

A case of adrenal Cushing's syndrome and primary hyperparathyroidism due to an atypical parathyroid adenoma

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Abstract: Cushing's syndrome is a rare disorder of cortisol excess and is associated with significant morbidity and mortality. Hypercalcaemia due to hyperparathyroidism is a common condition; however, in 10% of young patients, it is associated with other endocrinopathies and occurs due to a genetic variant [e.g. multiple endocrine neoplasia (MEN) type 1 (MEN1), MEN2 or MEN4]. We report the case of a 31-year-old woman who was referred to the endocrinology out-patient service with an 8-month history of hirsutism, amenorrhoea and weight gain. Her biochemical work up was significant for adrenocorticotrophic hormone (ACTH)-independent Cushing's syndrome. Radiological investigations revealed an adrenal adenoma. During investigation she was also found to have primary hyperparathyroidism due to a parathyroid adenoma. Pre-operatively, the patient was commenced on metyrapone and both her adrenal and parathyroid lesions were resected successfully. There were several concerning findings on initial examination of the parathyroid tumour, including possible extension of the tumour through the capsule and vascular invasion; however, following extensive review, it was ultimately defined as an adenoma. Given the unusual presence of two endocrinopathies in a young patient, she subsequently underwent genetic testing. Analysis of multiple genes did not reveal any pathogenic variants. The patient is currently clinically well, with a normal adjusted calcium and no clinical features of cortisol excess. She will require long-term follow up for recurrence of both hypercalcaemia and hypercortisolaemia.

Keywords: Cushing's syndrome, adrenal adenoma, atypical parathyroid adenoma

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Background

Hypercalcaemia and Cushing's syndrome are both important health conditions that cause disabling symptoms. They can occur together in the setting of multiple endocrine neoplasia (MEN) but rarely co-exist outside of these conditions. Atypical parathyroid adenomas are rare, benign lesions that share overlapping features with parathyroid carcinoma.

We report the unique case of a 31-year-old woman who was diagnosed with both conditions in the absence of a known genetic condition. To our knowledge, this is the first reported case of an

atypical parathyroid adenoma and adrenal adenoma occurring in the same patient.

Case presentation

A 31-year-old Caucasian woman was referred to the Endocrinology service with an 8-month history of secondary amenorrhoea, fatigue, hirsutism and a 13-kg weight gain. She denied easy bruising and proximal myopathy and had no past medical history. On examination the patient was hypertensive and had a body mass index of 26.2 kg/m². She exhibited marked clinical features of cortisol excess including dorsal skin thinning, hirsutism,

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Table 1. Laboratory results.

Result	Level	Reference interval
Testosterone	<0.5	0.3–1.7 nmol/l
Androstenedione	1.3	2–5.4 nmol/l
DHEAS	<0.4	1.6–7.8 μ mol/l
17-hydroxyprogesterone	<1.0	<18 nmol/l (adult female)
Oestradiol	<100	Varies with cycle phase (pmol/l)
FSH	4.4	Varies with cycle phase (IU/l)
LH	3.0	Varies with cycle phase (IU/l)
Free T4	15.1	10.5–22 pmol/l
TSH	0.71	0.27–4.2 mIU/l
Prolactin	704	102–496 nmol/l
IGF-1	152	73–244 μ g/l
Normetanephrine	<300	0–1180 pmol/l
Metanephrine	<100	0–510 pmol/l
3-methoxytyramine	<100	0–180 pmol/l
Aldosterone	130	122–1179 pmol/l
Direct renin	25.8	6.1–62.7 mIU/l

DHEAS, dehydroepiandrosterone; FSH, follicle stimulating hormone; IGF1, insulin like growth factor 1; LH, luteinising hormone; TSH, thyroid stimulating hormone.

facial flushing, characteristic moon facies, inter-scapular fat pad, central adiposity and purple abdominal striae.

