ADRENAL HAEMORRHAGE ASSOCIATED WITH PHEOCHROMOCYTOMA

A Case Report

Philip Thomas, MBChB

INTRODUCTION

A pheochromocytoma is a rare catecholamine-producing tumour that occurs in around two per million of the population.⁽¹⁾ It is a diagnosis that should be suspected in any patient with resistant hypertension but it can present with a number of non-specific symptoms and signs that can render diagnosis difficult.

Adrenal haemorrhage is a relatively uncommon condition with a variable and non-specific presentation that may lead to acute adrenal crisis, shock, and death unless it is recognised promptly and treated appropriately.⁽²⁾

This case report is an example of how these two relatively uncommon conditions presented together in a patient.

CASE REPORT

A 66-year-old man was admitted to the medical admissions ward of Furness General Hospital with a cough productive of green sputum, right-sided pleuritic chest pain, dizziness and some mild generalised abdominal discomfort. There was no history of trauma or cardiac sounding chest pain.

Abnormalities present on clinical examination were hypotension (90/60mmHg) and tachycardia (100bpm). The only other abnormality on examination was some tenderness on the right chest wall.

The patient's past medical history included ischaemic heart disease (myocardial infarction in 2002), right upper lobe pneumonia and hypertension. His drug history on admission included amlodopine 5mg, simvastatin 40mg and clopidogrel 75mg (the patient was allergic to aspirin).

Initial investigations showed a picture of infection and dehydration with an elevated white cell count (14.5, neutrophils 10.0), C-reactive protein (157), a urea of 9.0 and a creatinine of 133. Other blood tests were normal, including a haemoglobin (Hb) of 13.3, amylase of 44, international normalised ratio (INR) of 1.1, and normal arterial blood gases. A troponin level was measured as well and found to be normal (<0.03). Electrocardiogram and chest X-ray were normal.

D-Dimers were elevated at 615, thus a computerised tomography pulmonary angiogram (CTPA) was obtained that was negative for a pulmonary embolus. The CTPA did reveal mild pleural reaction noted on both sides with minimal right pleural effusion and underlying basal consolidation in both the lower zones.

With the above results an initial diagnosis of pneumonia was made and the patient was started on a standard regimen of fluids and antibiotics.

Four days post-admission the patient's Hb had dropped from 13.5 to 8.5. His clopidogrel was stopped and he was transfused four units of blood and subsequently his hypotension improved and he was no longer tachycardic. His INR was stable at this point at 1.1.

Around this time the patient mentioned that his abdominal discomfort had shifted and was located in a large area from the right upper quadrant to the right iliac fossa. There were no signs of an acute abdomen otherwise.

An ultrasound scan was requested based on the above findings; this was followed up by CT scan on the radiologist's recommendation.

Figure 1 Ultrasound scan shows a grossly abnormal right kidney but no signs of hydronephrosis

Figure 2 The CT scan revealed no abnormality of the right kidney, but there was a large subphrenic abscess and possibly an adrenal mass

Prior to drainage of the suspected abscess a second radiologist reviewed the films and felt that it was more likely to be haemorrhage as opposed to an abscess. The patient's haemoglobin had dropped from 13.5 to 8.5 during admission; the radiological findings coincided with this. The procedure was abandoned and instead a magnetic resonance imaging (MRI) scan was done that showed similar findings to the previous CT scan.

Ten days post-admission the patient had improved. His blood pressure, pulse and biochemical markers had returned to normal. His Hb had gone up to 11 and was stable.

Together with discussion with the radiologists a plan was put in place to discharge the patient with a follow-up CT scan two weeks post-discharge to assess the mass again further once the haemorrhage had reduced.

Additional tests that were done whilst an inpatient included a short synacthen test, which was normal. A plasma renin and aldosterone level was also obtained that was deemed to be normal.

Tests done as an outpatient included 24-hour urinary catechaloamines and 24-hour urinary cortisol. Twenty-four-hour urinary cortisol was found to be normal. However, the urinary catechaloamines showed a metadrenaline of 3.7(normal 0-2) and normetadrenaline of 7.3(0-5.3). This test was performed again and confirmed persistently elevated catechaloamines.

CT scans of the abdomen and pelvis taken two weeks post-discharge revealed a reduced haemorrhage with a clear 4.5cm arterial enhancing right adrenal mass underneath.

A diagnosis of pheochromocytoma was made based on the results above. Surgeons and specialist endocrinologists in a regional specialist centre have been involved. Staging CT scans to look for metastatic spread have all been negative. The patient is currently awaiting surgery and is on alpha blockade in the interim. He is also having a full hormonal assessment done to make sure that this process is not part of a genetic syndrome.

Further delving into the history showed that the patient had been suffering for several years with intermittent symptoms consisting of sudden onset palpitations, chest pain, dizziness, panic attacks and paraesthesiae of the hands. He also was previously hypertensive, needing three agents to control his blood pressure. In addition, there was no family history of endocrine tumours that the patient is aware of.

DISCUSSION

In 1886, Frankel made the first description of a patient with pheochromocytoma. However, the term was invented by a pathologist, Ludwig Pick, in 1912.

A pheochromocytoma is a neuroendocrine tumour of the adrenal medulla. Excess amounts of adrenaline and noradrenaline are produced. The symptoms and signs are from the systemic effects of these hormones. Ten to 15 per cent of catecholamine-producing tumours are extra-adrenal, these are referred to as catecholamine-secreting paragangliomas.

