Ectopic Cushing’s syndrome from an ACTH-producing pheochromocytoma with a non-functioning pituitary adenoma

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Summary

An adrenocorticotropic hormone (ACTH)-producing pheochromocytoma (PCC)/paraganglioma is the cause of ectopic Cushing's syndrome (CS) in 5.2% of cases reported in the literature. We present a previously healthy 43-year-old woman admitted to our hospital with cushingoid features and hypertensive urgency (blood pressure = 200/120 mmHg). Her 24-h urinary free cortisol was >4270 nmol/day (reference range (RR) = 100–380 nmol/day) with a plasma ACTH of 91.5 pmol/L (RR: 2.0–11.5 pmol/L). Twenty-four-hour urinary metanephrines were increased by 30-fold. Whole-body CT demonstrated a 3.7-cm left adrenal mass with a normal-appearing right adrenal gland. Sellar MRI showed a 5-mm sellar lesion. MIBG scan revealed intense uptake only in the left adrenal mass. She was managed pre-operatively with ketoconazole and phenoxybenzamine and underwent an uneventful left laparoscopic adrenalectomy, which resulted in biochemical resolution of her hypercortisolemia and catecholamine excess. Histology demonstrated a PCC (Grading System for Adrenal Pheochromocytoma and Paraganglioma score 5) with positive ACTH staining by immunohistochemistry. A PCC gene panel showed no mutations and there has been no evidence of recurrence at 24 months. This case highlights the difficult nature of localizing the source of CS in the setting of a co-existing PCC and sellar mass.

Learning points:

• An adrenocorticotropic hormone (ACTH)-producing pheochromocytoma (PCC) is an important item to be considered in all patients presenting with ectopic Cushing's syndrome (CS).
• In exceptionally rare cases, patients with ectopic CS may present with multiple lesions, and a systematic approach considering all potential sources is crucial to avoid misdiagnosis.
• CS with a large adrenal mass but lacking contralateral adrenal atrophy should raise suspicion of an ACTH-dependent process.
• In patients with clinical suspicion of PCC, clinicians should be mindful of the use of steroids and beta-blockers without appropriate alpha blockade as they may precipitate an adrenergic crisis.
Background

Cushing's syndrome (CS) is a rare disorder characterized by chronically elevated glucocorticoid levels (1). The incidence of endogenous CS is estimated to be between 0.7 and 2.4 cases per million per year, of which roughly 80–85% are adrenocorticotropic hormone (ACTH)-dependent and 15–20% are ACTH independent (1). Of ACTH-dependent CS, pituitary adenomas comprise 75–80%, while ectopic ACTH secretion (EAS) accounts for the remaining 15–20% from neuroendocrine tumors (NETs). In the largest EAS case series (n = 106) published to date, the most commonly reported sources of ACTH included bronchial carcinoid (24.5%), gastrointestinal NETs (17%), and small cell lung cancer (11.3%) (2). Data from several large ectopic CS case series reveal that a pheochromocytoma (PCC) or paraganglioma (PGL) is the cause in 5.2% of cases (3).

PCC is a rare catecholamine-secreting neuroendocrine tumor originating from chromaffin cells in the adrenal medulla (4). Of all chromaffin cell tumors, PCCs comprise approximately 85% whereas PGLs occur in the remaining 15%. The incidence of PCC and PGL is estimated to be between 2 and 8 per million per year (4). Notably, the incidence appears to be slightly higher in Alberta, Canada (6.6 cases per million) compared to other areas of the world perhaps due to the higher altitude which may encourage PCC tumor growth through potentiation of pseudohypoxia pathways already affected by mutations in PCC-related SDHx genes (5). Patients with PCC may classically present with paroxysmal headaches, tachycardia, and/or diaphoresis or with very common, yet non-specific symptoms including anxiety, nausea, vomiting, and/or febrile illness (6).

Herein, we present a challenging case of a 43-year-old woman who presented with hypertensive urgency, mild cushingoid features, adrenal mass, and sellar lesion and was found to have ectopic CS from an ACTH-producing PCC.

Case presentation

A 43-year-old woman presented to the emergency department with complaints of episodic throbbing headaches, chest discomfort, and palpitations lasting 10–30 min in the preceding 8 months. On further history, she reported facial swelling, generalized weakness, worsening abdominal obesity, anxiety, and confusion that progressed subacutely over the course of 2 months.

