

Cushing's syndrome caused by an occult source: difficulties in diagnosis and management

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SUMMARY

Background A 24-year-old woman presented with a 12.5 kg weight gain over 6 months (mostly abdominal), hirsutism, acne, ankle edema, polydipsia, nocturia, back pain, pigmentation, poor libido and lightened menses to our hospital in May 1986. She had been treated for the previous 2 years with furosemide and spironolactone for peripheral edema, and had stopped the combined oral contraceptive 2 months previously. She did not take tobacco, recreational drugs or alcohol. Upon physical examination she was grossly Cushingoid with florid clinical manifestations.

Investigations Serum potassium and bicarbonate, circadian rhythm of cortisol, low-dose and high-dose dexamethasone suppression tests, plasma adrenocorticotrophic hormone (ACTH), corticotropin-releasing-hormone stimulation test, CT scan of the pituitary, plain chest radiology, CT scan of the chest and abdomen, trans-sphenoidal pituitary biopsy and histology, CT scan and MRI of the thorax, MRI of the pituitary, octreotide scintigraphy, gastroscopy, colonoscopy, gut peptides, tumor markers, urine 5-hydroxyl-indole-acetic acid, resection, histology, immunocytochemistry and *in situ* hybridization.

Diagnosis Occult ectopic ACTH syndrome from a presumed appendiceal neuroendocrine tumor. The tumor was only identified some 20 years from initial presentation.

Management Adrenolytic therapy before bilateral adrenalectomy to cure Cushing's syndrome, glucocorticoid and mineralocorticoid replacement therapy, and then repeated surveillance over 20 years to locate the ectopic source of ACTH. This was finally identified by CT scan and excised at laparotomy.

KEYWORDS carcinoid tumor, Cushing's syndrome, ectopic ACTH syndrome, neuroendocrine tumor, therapy

CME

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THE CASE

A 24-year-old woman presented with a 12.5 kg weight gain over 6 months (mostly abdominal), hirsutism, acne, ankle edema, polydipsia, nocturia, back pain, pigmentation, poor libido, and lightened menses to our hospital in May 1986. Peripheral edema had been treated with furosemide and spironolactone for the previous 2 years, and she had stopped the combined oral contraceptive 2 months previously when the referring endocrinologist had suspected Cushing's syndrome. She did not take tobacco, recreational drugs or alcohol.

Upon physical examination she was grossly Cushingoid with thin skin, round, plethoric facies with acne and severe hirsutism, supraclavicular and interscapular fat pads, pigmented knuckles and axillae and purple, livid striae on the abdomen and around the shoulder girdle, and she had proximal myopathy. The patient was taken off diuretics and initial investigations revealed hypokalemia with alkalosis. The basal endocrinology and low-dose dexamethasone suppression test (LDDST; 2 mg dexamethasone per day for 48 h) confirmed Cushing's syndrome and suggested periodicity (Table 1). After a high-dose dexamethasone suppression test (HDDST; 8 mg dexamethasone per day for 48 h), she failed to suppress 09:00 h cortisol by more than 50%. ACTH was detectable at levels of 204 ng/l and 48 ng/l on two consecutive mornings, which also suggested cycling (Table 1). Pituitary CT scan showed no lesion. Circulating cortisol and ACTH levels did not rise after 100 µg ovine corticotropin-releasing hormone (CRH) was given. Bilateral inferior petrosal sinus sampling (BIPSS) for ACTH was abandoned twice as, on each occasion, the patient had 'cycled out' and become eucortisolemic. Chest CT scan was normal, while abdominal CT scan revealed hyperplastic adrenals. Whole-body catheter and sampling for

Table 1 Results of the patient's initial laboratory investigations.

