CASE REPORT

Phaeochromocytoma with hypercortisolism and hypercalcaemia

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SUMMARY

We report a case of phaeochromocytoma associated with hypercortisolism and hypercalcaemia in a 62-year-old man. The patient presented to clinic, with a 3-year history of exertional headaches, and a 4-month history of increasing fatigue, sweating and palpitations, loss of appetite and weight, and sleepiness. He did not have a medical, family or social history that could account for these symptoms. 24 h urinary catecholamines, plasma metanephrines, 24 h urinary cortisol and adjusted serum calcium, were elevated. Overnight low-dose dexamethasone suppression test did not suppress morning plasma cortisol. Serum intact parathyroid hormone and parathyroid hormone-related peptide were low, and adrenocorticotrophic hormone was normal. The patient was treated with intravenous 0.9% sodium chloride and disodium pamidronate to control hypercalcaemia. CT showed a 10 cm left adrenal mass. Following inpatient treatment with phenoxybenzamine, he underwent a left adrenalectomy and histology confirmed a phaeochromocytoma. Postoperatively, he required long-term steroids for contralateral adrenal suppression. Adjusted serum calcium returned to normal postoperatively.

BACKGROUND

Secretion of non-catecholamine hormones and peptides by phaeochromocytoma has been infrequently reported in the literature.¹ Given its rarity, screening for other hormones is therefore not routinely performed in every patient with phaeochromocytoma. However, since ectopic hormone secretion has implications for management in the perioperative period, prompt identification and appropriate management is important. Most often, only one additional hormone is secreted and this has been reported in a few case studies; the most common reported clinical association has been with hypercortisolism.^{1 2} This is thought to be due to either adrenocorticotrophic hormone (ACTH) or corticotrophin releasing hormone (CRH) co-secretion. Other co-secreted hormones reported are calcitonin, interleukin 6 (IL-6), parathyroid hormone (PTH), vasoactive intestinal peptide (VIP), growth hormone (GH), renin, aldosterone and testosterone.¹ A PubMed search did not find any reported cases of phaeochromocytoma presenting with both hypercortisolism and hypercalcaemia.

CASE PRESENTATION

A 62-year-old man presented to the endocrine unit, with a 3-year history of excruciating exertional

headaches, lasting for 5–10 min, which resolved following resting. In addition, he had a 4-month history of constant fatigue; intermittent sweating, palpitations, loss of appetite and weight, and sleepiness. He also reported a 3-week history of constipation, for which he was prescribed laxatives. He was not on any regular medications. His father and mother had both died following a stroke, at the age of 91. Apart from excision of a neck lipoma, his medical history was uneventful. Specifically, there was no medical or family history of any endocrine disorder. The patient did not smoke or drink alcohol. Examination of the neck, chest and abdomen was normal. His blood pressure was 120/72 mm Hg; heart rate was 80/min and weight was 54.5 kg.

INVESTIGATIONS

The headache was initially assessed by neurology. A CT scan of the head found no underlying cause of the headache and the patient was discharged. Abdominal ultrasound at the referring hospital revealed a 9 cm well-defined slightly heterogeneous soft tissue mass in the left upper quadrant. CT scan of the thorax in arterial phase and abdomen in portal venous phase demonstrated a 10.3 cm maximum diameter diffusely heterogeneous left supra-renal mass with a central attenuation of 74 Hounsfield units, in keeping with an enhancing suprarenal lesion (figure 1). It also showed multiple sclerotic bone lesions in the pelvis and upper femur, thought to be bone islands. A small left renal calculus was shown but the liver, spleen and pancreas were normal. There was no lymphadenopathy in the chest or abdomen and no lung metastases.

On presentation, the elevated adjusted serum calcium (3.45 mmol/L, normal range 2.20–2.60 mmol/L) with a low intact PTH (7 ng/L normal range: 11–54 ng/L) and elevated serum alkaline phosphatase (720 IU/L, normal range 30–130 IU/L) were suggestive of a non-parathyroid cause of hypercalcaemia (such as malignancy or granulomatous disease). Serum immunoglobulin electrophoresis was normal and urine protein electrophoresis did not show any monoclonal free light chains. PTHrP was undetectable (<1 pmol/L, normal range 0.7–1.8 pmol/L).

