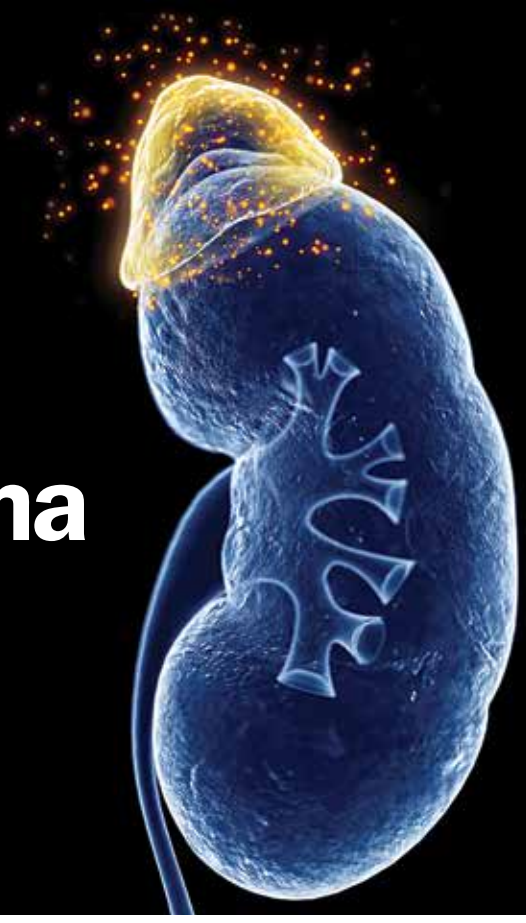

The many faces of phaeochromocytoma

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Phaeochromocytomas are rare catecholamine-secreting tumours that pose significant risk of cardiovascular morbidity and mortality and potential for metastasis. Delayed or missed diagnosis is common due to their wide spectrum of clinical manifestations.

Key points

- **Timely diagnosis of a phaeochromocytoma is important because of the associated cardiovascular morbidity and mortality and potential for metastatic disease.**
- **Clinical presentation is highly variable and features may be nonspecific, mimicking a spectrum of medical and psychological conditions.**
- **The most common features of a phaeochromocytoma are hypertension, headache, sweating, palpitations and anxiety.**
- **Patients may be asymptomatic, especially with the rising detection of incidental adrenal lesions.**
- **Diagnosis requires biochemical assessment for catecholamine excess, followed by imaging.**
- **Of people with phaeochromocytomas or paragangliomas, 40% carry an autosomal dominant germline mutation. Genetic testing should be considered for all patients.**

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Phaeochromocytomas and paragangliomas are rare catecholamine-secreting tumours. Phaeochromocytomas arise from the adrenal medulla whereas sympathetic paragangliomas arise from the sympathetic and parasympathetic ganglia. These tumours have an estimated incidence of 0.6 to 0.8 per 100,000 person-years, but this is likely to be an underestimate due to missed diagnoses, with a higher frequency noted in autopsies.[1-3] Phaeochromocytomas make up about 85% of these tumours,[4] and are the main focus of this article.

The diagnosis of phaeochromocytoma can be delayed or missed due to the wide spectrum of potential clinical presentations. Timely diagnosis is paramount because of the association of phaeochromocytoma with potentially catastrophic cardiovascular morbidity, risk of metastatic disease (which occurs in 10 to 15% of patients with phaeochromocytomas or paragangliomas) and potential for detection of a germline mutation.[3,5]

Presentation

The clinical manifestations of phaeochromocytomas are attributable to the actions of excess circulating catecholamines on the sympathetic nervous system. Symptoms and signs are thus nonspecific. Presentation at diagnosis is highly variable, ranging from catecholaminergic crisis with multiorgan failure, asymptomatic hypertension, normotension or hypotension to mimicking of psychological conditions.

The often described classic triad comprises paroxysmal headache, spontaneous or excessive sweating and palpitations. However, only a minority of patients present with this classic triad.

The most common feature of phaeochromocytoma is hypertension, which may be paroxysmal or sustained. Postural hypotension may also occur. Other cardiovascular manifestations include chest

1. Case study: an undiagnosed phaeochromocytoma and the potential for catastrophic cardiovascular complications

A 71-year-old woman underwent a hysterectomy with no intraoperative complications. However, her postoperative recovery was complicated by chest pain and hypertension, with her blood pressure exceeding 170/100 mmHg despite use of multiple agents. Echocardiogram revealed new severe systolic impairment but coronary angiogram demonstrated only minor coronary artery disease, suggesting Takotsubo cardiomyopathy. A CT scan of the abdomen to investigate anaemia incidentally noted a 78 mm heterogeneously enhancing left adrenal mass.