Test (units)	Time	Result	Normal range
Serum potassium (mmol/l) 25 May 1986	09:00 h	3.2	3.5–5.0
Serum bicarbonate (mmol/l) 25 May 1986	09:00 h	33	22–30
Circadian serum cortisol (nmol/l) 25 May 1986	09:00 h 00:00 h asleep	>2,000 590	170–700 <50
Plasma ACTH (ng/l) 25 May 1986	09:00 h	204	<80
Circadian serum cortisol (nmol/l) 26 May 1986	09:00 h 00:00 h asleep	750 480	170–700 <50
Plasma ACTH (ng/l) 26 May 1986	09:00 h	48	<80
LDDST serum cortisol (nmol/l) 27–29 May 1986	Basal, pre-dex 2 mg dex per day for 48 h	760 760	170–700 <50
HDDST serum cortisol (nmol/l) 29–31 May 1986	4 mg dex per day for 48 h	920	NA

Abbreviations: ACTH, adrenocorticotrophic hormone; dex, dexamethasone; HDDST, high-dose dexamethasone suppression test; LDDST, low-dose dexamethasone suppression test; NA, non applicable.

ACTH during active disease revealed no gradient. Basal gonadotropin levels were normal, she was growth-hormone deficient with no diabetes insipidus, and testosterone levels were 4.3 nmol/l (normal range <3 nmol/l) and suppressed on the LDDST with otherwise normal androgen levels. The diagnosis of Cushing's syndrome was made. Although the results of the HDDST and CRH tests suggested the possibility of an ectopic source, because of her youth, and the presence of ACTH-dependent Cushing's syndrome with no ectopic source being found after a detailed search, it was felt that this was probably a case of pituitary-dependent Cushing's syndrome, Cushing's disease. Adrenolytic therapy (750 mg metyrapone every 8 h) was commenced for 6 weeks before trans-sphenoidal pituitary surgery. As mean daily cortisol levels were below 100 nmol/l, 2.5 mg prednisolone twice daily was prescribed, together with metyrapone.

At trans-sphenoidal surgery no tumor was found, despite a thorough exploration and biopsy. Postoperatively, hypercortisolemia persisted (at 09:00 h, basal serum cortisol level was 900 nmol/l); the histology did not show any evidence of a pituitary tumor. ACTH was now, therefore, considered to probably originate from an ectopic source. Every 6 h, 750 mg metyrapone (with 2.5 mg prednisolone twice daily) were recommenced, together with 2 g mitotane (also known as o,p'-DDD) every 8 h. Despite this treatment, biochemical

control was suboptimal, and necessitated bilateral adrenalectomy in October 1986, and subsequent routine replacement therapy with hydrocortisone (10 mg on waking, and 5 mg at lunch and early evening time) and fludrocortisone (100 µg once daily) for life.

After convalescence, the ectopic ACTH source was again sought, by CT scanning and MRI of the thorax and octreotide scintigraphy, as well as surveillance procedures—but to no avail. On extended follow-up, every 6–12 months, the patient remained well and searches for the source were periodically made with thoracic and abdominal CT scanning, octreotide scintigraphy and, on a single occasion, gastroscopy and colonoscopy. Tests for the presence of gut peptides, tumor markers, and urine 5-hydroxyl-indole-acetic acid were negative; Nelson's syndrome did not occur, and levels of ACTH remained approximately constant in the region of 20–60 ng/l, 2 h after morning hydrocortisone. Pituitary MRI did not reveal a lesion. The patient married, had two children, and then divorced and remained well with regular menstruation.

In late 2005, CT scan showed a small lesion with the characteristics of a neuroendocrine tumor, in front of the aortic bifurcation which seemed to be arising from the appendix or cecal mesentery (Figure 1). Prior imaging was reviewed; this mass was present, although smaller, in May 2004 (Figure 2), but was absent



Figure 1 Venous phase intravenous and oral contrast enhanced CT scan (LightSpeed Ultra®, GE Healthcare, Waukesha, WI), 5 mm slice, pitch 1.35, showing a tumor (arrow) with a fleck of calcification, typical of a neuroendocrine tumor. The tumor seemed to be arising from the tip of the appendix. Taken late in 2005.