Pheochromocytomas are rare, occurring in less than 0.2 per cent of patients with hypertension.^(3,4)

This disease has been classically described to be suspected in patients with the clinical triad of headache, sweating and tachycardia.⁽³⁾ However, most patients do not have this clinical triad.⁽⁵⁾

Sustained or paroxysmal hypertension is the most common sign of pheochromocytoma. Paroxysmal hypotension can also occur, confusing the picture.

Due to the above symptoms being present in a variety of conditions, diagnosis of this condition is usually difficult and thus around ten per cent are spotted incidentally due to the increased use of imaging, and many are found on autopsy.⁽⁵⁾

After the diagnosis was made the patient did mention intermittent symptoms present for many years suggestive of an underlying pheochromocytoma; however, this is easy to see in retrospect.

Investigations for pheochromocytoma include biochemical testing and imaging, with biochemical testing to be done first in suspected pheochromocytoma. The most common tests include the measurement of urinary and plasma fractionated metanephrines and catecholamines. There has been some controversy surrounding this issue with a lot of debate over which test is best, with recently plasma fractionated metanephrines being proposed by investigators as the best test.⁽⁶⁾

Certain medications that include tricyclic antidepressants and other psychoactive agents should, if possible, be stopped or tapered down prior to the test being performed as they interfere with test interpretation.

Imaging involves CT or MRI. As mentioned above, ten per cent are found incidentally. Either modality is appropriate for picking up tumours. These modalities need to be used to detect any possible metastases as well. If both modalities are negative and there is still a high index of suspicion, a 123-I-metaiodobenzylguanidine (MIBG) scintigraphy can detect undetectable tumours.⁽⁷⁾

Pheochromocytoma is associated with disorders such as Von Hippel Lindau (VHL) syndrome, multiple endocrine neoplasia type 2, and familial paraganglioma.

Sporadic pheochromocytomas are also associated with specific genetic mutations specifically to do with the certain tumour suppressor genes that include the VHL, rearranged during transfection (RET), succinate dehydrogenase complex subunit D (SDHD) and succinate dehydrogenase complex subunit B (SDHB) genes.⁽⁸⁾

Based on a literature review from the online review database *Uptodate*, genetic testing should be considered if the patients have one of the following symptoms that include paraganglioma, bilateral adrenal pheochromocytoma, unilateral adrenal pheochromocytoma and a family history of pheochromocytoma/paraganglioma and a unilateral adrenal pheochromocytoma onset at a young age (eg, <20 years).⁽⁹⁾

Definitive treatment involves surgical removal of the tumour. This can be done laparoscopically or via open

anterior midline approach. As expected, the laparoscopic route is preferred now due to the reduced post-operative hospital stay and complications.⁽¹⁰⁾

Prior to surgery, patients should undergo alpha blockade and then beta blockade. There is no significant consensus on how to do this, but general concepts involve the use of phenoxybenzamine, which is an irreversible, long-acting, non-specific alpha blocker, with the addition of a beta blocker towards the final two to three days prior to surgery.

The patient had an adrenal haemorrhage that was masking the pheochromocytoma initially. There are very limited case reports of this phenomenon, with only around 50 cases being reported.^(11,12) However, the patient was on clopidogrel, which could have worsened the situation. The chest infection was an additional problem that the patient presented with.

In retrospect, a diagnosis of pheochromocytoma could have been suspected for many years in this patient; however, a combination of various other medical issues made this diagnosis difficult.

In addition, adrenal haemorrhage is a relatively uncommon condition with a variable and non-specific presentation that may lead to acute adrenal crisis, shock, and death unless it is recognised promptly and treated appropriately.⁽²⁾

REFERENCES

1. Fernández-Calvet L, García-Mayor RV. Incidence of pheochromocytoma in south Galicia, Spain. *J Intern Med* 1994;236(6):675-7
2. Vella A, Nippoldt TB, Morris JC 3rd. Adrenal hemorrhage: a 25-year experience at the Mayo Clinic. *Mayo Clin Proc* 2001;76(2):161-8
3. Stein PP, Black HR. A simplified diagnostic approach to pheochromocytoma. Review of the literature and report of one institution's experience. *Medicine (Baltimore)* 1991;70(1):46-66
4. Pacak K; Linehan WM; Eisenhofer G; Walther MM; Goldstein DS. Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. *Ann Intern Med* 2001;134(4):315-29
5. Kudva YC, Young WF Jr, Thompson GB, Grant CS, van Heerden JA. Adrenal incidentaloma: an important component of the clinical presentation spectrum of benign sporadic adrenal pheochromocytoma. *Endocrinologist* 1999;9(2):77-80
6. Lenders JW, Pacak K, Walther MM, *et al.* Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA* 2002;287(11):1427-34
7. Bravo EL. Pheochromocytoma: new concepts and future trends. *Kidney Int* 1991;40(3):544-56
8. Neumann HP; Bausch B; McWhinney SR. Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med* 2002;346(19):1459-66
9. Young WF Jr, Kaplan NM. Pheochromocytoma in genetic disorders. Last literature review version 17.2: *uptodate* database (uptodate.com). May 2009
10. Matsuda T; Murota T; Oguchi N; Kawa G; Muguruma K. Laparoscopic adrenalectomy for pheochromocytoma: a literature review. *Biomed Pharmacother* 2002;56 Suppl 1: 132s-138s
11. Sutton MG, Sheps SG, Lie JT. Prevalence of clinically unsuspected pheochromocytomas. Review of a 50-year autopsy series. *Mayo Clinic Proc* 1981;56(6):354-60
12. Arora S, Vargo S, Lupetin AR. Computed tomography appearance of spontaneous adrenal hemorrhage in a pheochromocytoma. *Clin Imaging* 2009;33(4):314-17