Her plasma and urine metanephrine levels were markedly elevated. Intense avidity was demonstrated in the left adrenal bed on metaiodobenzylguanidine scintigraphy. She underwent a laparoscopic left adrenalectomy with alpha blockade then beta blockade. Postoperatively, her blood pressure normalised without pharmacotherapy, and serial echocardiograms have confirmed normalisation of her left ventricular function.

This case highlights potentially catastrophic cardiovascular complications of an undiagnosed phaeochromocytoma. Reassuringly, the patient had normalisation of her blood pressure and cardiac function postoperatively, showcasing the importance of timely diagnosis and management.

2. Case study: typical clinical features of a phaeochromocytoma but with delayed diagnosis

A 37-year-old man presented to the emergency department with sudden onset occipital headache, chest tightness and shortness of breath. He had been diagnosed with hypertension at 35 years of age, had a one-year history of intermittent episodes of similar headaches often associated with palpitations, and had presented several years earlier with panic attacks. His blood pressure was 155/90 mmHg. He underwent investigations for acute coronary syndrome, which were unremarkable, and he was discharged from the emergency department. He had subsequent re-presentations with similar symptoms, and was assessed as being anxious with excessive self-monitoring of his blood pressure.

Several weeks later, he underwent an MRI for back pain, which found an incidental right adrenal mass. A dedicated CT scan demonstrated a 40 mm right adrenal lesion of 51 Hounsfield units precontrast. He was referred to a surgeon who organised biochemical investigations and referred him to the endocrine clinic. Plasma free metanephrine levels were markedly elevated and a metaiodobenzylguanidine scintigraphy scan demonstrated intense avidity in the right adrenal gland. He underwent a right laparoscopic adrenalectomy after alpha blockade then beta blockade and preoperative volume expansion. No genetic mutations were identified.

This case represents a patient presenting with typical clinical features, but with delayed diagnosis due to their nonspecificity. It highlights the importance of considering the diagnosis of phaeochromocytoma in patients with symptoms that may be consistent with catecholamine excess.

pain and nonspecific electrocardiographic changes that may mimic ischaemia. Presenting features may also include pallor, anxiety or panic attacks, tremor, fatigue, gastrointestinal manifestations and hyperglycaemia.[3,6] Rarely, patients may present with catecholaminergic crisis causing organ dysfunction (as illustrated in the case in Box 1). Other features include haemodynamic instability with severe hypertension or hypotension, arrhythmia, myocardial infarction, cardiomyopathy, encephalopathy, stroke and fever.[7]

Earlier diagnosis is increasingly being made in relatively asymptomatic patients due to the detection of incidental adrenal masses or through germline mutation testing. Phaeochromocytomas comprise 5% of adrenal incidentalomas.[2]

Given the wide spectrum of clinical manifestations and potential for asymptomatic disease, it is important to consider the diagnosis of phaeochromocytoma if consistent features, including atypical presentations, are present (as illustrated in the case described in Box 2). A biochemical assessment should also be conducted in patients with adrenal masses, including those who are asymptomatic.

Biochemical diagnosis and imaging

Indications for biochemical assessment for catecholamine excess are a clinical suspicion of phaeochromocytoma or paraganglioma, detection of an adrenal or retroperitoneal mass, and carriers of phaeochromocytoma or paraganglioma susceptibility genes.[3]

Initial biochemical assessment should comprise measurement of fasting plasma free metanephrines (this includes metanephrine [also called metadrenaline] and normetanephrine [also called normetadrenaline]) and 3-methoxytyramine levels, or alternatively measurement of 24-hour urinary metanephrine levels. These catecholamine metabolites have a sensitivity of 97% and have greater diagnostic accuracy than measurement of catecholamines (adrenaline, noradrenaline and dopamine).[2] Measurement of fasting plasma 3-methoxytyramine levels is carried out to increase sensitivity and for detection of rare tumours that predominantly secrete dopamine, particularly if paraganglioma or metastatic disease are suspected.

