup>16,17</sup>

Once biochemical evidence for a pheochromocytoma has been found, radiological evaluation should follow to locate the tumour. Computerised tomography (CT) is the modality most often used as it has the advantages of moderate cost, with a sensitivity of 93–100% for adrenal tumours<sup>3,4</sup> and about 90% for extra adrenal tumours.<sup>18</sup> Due to the risk of precipitating a hypertensive crisis by the administration of radiographic contrast media, patients should be protected by both  $\alpha$  and  $\beta$  adrenergic receptor blockade. Magnetic resonance imaging (MRI) has similar diagnostic sensitivity and has the advantage of not exposing the patient to radiographic contrast media. MRI is superior to CT imaging in the assessment of the relationship between the tumour and the surrounding vessels.<sup>4,18</sup> Both CT and MRI have poor specificity, reportedly as low as 50%.<sup>4</sup> I-metaiodobenzylguanidine (MIBG) scintigraphy has a higher specificity, ranging from 95–100%, but lower sensitivity of 77–90%.<sup>4</sup> MIBG scintigraphy is particularly useful in localising tumours detected biochemically, as well as detecting recurrent or metastatic pheochromocytomas. It is also used to confirm functional tumour tissue localised by CT or MRI.<sup>3</sup> Scintigraphy with <sup>111</sup>In-octreotide provides another method for detecting metastasis, but only limited success has been reported in the literature.<sup>6,18</sup> Position emission tomography (PET) studies using F-fluorodopamine, F-fluorodopa or F-fluorodeoxy-glucose (FDG)

may also be used.<sup>3,18</sup> FDG, the only PET imaging compound mostly used<sup>2</sup> is very successful in detecting metastatic disease, but has low specificity.<sup>3,18</sup> Due to its cost it is not recommended for the initial localisation of the tumour.

Once a pheochromocytoma has been diagnosed, surgical resection is the definitive treatment. Induction of anaesthesia before surgery or manipulation of the tumour may cause massive catecholamine release from the tumour, which can result in a hypertensive crisis, myocardial infarction, arrhythmia or stroke.<sup>2,6</sup> Prior to surgery patients should be adequately prepared in order to prevent these life threatening catecholamine induced complications.

This includes adequate alpha-adrenergic blockade<sup>19</sup> with phenoxybenzamine, a long acting, non-selective, non-competitive  $\alpha$ -blocker that has been most commonly used.<sup>2,4</sup> Other regimens include the use of prazosin and doxazosin. Beta-adrenergic blockade is added to oppose the reflex tachycardia associated with  $\alpha$ -blockade. Beta blockade should only be initiated after  $\alpha$ -blockade is established. This is because it does not prevent and can augment the effects of catecholamines at the  $\alpha$ -adrenoreceptors, causing a hypertensive crisis. Selective  $\beta_1$ -receptor blockers such as atenolol or bisoprolol are recommended.<sup>19</sup> Calcium channel blockers can be used in combination with  $\alpha$ -blockers for hypertension control. If used alone, they do not completely prevent haemodynamic instability.<sup>2</sup> Liberal salt and fluid intake from two weeks prior to surgery is recommended, to decrease the risk of severe orthostatic hypotension.<sup>4</sup> The criteria<sup>2</sup> used to assess adequate preoperative preparation include: 1. Blood pressure less than 160/90 mmHg for 24h prior to surgery; 2. The presence of orthostatic hypotension, with the blood pressure in the upright position not below 80/45mmHg; 3. Not more than one ventricular extra systole every five minutes; and 4. No ST-segment changes or T-wave inversion seen on the ECG for one week.

Surgical removal of the tumour has previously been performed through a trans abdominal incision,<sup>3</sup> with palpation of the contra lateral adrenal gland and the sympathetic chain to identify other possible tumours. Laparoscopic removal of intra- or extra-adrenal tumours is now the preferred surgical method,<sup>2,3</sup> with the advantages of less release of catecholamines, more rapid recovery and shorter hospital stay.

There is no curative treatment for malignant pheochromocytomas, but surgical resection of the tumour is suggested to control symptoms and prolong survival.<sup>20</sup> Metastatic lesions should be resected if possible and I-MIBG can be used as a therapeutic option in cases where the tumour shows uptake.<sup>3</sup> This yields partial remission in about 25% of patients.

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