Investigation

Laboratory studies revealed hypercortisolaemia. Her baseline morning cortisol level was 704 nmol/l. A 48 h low-dose dexamethasone suppression test was performed; cortisol values at 24 h and 48 h were 702 nmol/l and 703 nmol/l, respectively (normal suppression <50 nmol/l).¹

Her baseline adrenocorticotrophic hormone (ACTH) level was appropriately suppressed at 1.4 ng/l [reference interval (RI): 7.2–63.3 ng/l], which was consistent with a diagnosis of ACTH-independent Cushing's syndrome. Concentrations of androstenedione and dehydroepiandrosterone sulphate were both less than the respective lower reference limits [1.3 nmol/l (2.0–5.4 nmol/l) and

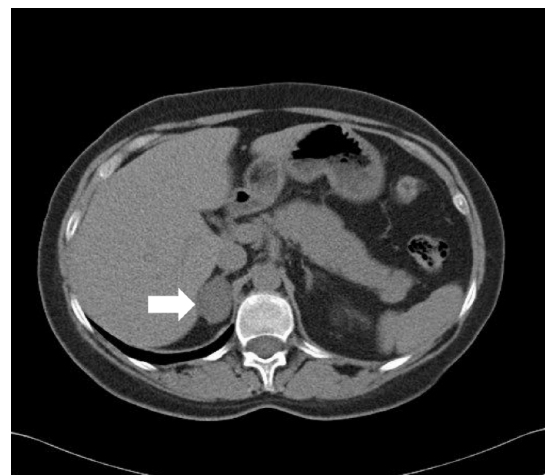


Figure 1. Dedicated adrenal CT showing an adenoma (white arrow). CT, computed tomography.

<0.4 μ mol/l (1.6–7.8 μ mol/l), respectively] due to ACTH suppression.

Other relevant laboratory results including a pituitary profile and a biochemical work-up of amenorrhoea are depicted in Table 1.

A 24-h urinary steroid profile (analysed at St Bartholomew's Hospital, London) demonstrated elevated 11-hydroxy cortisone and low concentrations of corticosterone/cortisol metabolites, which further supported the diagnosis of autonomous cortisol secretion. A 24-h urinary free cortisol was not performed.

With evidence of clinical and biochemical cortisol excess, a dedicated adrenal computed tomography (CT) was performed to localise the site of disease and revealed a 3.3 \times 2.2 cm lesion of the right adrenal gland. Hounsfield units were <10 and radiological features were consistent with an adrenal adenoma (Figure 1). The contralateral adrenal gland appeared normal on imaging and both kidneys appeared structurally normal.

During the course of her outpatient investigations, the patient was also found to have an elevated adjusted calcium level of 2.7 mmol/l (RI: 2.17–2.51 mmol/l). This was accompanied by an elevated parathyroid hormone level of 113.5 ng/l (15–65 ng/l), a Vitamin D level of 27 nmol/l (>50 nmol/l considered sufficient), a reduced phosphate level of 1.06 mmol/l (RI: 1.12–1.45 mmol/l) and a normal renal profile.

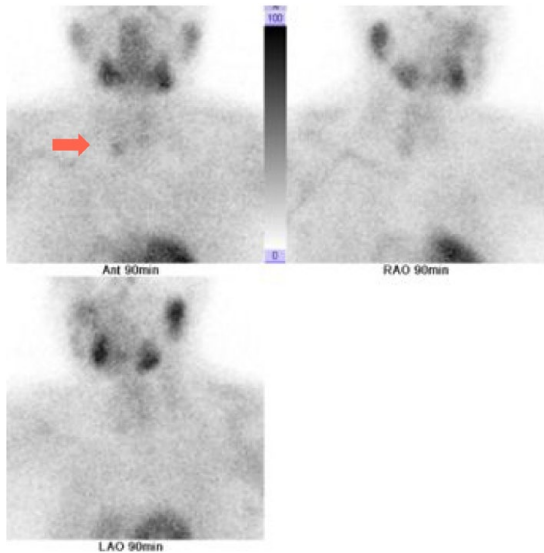


Figure 2. Sestamibi scan showing tracer uptake in the lower right parathyroid gland (red arrow).