Biochemical investigations are prone to false positives. These investigations should be performed in the fasting state, in supine position and avoided at times of stress because of stimulation of the sympathetic nervous system. Metanephrine levels more than three times the upper reference limit are rarely false positive.[8] Medications that may interfere with biochemical testing should be tapered and withheld for at least two weeks before testing (Box 3).[9-11] For example, tricyclic antidepressants and nonselective alpha blockers such as phenoxybenzamine increase plasma and urinary normetanephrine levels, whereas beta adrenoceptor blockers may cause false elevation of plasma and urinary metanephrine levels.[9] Marginal elevation of screening test results warrants consideration of factors causing false elevation and repeat of the investigations after eliminating these factors if possible.

3. Medications that can lead to false-positive results in biochemical testing for phaeochromocytomas[9-11]

- Tricyclic antidepressants
- Noradrenaline reuptake inhibitors
- Serotonin–noradrenaline reuptake inhibitors
- Levodopa
- Amphetamines
- Monoamine oxidase inhibitors
- Prochlorperazine
- Alpha and beta blockers
- Withdrawal from medications such as clonidine
- Ethanol

Imaging for localisation should generally be performed only after demonstrating biochemical evidence of catecholamine excess. Abdominal CT with contrast is preferred and is safe as there is no risk of exacerbation of hypertension.[12] MRI may be performed if CT with contrast is contraindicated or to assess for extra-adrenal disease if CT is unremarkable. Bilateral disease and extra-adrenal disease are associated with a higher risk of an underlying germline mutation. Phaeochromocytomas typically show marked and heterogeneous hyperenhancement on CT (Figure), and peripheral rim enhancement is characteristic of a phaeochromocytoma with central necrosis. In contrast to lipid-rich adenomas, the unenhanced attenuation is almost always greater than 10 Hounsfield units, with less than 50% contrast washout at 10 minutes. There is, however, considerable variability in radiological appearance.[13]

Functional imaging may be considered following CT and/or MRI. It is generally considered to have additional benefit only in specific circumstances, such as if there is known metastasis or a high risk of metastatic disease (e.g. in patients with certain underlying genetic mutations). Traditionally, metaiodobenzylguanidine scintigraphy (MIBG) has been used for localisation, if CT and/or MRI are negative, and for detection of metastatic disease. However, sensitivity for detection of metastases or paraganglioma may be higher with fluorodeoxyglucose positron emission tomography and 68-gallium DOTATE positron emission tomography, depending on the underlying genetic mutation, if present, location of the primary tumour and location of metastases.[14,15]

Management

Patients with suspected or diagnosed phaeochromocytoma should be referred to an endocrinology service to guide management. Surgical resection is the cornerstone of therapy for phaeochromocytoma, but appropriate preoperative evaluation and medical preparation is crucial to minimise the risk of perioperative cardiovascular complications from the surge of catecholamine release in the setting of operative manipulation. Perioperative mortality is low with suitable medical preparation.[3]

Patients should be started on an alpha-adrenergic receptor blocking agent one to two weeks before scheduled surgery. It is crucial that adequate alpha blockade is achieved before beta adrenergic receptor blocking agents are introduced, with monitoring of sitting and upright blood pressures to guide dosing. Beta blockade should not be started before this due to the risk of unopposed alpha adrenergic stimulation precipitating a hypertensive crisis.

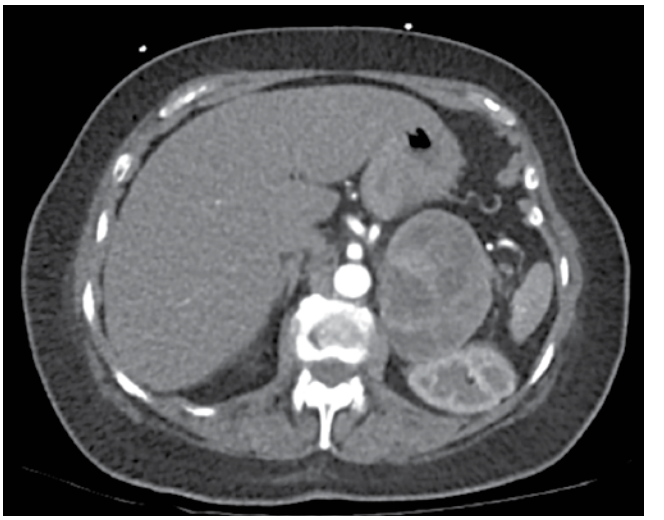

Figure. Contrast CT scan in arterial phase in axial view, showing large heterogeneously enhancing left adrenal mass.