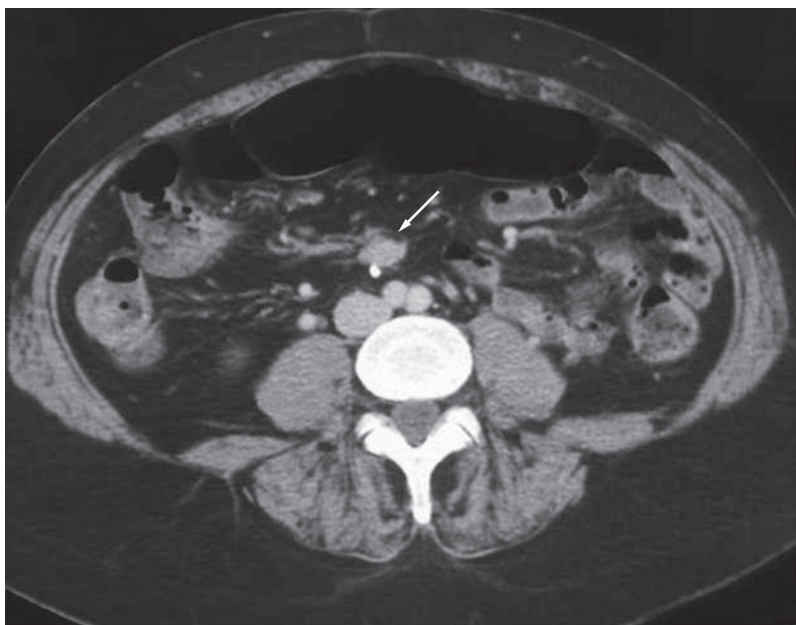


Figure 2 Venous phase intravenous and oral contrast enhanced CT scan (LightSpeed Ultra®), 5 mm slice, pitch 1.35, showing the tumor (arrow) depicted in Figure 1 to have been present and smaller, yet overlooked 18 months earlier; however, as the tumor, being attached to the mesoappendix, was potentially mobile the apparent change in size might have been caused by a change in orientation. Taken in May 2004.

before that. This suggested an ectopic source. In January 2006, a 3 cm by 2 cm tumor arising from the tip of the appendix and adherent to the retroperitoneum and ileal mesentery was found at laparotomy and removed at appendectomy with *en bloc* resection of the adherent mesentery. The histology was typical of a carcinoid tumor with metastases to mesenteric and local nodes. Immunostaining for ACTH was negative; the block was sent for *in situ* hybridization for the ACTH precursor, pro-opiomelanocortin, but this was also negative. Postoperatively, the patient recovered well and was discharged.

DISCUSSION OF DIAGNOSIS

The difficulties in diagnosing and managing Cushing's disease have recently been described.¹ When faced with ACTH-dependent Cushing's syndrome, Cushing's disease is likely to be the diagnosis in approximately 85% of cases, representing some 70% of all patients with Cushing's syndrome. Most of the remaining patients with ACTH-dependent Cushing's syndrome have nonpituitary tumors that secrete ACTH (ectopic ACTH syndrome [EAS]), usually a bronchial lesion—for example, a bronchial carcinoid or a small-cell lung carcinoma, the latter of which follows a clinical course quite distinct from that of Cushing's disease (Table 2).^{2,3} Very rarely, a tumor will ectopically secrete CRH, but this is usually in the context of also ectopically secreting ACTH.

In the case described, only a CT scan of the pituitary was available upon presentation, but subsequent MRI failed to demonstrate a pituitary tumor. This lack of demonstrable tumor is often seen in cases of Cushing's disease; a normal MRI is compatible with the diagnosis. Furthermore, around 10% of the normal population harbor an incidental pituitary tumor; therefore, it is important to interpret pituitary imaging cautiously.³ We routinely perform CT scanning of the chest and upper abdomen in all cases of Cushing's disease as the presence of a mass should make one re-examine the data more critically, although this is not universal practice. Once in search for an ectopic source, however, dedicated imaging with chest, abdominal, and pelvic CT scan, plus possibly MRI of the mediastinum and pelvis, in addition to thyroid ultrasound, are prudent. MRI of the abdomen is not used routinely, in part because of the problem of bowel movement artefact; furthermore, calcification associated with the primary tumor is easier to identify on

Table 2 Causes of endogenous Cushing's syndrome.