This biochemical profile was suggestive of a diagnosis of primary hyperparathyroidism. The patient denied any family history of hypercalcaemia, hypercortisolaemia or other endocrinopathies. A 24h urinary calcium level of 6.45 mmol/day (RI: 2.5–7.5) excluded a diagnosis of benign familial hypocalciuric hypercalcaemia.

Other investigations including serum glucose, gastrin, vasoactive intestinal peptide and pancreatic polypeptide were not performed as the patient did not display any gastrointestinal symptoms at that time. A DEXA scan to determine bone density was not performed.

A parathyroid ultrasound and sestamibi scan (Figure 2) showed concordance, identifying a 1 cm right inferior parathyroid adenoma.

A specialist surgical opinion was sought for these two synchronous findings and, following multidisciplinary team discussion, the decision was made to treat the patient's Cushing's syndrome with a laparoscopic adrenalectomy before performing a parathyroidectomy to treat her primary hyperparathyroidism.

Prior to the adrenalectomy, the patient was commenced on metyrapone to reduce serum cortisol levels and minimise peri-operative complications. She was commenced on metyrapone at a dose of 250 mg three times daily (tds), which was

gradually increased to 500 mg tds. She was educated on potential side effects and the importance of use of effective contraception while using metyrapone. She was counselled regarding possible hypocortisolaemia and provided with hydrocortisone supplementation for emergency use. Given the short duration of metyrapone use, the patient was monitored clinically and initially with daily and then weekly serum sodium, potassium and cortisol measurements until her serum cortisol was below 200 nmol/l. At each hospital visit her blood pressure was checked and she was asked about symptoms of hypocortisolaemia.

Treatment

The patient's hirsutism, hypertension and facial swelling improved significantly with a combination of metyrapone and anti-hypertensive medications.

She underwent successful adrenalectomy from a retroperitoneal laparoscopic approach after 4 weeks of metyrapone therapy.

She was able to discontinue anti-hypertensive medications and had spontaneous recovery of menstruation. She initially had symptoms of hypocortisolaemia and was treated with oral hydrocortisone; however, this was discontinued after 9 months as the patient's morning cortisol was 398 nmol/l, indicating contralateral adrenal gland recovery.

To treat her second endocrinopathy, the patient underwent a four-gland neck exploration with intra-operative parathyroid hormone (PTH). There was an interval of 5 months between surgeries and during this time the patient's serum corrected calcium fluctuated between 2.7 and 2.9 mmol/l. She denied symptoms of polydipsia, polyuria or constipation, and maintained a fluid intake of 2.5–3 l of water per day. She did not require pharmacological therapy to reduce her serum calcium during this time.

During surgery, the right lower parathyroid gland was excised and the intra-operative PTH reduced from a baseline of 193 ng/l to 55 ng/l at 10 min, which satisfied the Miami Criterion for successful parathyroid gland resection. The patient's post-operative biochemistry was satisfactory, with an adjusted calcium of 2.37 mmol/l, intact PTH (iPTH) of 19.6 ng/l and phosphate of 1.11 mmol/l.

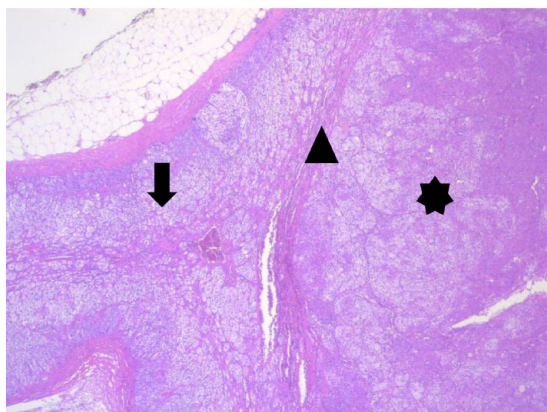


Figure 3. Adrenal adenoma (asterisk), normal adrenal tissue (downwards arrow) and capsule intact (triangle). Magnification factor $\times 5$.