The patient's 8:00 serum cortisol (1046 nmol/L, reference range: 171–536 nmol/L) and 24 h urinary cortisol (354 nmol/24 h, normal range: 10–147 nmol/24 h) levels were significantly elevated. Cortisol failed to suppress following overnight low-dose (1 mg) dexamethasone (279 nmol/L, normal response <50 nmol/L). An 11.8 ng/L (range

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Figure 1 Coronal images of venous phase CT and positron emission tomography-CT scan showing large left adrenal mass displacing the left kidney inferiorly.

at midnight <15 ng/L, range at 9am < 46 ng/L) plasma ACTH measured at 14:30 indicated an ACTH-independent cause of Cushing's syndrome. Testosterone, dehydroepiandrosterone and renin levels were normal.

Biochemistry showed elevated plasma normetanephrine (>25 000 pmol/L, reference range: 120–1180 pmol/L) and 24 h urine norepinephrine (12 342 nmol, reference range <500 nmol/L) were markedly raised, suggestive of a pheochromocytoma.

The patient was also noted to have microcytic anaemia: haemoglobin, 107 g/L (normal range: 130–180 g/L); mean cell volume, 79.8 fL (normal range: 81.8–96.3 fL). Serum B12, folate and ferritin levels were normal.

The provisional diagnosis was that of a malignant adrenal neoplasm. Whole body ¹⁸fluorodeoxyglucose positron emission tomography (¹⁸FDG-PET) was therefore arranged and this showed a markedly hypermetabolic left supra renal mass (maximum standard uptake value (SUV) of 15.5) without uptake elsewhere (figure 1). The right adrenal gland was normal. There were no hypermetabolic destructive bone lesions.

TREATMENT

The patient was admitted at presentation to the endocrine unit where he received intravenous 0.9% sodium chloride and disodium pamidronate for hypercalcaemia. He was normotensive throughout, which is unusual for a pheochromocytoma, particularly of this size. It is possible that episodes of paroxysmal hypertension occurred in association with headaches and other reported symptoms. He was also started on phenoxybenzamine (which caused significant postural hypotension, as expected); the dose was titrated up to 20 mg twice daily. Iron supplements were also started for anaemia. Approximately 4 weeks after presentation, he underwent hand-assisted laparoscopic left adrenalectomy. The adrenal gland was completely excised; it weighed 264 g and measured 98×55×67 mm. Histological sections confirmed a pheochromocytoma with no histological features to suggest aggressive behaviour (no diffuse growth, no evidence of vascular or capsular extension, no necrosis and very occasional mitosis). The tumour expressed synaptophysin, CD56 and chromogranin A, but there was no staining with ACTH. PTHrP or CRH were not stained for.

OUTCOME AND FOLLOW-UP

The patient recovered in the postoperative period and the headaches completely settled. The short synacthen test (SST) 4 days after surgery showed mild adrenal insufficiency (300 nmol/L and 450 nmol/L at 0 and 30 min, respectively, after intravenous synacthen). Hydrocortisone was not given as it was thought that the right adrenal gland would recover spontaneously.

The patient re-presented 12 days postoperatively with fatigue, nausea and dizziness. He had a low blood pressure 90/

54 mm Hg, elevated white cell count ($25.3 \times 10^9/L$) and raised C reactive protein (289.6 mg/L). Blood cultures, urine analysis, microscopy and other cultures were all negative. The patient was started empirically on intravenous coamoxiclav for presumed sepsis and stat single dose of intravenous hydrocortisone 100 mg (later reduced to 50, then 20 and finally to 10 mg three times a day). His symptoms settled and blood pressure improved following treatment. A SST at 6 weeks after surgery remained subnormal (270 and 316 nmol/L at 0 and 30 min, respectively, after intravenous synacthen).

He was successfully weaned off hydrocortisone around 1 year postoperatively, when his SST was normal (402 and 516 nmol/L at 0 and 30 min, respectively, after intravenous synacthen). Urine catecholamines and metanephrines, plasma free metanephrines and adjusted serum calcium were normal at outpatient follow-up. A postoperative colonoscopy and gastroscopy did not identify a gastrointestinal cause for the anaemia and his iron supplements were continued for 1 year.