Type of endogenous Cushing's syndrome	Proportion of total cases (%)
ACTH-dependent disease (82% of total cases)	
Cushing's disease (pituitary-dependent)	70
Ectopic ACTH syndrome	12
ACTH-independent disease (18% of total cases)	
Adrenal adenoma	10
Adrenal carcinoma	7
Macronodular hyperplasia	Rare
Primary pigmented micronodular hyperplasia	Rare
McCune–Albright syndrome	Rare
GIP-induced or food-induced macronodular hyperplasia	Rare

Abbreviations: ACTH, adrenocorticotropic hormone; GIP, gastric inhibitory polypeptide.

Table 3 Other biochemical parameters that are elevated in patients with ectopic ACTH syndrome.

Peptide, marker, or hormone (% of total cases in which it is present)	Notes
Calcitonin (<30)	Medullary thyroid carcinoma, pheochromocytoma, MEN2, carcinoid, SCC, NET, gastrinomas, occult disease
Gastrin (<30)	Islet-cell tumors
Glucagon (~8)	Islet-cell tumors
5-HIAA (<10)	Up to one quarter of bronchial carcinoids, midgut or hindgut carcinoids, NET
Somatostatin (0.5)	Islet-cell tumors
Pancreatic polypeptide, vasoactive intestinal peptide, β -hCG, α -fetoprotein, α -subunit, neuron-specific endolase, GHRH, CRH, and carcinoembryonic antigen	Sporadic cases

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; β -hCG, β human chorionic gonadotropin; ACTH, adrenocorticotropic hormone; CRH, corticotrophin-releasing hormone; GHRH, growth-hormone-releasing hormone; MEN, multiple endocrine neoplasia; NET, neuroendocrine tumor; SCC, small-cell carcinoma of the lung.

CT scan.⁴ Whole-body catheter and sampling is rarely of value.⁵ Other hormones are abnormally secreted in 70% of patients with EAS; if present, these hormones are useful in making a diagnosis, especially calcitonin (Table 3).³ Scintigraphy with either ¹²³I-meta-iodobenzylguanidine or preferably ¹¹¹In-octreotide has varying reported use, but in the absence of corroboration with cross-sectional imaging, positive scans might be difficult to interpret.^{5,6} PET with ¹⁸F-fluorodeoxyglucose is an interesting technique that might prove useful, at least for detecting fast-growing tumors, although ¹¹C-5-hydroxytryptophan, if available, might be more promising.^{7,8}

In our case, the suspected Cushing's syndrome (see clinical features of Cushing's syndrome in Box 1) was confirmed by failure to suppress levels of cortisol after LDDST, plus elevated midnight cortisol levels; this was a case of ACTH-dependent disease (Table 2). In spite of the presence of hypokalemia and lack of response to the HDDST and CRH tests,⁹ attention was originally focused on her classic Cushingoid appearance, her youth, and the absence of an obvious ectopic source, and she was initially treated for probable Cushing's disease. We now know that patients with these biochemical findings are likely to have EAS, except those with a clear corticotroph

Box 1 Clinical features of Cushing's syndrome.

- Weight gain or central obesity
- Proximal weakness with or without muscle atrophy
- Decreased libido—especially in men
- Plethoric, round facies
- Menstrual irregularities
- Hirsutism
- Hypertension
- Purple, livid abdominal striae
- Acne
- Thin skin
- Easy bruising or ecchymosis
- Lethargy or malaise
- Agitated depression and/or psychosis
- Supraclavicular and dorsal fat pads
- Female balding
- Edema
- Backache and vertebral collapse
- Infection
- Poor wound healing
- Abnormal glucose homeostasis

macroadenoma, in whom the biochemistry can be confusing.¹⁰ It was unfortunate that because of cyclicity, BIPSS twice proved impossible, as a clear central gradient is almost pathognomonic of Cushing's disease in a patient with ACTH-dependent Cushing's syndrome,¹¹ although a negative central gradient might be seen in a minority of patients with Cushing's disease. We would now be more robust in carrying out BIPSS in virtually all patients with ACTH-dependent Cushing's syndrome, unless a clear macroadenoma is present. In this patient, pituitary exploration revealed no tumor, and more than 20 years' follow-up showed no evidence of Nelson's syndrome.¹² We were confident, therefore, in the diagnosis of EAS, and this patient was included in our series of patients with an 'occult source'.⁵ Our series of 318 patients with ACTH-dependent Cushing's syndrome included 40 with EAS followed up for at least 2 years, of whom 5 had occult EAS.³ EAS was, therefore, present in just over 10% of our series, and in approximately

20% of patients in the NIH series,⁶ the latter with a notably shorter follow-up.