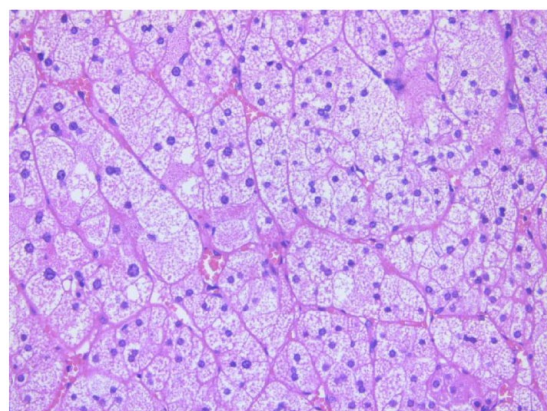


Figure 4. High-magnification view of adrenal adenoma. Magnification factor $\times 20$.

Outcome and follow up

Histology of the adrenal gland confirmed a 2.6 cm encapsulated adenoma confined to an otherwise normal adrenal gland. A mixture of clear and compact cells was identified without capsular or vascular involvement and the Ki67 index was $<5\%$ (Figures 3–5).

Histology of the parathyroid gland showed an atypical parathyroid adenoma with a calcified capsule, partial extension of the tumour through the capsule and morphological changes raising the possibility of vascular invasion. The Ki67 proliferation index was $<2\%$ (Figures 6–9). The sample weighed 1.485 g in total (including a portion of thymic tissue). Given the neoplastic features and

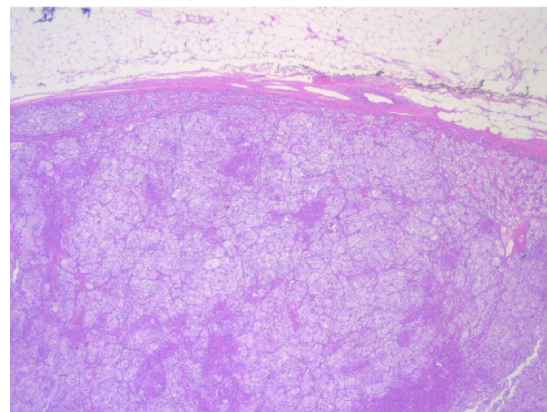


Figure 5. Intact capsule of the adrenal adenoma.

the complexities of this case, the specimen was sent to St. Guy's and Thomas' Hospital in London for a second pathological opinion. There was no necrosis or increased mitotic activity. The appearances of entrapped tumour cells within the capsule, without complete invasion, were considered in keeping with an atypical adenoma.

Given the atypical nature of the parathyroid adenoma, the presence of two endocrinopathies and her young age, the patient was tested genetically for the following panel of genes: *MEN1*; *Cyclin Dependent Kinase Inhibitor (CDKN) 1A, 1B, 2B and 2C*; *RET*; *Cell Division Cycle 73 (CDC73)*/hyperparathyroid jaw-tumour syndrome and *Calcium sensing receptor (CASR)*. No pathogenic variants were identified.

The patient is currently clinically well. She does not have any features of cortisol excess or hypertension and her adjusted calcium is in the normal range. The multidisciplinary team determined the patient will require long-term follow up for recurrence of hypercalcaemia and hypercortisolaemia as atypical adenomas are associated with occasional recurrence.

Discussion

We present this interesting case of synchronous Cushing's syndrome and hypercalcaemia secondary to an atypical parathyroid adenoma. We will discuss the interesting aspects of this case, namely the use of metyrapone pre-operatively in a patient with adrenal Cushing's; the occurrence of Cushing's syndrome and hyperparathyroidism together outside of a known genetic variant; and the presence of atypical parathyroid histology.