Her medical profile consisted of anxiety and depression treated with vortioxetine and prior spinal surgery for scoliosis. She had two uncomplicated pregnancies, the last of which was 18 years prior to her presentation. Both of her children were healthy. Her only other medication was an oral progestin-only contraceptive. One year prior to her presentation, her hemoglobin A1c, documented blood pressure, and potassium were 4.7%, 125/77 mmHg, and 3.7 mmol/L (RR: 3.5–5.0 mmol/L), respectively. Her family history was unremarkable for adrenal disease, multiple endocrine neoplasia, or other known endocrinopathies.

On physical examination, her heart rate was 75 b.p.m. with a blood pressure of 200/120 mmHg. Her weight was 47.5 kg. Clinically, she had potential features of glucocorticoid excess including mild facial plethora, abdominal adiposity despite low body weight with subtle striae, and significant proximal muscle weakness.

Investigation

Pertinent investigations included a potassium of 3.0 mmol/L (RR: 3.5–5.0 mmol/L), bicarbonate of 34 mmol/L (RR: 22–26 mmol/L), and a high-sensitivity troponin of 68 ng/L (RR: 0–18 ng/L) (Table 1). Her random blood glucose was normal. Her ECG demonstrated T-wave inversions in the precordial leads.

Given the initial concern for an acute coronary syndrome or vasospastic angina in the setting of a hypertensive emergency, she was admitted to cardiology with telemetry. She was managed with amlodipine, bisoprolol, perindopril, and a nitroglycerin patch. A coronary angiogram was performed and was unremarkable. Despite four anti-hypertensives, she continued to have resistant and labile blood pressures ranging between 140/86 and 227/137. This prompted a secondary hypertension investigation that revealed a profoundly elevated 24-h urinary cortisol (>4270 nmol/day, RR: 100–380 nmol/day) with a concomitantly elevated ACTH (91.5 pmol/L, RR: 2.0–11.5 pmol/L) (Table 2).

An overnight 1 mg dexamethasone suppression test was abnormal yielding an AM cortisol of 1331 nmol/L (RR: <50 nmol/L). Her clinical features in combination with markedly abnormal and concordant results on two different tests was highly suggestive of ACTH-dependent CS.

A CT of her chest/abdomen/pelvis demonstrated a well-circumscribed, low-grade enhancing homogenous 3.7-cm left adrenal mass with a normal-appearing right adrenal gland (Figs 1 and 2). The lack of contralateral adrenal atrophy, elevated DHEAS, and presence of high ACTH level suggested that the diagnosis would not be a primary adrenal cortisol-producing tumor. In addition to the elevated ACTH, her thyroid indices were suggestive of central hypothyroidism (CH) (Table 2). Despite this, there was no evidence of
clinically overt hypothyroidism. An MRI sella revealed a 0.5-cm left-sided pituitary lesion, most likely representing an adenoma. It was decided to proceed with inferior petrosal sinus sampling (IPSS), believing that pituitary CS was the most likely diagnosis. However, just prior to her IPSS, the urinary metanephrine result returned positive at 30-fold the upper limit of normal (Table 2) suggesting a co-existing epinephrine-producing PCC. Therefore, IPSS was canceled as the patient had not been receiving alpha-blockade. To confirm her PCC, a metaiodobenzylguanidine (MIBG) scan was undertaken and revealed intense focal accumulation within the left adrenal mass (Figs 3 and 4). In concert with ACTH-dependent cortisol excess, a diagnosis of ACTH-secreting PCC was proposed.

Table 1  Labs at presentation.

| Lab                                      | Patient value | Reference range |
|------------------------------------------|---------------|-----------------|
| Hemoglobin (g/L)                         | 118           | 120–160         |
| Mean corpuscular volume (fL)             | 69            | 82–100          |
| White blood cells (×109/L)               | 16.5          | 4–11            |
| Platelets (109/L)                        | 246           | 150–400         |
| Sodium (mmol/L)                          | 140           | 133–145         |
| Potassium (mmol/L)                       | 3.0           | 3.5–5.0         |
| Phosphate (mmol/L)                       | 0.83          | 0.80–1.50       |
| Magnesium (mmol/L)                       | 0.93          | 0.65–1.05       |
| Calcium (mmol/L)                         | 2.36          | 2.10–2.60       |
| Albumin (g/L)                            | 41            | 33–48           |
| Creatinine (µmol/L)                      | 70            | 40–100          |
| Glomerular filtration rate (mL/min/1.73 m²) | 91            | >60             |
| Bicarbonate (mmol/L)                     | 34            | 21–27           |
| Random glucose (mmol/L)                  | 8.3           | 4–11            |
| Hemoglobin A1c (%)                       | 5.4           | <6.4            |
| Troponin (ng/L)                          | 68            | <18             |
| Alanine transaminase (U/L)               | 98            | 1–40            |
| Aspartate transaminase (U/L)             | 77            | 8–32            |
| Total bilirubin (µmol/L)                 | 16            | <24             |
| Lactate dehydrogenase (U/L)              | 353           | 100–235         |
| Alkaline phosphatase (U/L)               | 57            | 30–115          |
| Gamma glutamyl transferase (U/L)         | 56            | 8–35            |
| LDL cholesterol (mmol/L)                 | 1.40          | <3.40           |
| HDL cholesterol (mmol/L)                 | 2.78          | >1.30           |
| Triglycerides (mmol/L)                   | 3.32          | <1.70           |
| Total cholesterol (mmol/L)               | 5.68          | <5.0            |
| C-reactive protein (mg/L)                | 0.4           | <8.0            |
| Beta HCG (IU/L)                          | <1            | <5.0            |