The lesion in the patient we describe was eventually diagnosed on CT scan, but could not be detected some 5 years earlier; its appearance was suggestive of a neuroendocrine tumor and its histology confirmed the presence of nodal metastases. The question remains: was this the original source of ACTH? Immunostaining for ACTH was negative—although this might be seen in ectopic sources with a high secretory capacity, this was not a feature in this case. The negative *in situ* hybridization, however, suggests that either the tumor was unrelated to the EAS, or represents dedifferentiation of the original tumor. We tend to the latter explanation, and believe that the periodic scanning had identified a neuroendocrine tumor at a stage of local, rather than extensive, metastasis. Our own data indicate that removal of an ectopic source is associated with prolonged survival, even if local lymph-node metastases are present.⁵

TREATMENT AND MANAGEMENT

In the past, for cases of ACTH-dependent Cushing's syndrome in which the source of ACTH was uncertain, exploration and biopsy of the pituitary was used; however this is now rarely necessary. We generally perform BIPSS in all patients with ACTH-dependent Cushing's syndrome. In cases in which either the BIPSS does not indicate a central source, or several dynamic tests are suggestive of an ectopic source, a determined search is initiated together with medical control. We generally start with metyrapone because it has a rapid therapeutic onset,¹³ and if necessary either add or replace with ketoconazole. Mitotane creates problems with measurement of cortisol levels, causes hypercholesterolemia, and is slow in onset.¹⁴ Very rarely, if the hypercortisolemia is resistant and acutely life threatening, intravenous etomidate is available.^{15,16} If control of symptoms is difficult, particularly in cases of cyclicity, it might be better to resort to bilateral laparoscopic adrenalectomy sooner rather than later.¹⁷ After adrenalectomy, our patient was immediately cured of biochemical Cushing's syndrome, and with the exception of replacement therapy, review and regular reimaging, has led a completely normal life with no morbidity.

Survival of patients with EAS depends on the source of the primary tumor; those with

small-cell lung carcinoma fare badly,¹⁸ but the more indolent tumors, especially the bronchial carcinoids, show prolonged survival followed by pancreatic and appendiceal carcinoids.^{5,6} Our case represents one extreme in the delayed diagnosis of the probable source of ectopic ACTH. An appendiceal carcinoid that secretes ACTH is exceptionally rare, the commonest ectopic sources arise from the neck or thorax. It is noteworthy that these tumors, however, can arise from almost any tissue. We believe that the patient now has an excellent prospect of cure, and our plan is to repeat a CT scan of the abdomen every 6 months for 1 year, then at 2 years, and thereafter every 5 years.

The presentation of EAS and Cushing's disease can be identical, and because the *a priori* odds of Cushing's disease are high, severe demands are placed on the diagnostic tests; currently, the most discriminate is BIPPS. Once EAS has been suggested as a possible diagnosis, modern imaging will locate a source in the majority of patients, either at diagnosis or at reassessment. Biochemical control of Cushing's disease must be secured regardless of the etiology, and this also facilitates repeated reassessment. It is of note that, if a source repeatedly fails to be found, the prognosis is often favorable, as our case demonstrates. The appearance of a malignant tumor, albeit of low grade, must be sought during follow-up, which should be lifelong. For follow-up, we used interval thoracic CT scan augmented by ¹¹¹In-octreotide, plus MRI of suspicious areas.

CONCLUSION

It took 20 years to find the source for the ectopic ACTH in the patient described; once revealed the probable source was removed. This case highlights the importance of considering EAS in patients with ACTH-dependent Cushing's syndrome, the often occult nature of such sources, the importance of early bilateral adrenalectomy when medical therapy is ineffectual, and the lifelong need for careful follow-up.

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Competing interests

The authors declared they have no competing interests.