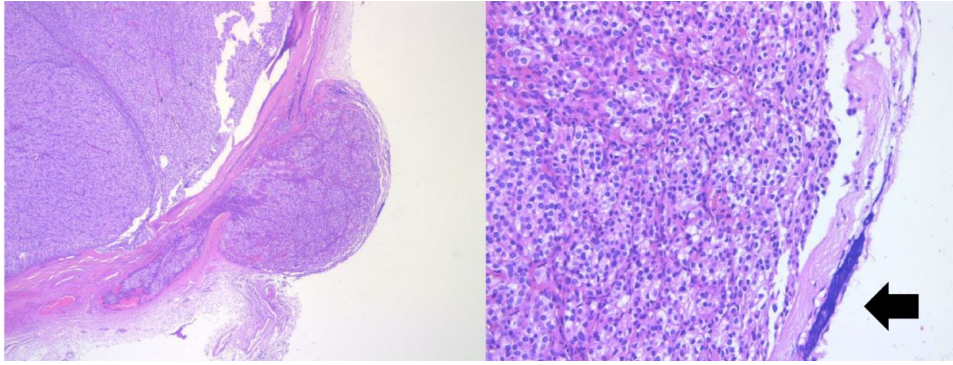


Figure 6. (a) Extension of the parathyroid adenoma through the capsule; (b) however, a thin rim of capsule was left intact (arrow).

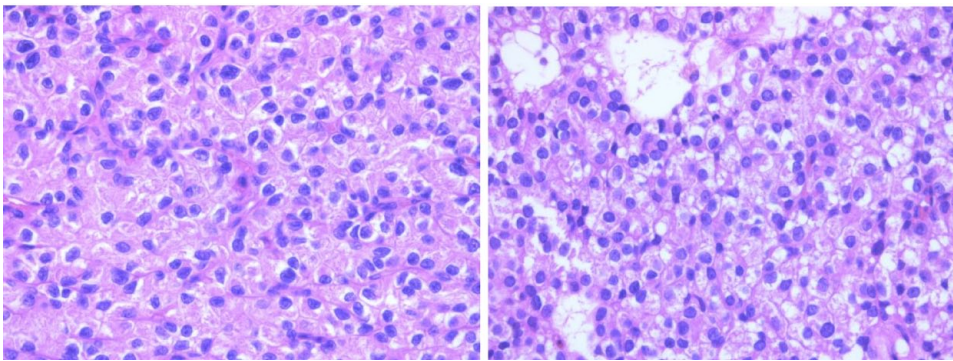


Figure 7. Cellular atypia.

Cushing's syndrome is a rare disorder caused by excess cortisol secretion. Untreated Cushing's syndrome is associated with an increased risk of mortality and multiple significant co-morbidities including diabetes, hypertension and cardiovascular disease.^{2,3}

Definitive treatment of Cushing's syndrome requires the excision of any causative lesion.⁴ Given the effects of hypercortisolaemia, patients are often high-risk surgical candidates. In such cases, adrenolytic agents or adrenal enzyme inhibitors (including metyrapone) can be used pre-operatively to normalise cortisol levels and reduce the operative risk.

Metyrapone is extremely effective at reducing cortisol levels and will reduce circulating cortisol in up to 90% of patients with hypercortisolaemia.⁵

Despite its efficacy, metyrapone can cause troubling side effects – most notably hirsutism, hypertension and oedema, through increased levels of

androgen and mineralocorticoid precursors; and not all patients receive metyrapone pre-operatively because of this reason.

In one recent study, only 20% of patients with Cushing's syndrome received pre-operative medical treatment and treatment (including metyrapone and ketoconazole) was reserved for patients with more complex disease and those deemed to have a high risk of complications and/or recurrence.⁶ A 2018 study also demonstrated that pre-operative metyrapone is well tolerated in patients with adrenal adenomas, including female patients who did not experience increased hyperandrogenism.⁷

One of the most interesting aspects of our case is the presence of adrenal Cushing's syndrome with hypercalcaemia, particularly given both the young age of the patient and the atypical parathyroid gland histological findings.