Phenoxybenzamine, a nonselective alpha adrenergic blocker, is typically used starting at 10 mg twice a day and the dose is increased until a target blood pressure of 120/80 mmHg with postural drop of up to 20/10 mmHg is achieved. Selective alpha blockers such as prazosin can also be used. After adequate alpha blockade is achieved, a beta blocker, such as atenolol or metoprolol, is subsequently administered to control tachycardia, with a target heart rate of 60 beats per minute.[2] Patients should be cautioned regarding potential adverse effects of medications, including nasal stuffiness and postural symptoms. In patients with no underlying cardiac or renal failure, salt and fluid intake are to be increased to reverse the catecholamine-induced volume contraction. In addition, preoperative intravenous saline may be used to prevent prolonged and severe hypotension postoperatively.

Retroperitoneal laparoscopic adrenalectomy, instead of open surgery, is now often performed by experienced surgeons and is considered standard of care. Postoperative follow up with an endocrinology service is essential to confirm complete tumour resection and for surveillance of recurrent disease.[2,5]

Genetic testing

Of patients with phaeochromocytomas or paragangliomas, 40% have an underlying germline mutation. Detection of germline mutations is important given the implications for family members and the higher risk of metastatic disease associated with some germline mutations (as illustrated in the case in Box 4).

Disease-causing germline mutations include RET mutations causing multiple endocrine neoplasia type 2A or 2B, succinate dehydrogenase (SDH) mutations (composed of four subunits – SDHA,

4. Case study: an incidental diagnosis of bilateral phaeochromocytoma and an underlying germline mutation

A 53-year-old woman was reviewed for lower back pain. She had no other symptoms or past medical history. Her mother had renal cell carcinoma. Her blood pressure was 130/90 mmHg and she had normal sinus rhythm. An MRI to investigate her back pain incidentally noted a lesion above the left kidney. A 67 mm left adrenal lesion as well as a 3 mm right adrenal lesion were found on a dedicated CT.

Biochemistry was notable for significantly elevated plasma and urinary metanephrine levels. Metaiodobenzylguanidine scintigraphy (MIBG) scan demonstrated MIBG-avid masses in both adrenal beds. She received preoperative alpha blockade then beta blockade before undergoing bilateral laparoscopic adrenalectomy. Postoperatively, she was commenced on glucocorticoid and mineralocorticoid replacement.

Given her bilateral phaeochromocytoma and family history of renal cell carcinoma, investigations for features associated with genetic syndromes were carried out. There was no haemangioblastoma on imaging and ophthalmology review. Her thyroid ultrasound and serum calcitonin levels were normal. Genetic testing revealed a transmembrane protein 127 (TMEM127) mutation with autosomal dominant inheritance. TMEM127 *is a tumour suppressor gene with mutations known to be associated with phaeochromocytomas and paragangliomas. Her family received genetic counselling and is participating in screening.*

This case reflects an incidental diagnosis of bilateral phaeochromocytoma. The patient had extensive investigations for an underlying genetic syndrome given the presence of bilateral tumours. She was subsequently found to have an autosomal dominant germline mutation, which has had significant implications for her family, highlighting the importance of considering genetic testing in all patients, especially in the presence of suspicious features.

SDHB, SDHC, SDHD), succinate dehydrogenase complex assembly factor 2 (SDHAF), von Hippel Lindau (VHL), neurofibromatosis type 1, MYC-associated factor X (MAX) and transmembrane protein 127 (TMEM127), which are associated with variable penetrance of phaeochromocytomas and paragangliomas, risk of metastatic disease and different biochemical phenotypes. For example, SDHB and VHL are associated with predominantly noradrenaline-secreting tumours. SDHB mutations confer higher risk of metastasis.[3,16]

It is advised that genetic testing be considered for all patients with phaeochromocytomas or paragangliomas, preferably with the assistance of clinical genetic services. Testing is particularly important if suspicious features, such as significant family history, bilateral or metastatic disease or presence of associated syndromal features such as other tumour types, are present. Next generation sequencing, which enables all genes known to be involved in phaeochromocytomas and paragangliomas to be simultaneously evaluated, is currently used mainly for research purposes. It may become widely available as a genetic diagnostic tool for phaeochromocytomas and paragangliomas in the future once it becomes more affordable.

Conclusion

Patients with phaeochromocytomas can present with a wide spectrum of clinical manifestations, most symptoms being non-specific and mimicking both medical and psychological conditions. Considering the diagnosis in the appropriate clinical setting is important, especially due to the cardiovascular complications of untreated disease. It is also paramount to consider the potential for an underlying germline mutation, which may help to guide early diagnosis and treatment in family members. **ET**

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