Laboratory values that fall outside of the reference range are bolded

Table 2  Endocrine profile.

| Lab                                      | Patient value | Reference range |
|------------------------------------------|---------------|-----------------|
| Prolactin (µg/L)                         | 8             | 4–25            |
| Thyroid-stimulating hormone (mIU/L)      | 0.43          | 0.20–4.00       |
| Free T3 (pmol/L)                         | 1.9           | 3.5–6.5         |
| Free T4 (pmol/L)                         | 3.9           | 10–25           |
| Renin direct (mIU/L)                     | <1.0          | <46             |
| Aldosterone (pmol/L)                     | 115           | 70–1090         |
| AM cortisol (nmol/L)                     | 2083          | 170–500         |
| ACTH (pmol/L)                            | 91.5          | 2.0–11.5        |
| DHEAS (µmol/L)                           | 15.5          | 1.5–13.0        |
| AM cortisol after 1 mg dexamethasone suppression test (nmol/L) | 1331 | <50 |
| 24-h urinary cortisol (nmol/day)         | >4270         | 100–380         |
| 24-h urinary metanephrine (µmol/day)     | 27.4          | 0.2–0.9         |
| 24-h urinary normetanephrine (µmol/day)  | 2.7           | 0.6–2.5         |
| Plasma-free metanephrine (nmol/L)        | 4.87          | <0.49           |
| Plasma-free normetanephrine (nmol/L)     | 0.59          | <0.89           |
Treatment

Treatment with ketoconazole and phenoxybenzamine was commenced (Table 3). Her liver enzymes were checked regularly and her alanine transaminase peaked at 119 U/L (RR: <40). Her phenoxybenzamine was up-titrated to 60 mg three times daily. Additionally, she required potassium supplementation given her mild hypokalemia, deep venous thrombosis prophylaxis, as well as trimethoprim/sulfamethoxazole for *Pneumocystis jirovecii* prophylaxis.

She developed coagulase-negative *Staphylococcus* bacteremia during her hospital stay and was treated with 2 weeks of IV antibiotics after a transthoracic echocardiogram ruled out infective endocarditis.

Phenoxybenzamine was titrated pre-operatively over the course of 1 week. Supine and standing blood pressures on the day of surgery were 124/86 and 106/74 mmHg, respectively. Her supine and standing heart rates were 84 and 99 b.p.m., respectively. She subsequently underwent

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**Figure 1**
Axial CT image demonstrating a 3.7-cm left-sided adrenal mass; note lack of contralateral adrenal atrophy.

**Figure 2**
Coronal CT image demonstrating the left-sided adrenal mass.

**Figure 3**
Anterior MIBG image revealing uptake in the left adrenal gland.

**Figure 4**
Posterior MIBG image revealing uptake in the left adrenal gland.
a successful and uncomplicated laparoscopic left adrenalectomy. She was given dexamethasone 10 mg by the anesthesia team intraoperatively to prevent postoperative nausea. After her resection, she was normotensive without medications and normokalemic without potassium supplementation. She remained on replacement hydrocortisone until one month postoperatively.

Pathology evaluation of the left adrenal gland (weight: 35 g) revealed a single well-circumscribed, solid, homogenous mass (3.2 × 2.0 × 2.4 cm) with a tan-pink cut surface (distinct from background bright-yellow adrenal cortex) (Fig. 5). Background adrenal gland appeared unremarkable, without evidence of medullary or cortical atrophy, hyperplasia, or nodularity. Extensive sampling of the lesion confirmed the diagnosis of PCC with a characteristic alveolar (Zellballen) architectural pattern comprised of large polygonal cells with granular amphophilic cytoplasm (Fig. 6). Mitoses were readily identifiable (8 per 10 high-power fields) with a Ki67 labeling index of 14%. Atypical mitoses or areas of necrosis were absent. The venous invasion was identified, but resection margins were uninvolved. Neoplastic cells were immunoreactive for chromogranin (strong diffuse) and synaptophysin (strong diffuse); negative for pancytokeratin. PCC chief cells were also positive for ACTH by immunohistochemistry. SDHB cytoplasmic expression was intact.