It is estimated that 10% of patients with hypercalcaemia aged <45 years have a genetic variant

causing hypercalcaemia. One such genetic cause is MEN type 1 (MEN1) syndrome, which is characterised by at least two endocrine neoplasia in the same patient and is caused by pathogenic variants in the tumour suppresser gene on chromosome 11. It can occur as either a familial autosomal dominant (roughly 90% of cases) or sporadic (10%) condition and is characterised by parathyroid (95%), pancreatic (41%) and pituitary nodules (30%).⁸ Non-secreting adrenal adenomas occur in 24% of patients with MEN1 and a total of 73% of patients will have some degree of adrenal involvement.⁹ While many patients with MEN1 will experience both ACTH-dependent Cushing's disease and hypercalcaemia, ACTH-independent Cushing's syndrome is rare in MEN1 syndrome.¹⁰

Patients with MEN4 (a recently described syndrome with similarities to MEN1) show high rates of hypercalcaemia; however, to date there have been no reported cases of adrenal Cushing's syndrome in such patients. MEN2 has been linked to ACTH-dependent Cushing's syndrome (from both pituitary and ectopic ACTH) but not with adrenal Cushing's syndrome.^{11,12} We have not identified any reported cases of adrenal Cushing's syndrome and hypercalcaemia in the setting of *CDC73*, *CASR*, *CDKN2B* or *CDKN2C* mutations in the literature.

Atypical parathyroid adenomas are rare lesions that demonstrate some features, but are not diagnostic, of carcinoma. They account for roughly 1.2% of all parathyroid adenomas.¹³ Histologically, they may contain features such as dense fibrous bands and prominent nuclear atypia; however, they do not display invasion into the lymphovascular, perineural or surrounding space.¹⁴

Patients presenting with atypical parathyroid adenomas have a higher calcium, PTH and urinary calcium than patients with typical adenomas.¹⁵ Clinically they present at the same age as patients with typical adenomas; however, the sex distribution is different and goes from a 1:1 ratio in typical adenomas to a female:male 4:1 ratio.¹⁶

From a histological perspective, one case series found a number of differences between typical and atypical adenomas,^{15,16} including increased rates of:

- Pseudocapsular invasion;
- Bands of fibrosis;

- Higher mitotic rates;
- Thick capsule;
- Ki-67 > 4%;
- Heavier gland (grossly).

Atypical adenomas may occur sporadically or as part of an inherited syndrome – they account for <1% of adenomas in MEN1,¹⁷ and have also been observed in Hyperparathyroidism-jaw tumor (HPT-JT) syndrome.¹⁸ They are seen more commonly in Asian countries.¹⁹

Patients with an inherited syndrome causing atypical parathyroid disease present much younger (often in the third decade) and are more likely to have a palpable neck mass. Up to 40% of these patients will experience a recurrence compared with just 2% of patients with sporadic disease.¹⁵

Although recurrence in sporadic atypical disease is rare, long-term follow up is advised. While there is no agreed follow-up protocol, in this case we have decided to perform biochemical testing for hypercalcaemia and hyperparathyroidism every 6 months for 5 years and annually thereafter, and assess for evidence of hypercortisolaemia annually.

Our case details the rare co-presentation of ACTH-independent Cushing's syndrome with atypical primary hyperparathyroidism in a young female with no known genetic variant. We have shown our centre's successful use of pre-operative metyrapone, which is not currently universal practice and outlined our evidence-based approach to the management of this patient's hypercalcaemia.

The learning points from this work are as follows:

- 10% of young patients (<45 years) with hypercalcaemia will have a genetic variant;
- Atypical adenomas are an uncommon cause of hypercalcaemia and account for the minority of parathyroid adenomas;
- Metyrapone can be used to improve symptoms of hypercortisolaemia pre-operatively even in those with mild-moderate Cushing's syndrome.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Ethics and consent

The patient provided written consent for the publication of this case report

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