DISCUSSION

Most pheochromocytomas originate from the adrenal medulla, secreting catecholamines. Around 20% arise from extra-adrenal paraganglionic tissue. Pheochromocytomas may present in association with multiple endocrine neoplasia 2 (MEN2), neurofibromatosis type 1, Von Hippel-Lindau disease type 2 and some other rare syndromes. MEN2 can present with pheochromocytoma and primary hyperparathyroidism causing hypercalcaemia (which was not present in our patient as PTH level was low).³

Pheochromocytomas usually secrete one or more catecholamines and their metabolites. Rarely, these tumours are associated with hypercortisolism, and this may occur through ectopic secretion of ACTH or CRH by the adrenal medullary tumour.^{4 5} Furthermore, pheochromocytomas may be associated with adrenal cortical hyperplasia in the same gland, thought to be due to paracrine stimulation from the pheochromocytoma. This may also present with subclinical Cushing's syndrome.^{6 7} This was unlikely in our patient as the histology of the background adrenal was normal. There are several clinical manifestations of hypercortisolism, but in a perioperative patient such as ours, important considerations need to be borne in mind, including hypertension, glucose intolerance and hypokalaemia necessitating preoperative treatment.⁴ Hypercortisolism causes tissue fragility and may increase the risk of perioperative bleeding.¹ In this case, the cause of hypercortisolism was uncertain as there was no staining for ACTH suggesting lack of detectable protein production.

Hypercalcaemia associated with pheochromocytoma has been documented and thought to be caused by the production of PTH or PTHrP by the tumour.^{2 8 9} The low preoperative blood levels of PTH and PTHrP suggest an alternative (but as

yet unexplained) cause of hypercalcaemia in this patient. The bone lesions were not thought to be associated with the hypercalcaemia as they were not metastases. Ectopic secretion of calcitriol (reported to cause hypercalcaemia in a patient with non-Hodgkin's lymphoma) might be a possibility.¹⁰ Unfortunately, vitamin D levels were not measured in this patient before surgery.

Though immunochemical staining for CRH and PTHrP was not available in our institution, the low serum levels of ACTH and PTHrP would suggest these were not produced by the tumour. Though the exact physiological aetiology is not confirmed, the production of ectopic secretions by the pheochromocytoma is clear as both serum calcium and cortisol levels recovered following removal of the tumour.

The cause of microcytic anaemia was unclear as there was no obvious source of bleed; and haematinics, gastrointestinal endoscopy and myeloma screen were normal. One explanation for microcytic anaemia in this patient could be occult haematuria secondary to renal calculus.

This case report highlights the rare occurrence of multiple endocrine abnormalities in a patient with pheochromocytoma and the potential for perioperative complications from ectopic hormone secretion. Our experience supports a role for routine preoperative overnight dexamethasone suppression test and calcium levels in patients suspected to have a pheochromocytoma.

Patient's perspective

I found that the medical care and treatment I received from the moment I was admitted into hospital and throughout was of the highest standard of professionalism and expertise. This really enabled me to feel at ease, and to have confidence in the medical staff and in the treatment I received over the weeks leading up to the operation, and in the operation itself and thereafter. I am extremely thankful and indebted to the consultants, registrar, anaesthetist, doctors, nurses and all the other medical staff who cared for me. And finally, as a Christian I am grateful to God for the peace He gave me.

Contributors OE acquired and analysed the data, and drafted the manuscript. JW analysed the data, and drafted and revised the paper. MF analysed the data,

Learning points

- ▶ Awareness of the potential for multiple endocrinopathies (such as hypercalcaemia and hypercortisolism in addition to catecholamine excess) in patients with pheochromocytoma.
- ▶ Routine screening for cortisol excess in patients with a pheochromocytoma would identify patients at risk of postoperative adrenal insufficiency.
- ▶ All patients with preoperative evidence of cortisol excess should have appropriate monitoring and steroid replacement (if required) following surgery.

and drafted and revised paper. RV analysed the data, and drafted and revised the paper. SPB was responsible for conception, and acquired and analysed data, and drafted the manuscript.

Competing interests None declared.

Patient consent Obtained.

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