The combined Grading System for Adrenal Pheochromocytoma and Paraganglioma Score was 5/10 based on Zellballen pattern (0), moderate cellularity (1), absence of necrosis (0), presence of vascular invasion (1), Ki67 labeling index >3% (2), and norepinephrine catecholamine type (1). An 11-gene panel (FH, MAX, NF1, RET, SDHAF2, SDHA, SDHB, SDHC, SDHD, TMEM127, and VHL) analysis by next-generation sequencing did not reveal pathogenic variants or variants of uncertain significance.

### Outcome and follow-up

When assessed 2 months postoperatively, she was off all exogenous steroids and antihypertensives. Her cushingoid features had improved, she was normotensive (blood pressure= 114/72), and her cortisol and catecholamine levels were within normal limits (Table 4). Given the high Ki67 labeling index, 24-h urinary cortisol and serum metanephrines were checked every six months and have been normal up to 24 months postoperatively. An abdominal MRI at 24 months post-adrenalectomy demonstrated no evidence of recurrence.

### Discussion

ACTH-producing PCC or PGL is an uncommon cause of ectopic CS occurring in roughly 5.2% of cases with approximately 100 patients reported in the English literature (3, 7). The ubiquitous expression of the glucocorticoid receptor explains the systemic effects that chronic hypercortisolemia can have on nearly every organ system (8). The addition of catecholamine excess leads to even further complexity as clinicians are required to simultaneously manage two conditions, each associated with a high degree of morbidity and mortality.
The pathogenesis behind ACTH production in PPGLs is not fully understood. It is believed that nearly all normal human tissues express the proopiomelanocortin (POMC) gene (9). However, outside of tumoral transformation, the POMC DNA promoter generates a shorter mRNA, which leads to inefficient translation, partly mediated by substantial methylation of the promoter. In NETs, it is postulated that neoplastic transformation leads to hypo-methylation of POMC DNA promoters, thus enabling the bioactive expression of POMC and eventual metabolism into ACTH as well other precursors (9).

Our patient presented with hypertensive urgency, hypokalemia, metabolic alkalosis, hypercortisolemia, and elevated catecholamine levels. Further complicating the diagnostic clarity was the presence of both an adrenal mass and sellar lesion. An important clue to an ACTH-driven process was the absence of contralateral adrenal gland atrophy, which we would have expected in a primary cortisol-producing adrenal tumor. Therefore, two separate explanations were plausible for her presentation:

1. ACTH-secreting PCC causing ectopic CS with an incidental non-functioning pituitary adenoma or other non-pituitary lesion or
2. Non-ACTH producing PCC with a concomitant pituitary corticotroph adenoma causing CS.

Generally, to assist with differentiating between pituitary CS and ectopic CS, a high-dose dexamethasone suppression test (HDDST) or IPSS can be performed (10). However, both are relatively contraindicated in the setting of PCC without appropriate alpha-adrenergic antagonism and therefore were not performed in our case. Nonetheless, our patient was given dexamethasone 10 mg during surgery to prevent postoperative nausea by the anesthesia team. This decision was not without risk. Roughly 25 cases of PCC crises associated with steroid administration have been reported in the literature (11). Although most cases were associated with sustained steroids or cosyntropin administration, three occurred in the context of HDDST, of which one was fatal. It is postulated that in the setting of impaired catecholamine regulation, steroids may further induce aberrant synthesis and secretion resulting in an adrenergic storm with a mortality rate of 32% (11). Therefore, despite the appropriate alpha blockade, perhaps a safer approach would have been to choose a different anti-emetic agent and forego intraoperative steroids all together.

Additionally, our patient was given bisoprolol early in her admission prior to the discovery of an adrenal mass. Beta-blockers in the absence of sufficient alpha blockade may also precipitate an adrenergic crisis and should be avoided in any patient for whom there may be clinical suspicion of PCC (12). Other medications that have been associated with adrenergic crises include metoclopramide, monoamine oxidase inhibitors, glucagon, succinylcholine, atropine, and opioid analgesics such as morphine (12).

### Table 4  Hormone profile 2 months after adrenalectomy.

| Lab                                      | Patient value | Reference range   |
|------------------------------------------|---------------|-------------------|
| Thyroid-stimulating hormone (mIU/L)      | 4.65          | 0.20–4.00         |
| Free T3 (pmol/L)                          | 5.0           | 3.5–6.5           |
| Free T4 (pmol/L)                          | 11.3          | 10–25             |
| 24-h urinary cortisol (nmol/day)         | 229.4**       | 100–380           |
| AM cortisol post 1 mg dexamethasone suppression test (nmol/L)| 24| <50 |
| AM ACTH post 1 mg dexamethasone suppression test (pmol/L) | <1.1 | <2 |
| Serum-free metanephrine (nmol/L)         | <0.2*         | <0.49             |
| Serum-free normetanephrine (nmol/L)      | 0.39*         | <0.89             |

*Performed 1 month postoperatively; **Performed 6 months postoperatively.
Trauma and tumor manipulation have also been reported as precipitants (13).

In general, ectopic CS is associated with greater degrees of hypercortisolemia than pituitary CS, albeit overlaps between the two disorders exist (10, 14). Although our suspicion for a pituitary corticotrophic adenoma was high, our patient’s severe hypercortisolemia and hypokalemia were perhaps features that were more suggestive of ectopic CS presumably from her confirmed PCC. Additionally, pituitary incidentalomas are not uncommon in the general population. The largest meta-analysis (n = 18,902) found that the average frequency of pituitary adenomas in autopsy reports of patients not suspected of having sellar pathology was 10.7% (15). As such, identifying an incidental pituitary mass was not unusual in the setting of an ACTH-producing PCC, although it did complicate our localization efforts.

Given that we were unable to delineate the source of our patient’s profound hypercortisolemia without first managing her biochemically and radiographically proven PCC, we proceeded with a laparoscopic left adrenalectomy with pre-operative alpha blockade. Pathology ultimately demonstrated features in keeping with a PCC. In addition to her tumor immunohistochemistry being positive for ACTH, her serum ACTH level fell below the threshold for detection in the morning following her adrenalectomy, albeit the latter can potentially be explained by the dexamethasone she was given intraoperatively. Nevertheless, the symptomatic and biochemical resolution of both her hypercortisolemia and catecholamine excess 2 months after hospital discharge demonstrate that the etiology was in fact an ACTH-producing PCC with a non-functioning pituitary lesion. ‘In the absence of an obvious and necessarily surgical target lesion, or had the surgery been non-curative for the ACTH excess, we would have required additional functional imaging perhaps with a Ga-68 DOTATATE scan (16).’

During the course of our investigations, our patient was also found to have biochemical indices resembling central hypothyroidism (CH) albeit without overt evidence of thyroid dysfunction on an exam, and therefore non-thyroidal illness would also be considered. The biochemical findings resolved 2 months after her adrenalectomy without replacement, as reported in other CS cases. One retrospective cohort study (n = 68) comprising both ACTH-dependent and ACTH-independent CS documented biochemical CH in 53% of patients, which subsequently resolved six to 12 months after cure (17). Another study (n = 35) demonstrated CH in 26% of patients, all of whom appeared clinically euthyroid without replacement and in whom thyroid indices normalized after cure as well (18). Multiple mechanisms appear to explain this effect including glucocorticoid-mediated hypothalamic and thyrotroph inhibition (19, 20) as well as diminished peripheral deiodination (21).

In general, the literature suggests that the prognosis of ACTH-producing PCCs is quite favorable (22). Our patient has had no evidence of recurrence at the time of this publication (24 months postoperatively).

Conclusion

An ACTH-producing PCC is an important source to consider in all patients presenting with ectopic CS and catecholamine excess given the high morbidity and mortality associated with both disorders. Our case was exceptionally unique due to the presence of both an adrenal mass representing a PCC and sellar lesion, which prohibited the use of guideline-directed diagnostic investigations used in differentiating ectopic CS from pituitary CS.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images and figures.

Author contribution statement

David Kishlyansky planned and co-wrote the manuscript. Gregory Kline was involved in the inpatient diagnostic care and contributed to the writing and editing of the manuscript. Amita Mahajan is the patient’s endocrinologist and contributed to the editing of the manuscript. Konstantin Koro was the consultant pathologist and provided images and descriptions of the specimens. Janice Pasielka was the endocrine surgeon and contributed to the editing of the manuscript. Patrick Champagne was the admitting physician and contributed to the editing of the manuscript.

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