CASE REPORT

Dual bronchial carcinoids and Cushing's syndrome with a paradoxical response to dexamethasone and a false positive outcome of inferior petrosal sinus sampling

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Abstract

Context: Establishing the cause of Cushing's syndrome (CS) can be a considerable challenge, in particular in ectopic adrenocorticotrophic hormone (ACTH) syndrome, and often requires a combination of biochemical tests and imaging procedures.

Subject: A 27-year-old man presented with signs of CS. P-ACTH levels were three times above the upper limit of normal (ULN) and free urinary cortisol around 2000 nmol/24 h. The work-up showed remarkable results.

Results: A 2-day low-dose dexamethasone suppression test demonstrated paradoxical increases in cortisol. Sampling from the bilateral inferior petrosal sinus sampling (BIPSS) showed a central to peripheral ACTH ratio of 4.7 after corticotrophin-releasing hormone (CRH) stimulation, i.e. indicated pituitary disease, but magnetic resonance imaging of the pituitary was normal. Computed tomography (CT) scan of the lungs showed two oval-shaped masses, 1.3 × 1.8 and 1.3 × 2 cm, in the middle lobe. Both were positive at somatostatin receptor scintigraphy, compatible with tumors or inflammatory lesions. Subsequently, ¹¹C-5-hydroxytryptophan-PET showed distinct uptake in the tumors but not elsewhere. Two carcinoids situated 3 cm apart, both staining for ACTH, were removed at surgery.

Conclusion: This unique case with dual bronchial carcinoids inducing hypercortisolism illustrates the problems with identifying the source of ACTH in CS. Possibly, an abnormal regulation of ACTH production in response to dexamethasone, or steroid-induced tumor necrosis, explains the paradoxical outcome at dexamethasone suppression, and the false positive result at BIPSS reflects an unusual sensitivity of the pituitary corticotrophs to CRH in this patient. The work-up illustrates the great value of ¹¹C-5-hydroxytryptophan-PET as a diagnostic procedure when other investigations have produced ambiguous results.

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Introduction

Differentiating between pituitary or ectopic adrenocorticotrophic hormone (ACTH) production in Cushing's syndrome (CS) frequently presents a challenge, as in the individual case, no single or combination of dynamic tests accurately predicts a pituitary or non-pituitary source of ACTH (1, 2). Ectopic ACTH production accounts for 10–20% of all cases of CS and is most commonly associated with small cell carcinoma of the lung and intra-thoracic carcinoid tumors (2). The clinical features and the findings at laboratory work-up in CS due to carcinoid tumors may be indistinguishable from those in Cushing's disease (CD) (3–5).

The procedure of bilateral inferior petrosal sinus sampling (BIPSS) described in 1991 (6, 7) represented a breakthrough in the diagnosis of CS and remains the gold standard in the search for the source of ACTH. The sensitivity and the specificity of this procedure supersede

all non-invasive dynamic tests, and for a long time a central to peripheral ACTH gradient of more than two in the basal state and/or more than three after corticotrophin-releasing hormone (CRH) stimulation was considered to predict a pituitary ACTH source with close to 100% accuracy. Since then it has become apparent that the procedure is associated with an average of 5% false-negative tests, i.e. the absence of a central to peripheral ACTH gradient indicating an ectopic source, mostly due to problems with catheter positioning or aberrant venous drainage. There are also a few reports on false positive outcomes. These cases have been attributed to eucortisolism at the time of sinus sampling, an ectopic secretion of CRH, or non-pituitary but centrally located ACTH production (4, 8–11).

Here we report an exceptional case of ACTH-dependent CS in whom the work-up for the origin of ACTH produced unusual and ambiguous findings.

Case history

A 27-year-old man with a history of lumbar pain for 3 years was found to have pronounced osteoporosis (T-score of -3.3 in the lumbar region and -2.8 in the left hip at dual x-ray absorptiometry (DEXA)) and lumbar fractures at imaging. He was a previously healthy non-smoking lacto-vegetarian with no family history of endocrine disease. Over the last 2–3 years he had gained 15 kg in weight, lost his libido, and since 1 year experienced weakness of the lower limbs. He had recently been started on an ACE-inhibitor (ramipril 5 mg daily) due to hypertension and received calcium–vitamin D supplementation. At referral to the Department of Endocrinology he presented several signs of CS, such as facial plethora, truncal obesity, thinning of the proximal limb muscles, and purple striae on the abdomen, on the inner sides of the thighs, and in the axillary regions. The skin and hair growth were normal. He weighed 75 kg and was 172 cm tall. The blood pressure was 150/100 mmHg.

Results

Lab

At the first examination: B-Hemoglobin 168 (ref. 134–170) g/l, p-creatinine 51 (60–100) $\mu\text{mol/l}$, p-potassium 3.6 (3.5–4.4) $\mu\text{mol/l}$, fasting p-glucose 5.1 (4.2–6.3) mmol/l, urinary free cortisol (UFC) 2049 and 1801 (183) nmol/24 h, p-ACTH 146 and 158 (<46 ng/l, Immulite 2000, DPC, Los Angeles, CA, USA), s-testosterone 5.5–5.8 (10–35) nmol/l, s-testosterone/sex hormone binding globulin (SHBG) ratio 0.35 (0.3–1.3), p-luteinizing hormone 1.3 (1.0–10) IE/l, p-follicle-stimulating hormone 7.5 (1.0–10) IE/l, s-insulin-like growth factor-I 83 (117–329) $\mu\text{g/l}$, S-growth hormone 0.85 mIE/l, p-prolactin 10 (3–13) $\mu\text{g/l}$, thyroid-stimulating hormone 0.9 (0.4–3.5) mU/l, fT_4 9 (8–14) pmol/l, fT_3 4.1 (3.8–6.0) pmol/l, p-chromogranin A <10 (0–18) IE/l, s-gastrin 20 (<50) pmol/l, u-5-hydroxyindole acetic acid 27 (<50) $\mu\text{mol/24 h}$.

The circadian s-cortisol was abnormal: 0800 h, 482; 1200 h, 542; 1600 h, 686; 2000 h, 707; and at 2400 h, 751 nmol/l. A two-day low-dose dexamethasone suppression test showed a paradoxical response of serum and urine cortisol (Table 1). Subsequently,

Table 1 Paradoxical increased cortisol response to a 2-day, low-dose dexamethasone suppression test (0.5 mg $\times$ 4 $\times$ II).

	Basal	+ day 1	+ day 3
S-Cortisol nmol/l	482	921	1423
UFC	534	5147	$>3000^a$

^aSample was not further diluted.

blood sampling from the inferior petrosal sinuses before and after an i.v. dose of 100 μg synthetic human CRH (Ferring GmbH) showed an increase in p-ACTH both at 2 and 5 min after injection. The calculated stimulated central to peripheral ACTH ratio was 4.7, >3 indicating a pituitary origin. At baseline the gradient was <2 (1.2) (Table 2). There was no venous anomaly at angiography. Plasma CRH sampled from the right atrium during BIPSS was <1 pmol/l (reference level <5), as determined by an RIA after extraction of small peptides in use at the Department of Clinical Chemistry, Karolinska Hospital, Stockholm, Sweden.

Imaging

Magnetic resonance imaging (MRI) of the pituitary was normal. Chest X-ray showed a rounded opacity in the lower part of the right lung, ~ 1 cm in size. Computed tomography (CT) examination of the thorax revealed two oval-shaped masses, 1.3×1.8 and 1.3×2 cm respectively in the middle lobe of the lung (Fig. 1, upper part). Somatostatin receptor scintigraphy showed two rounded lesions with moderate uptake in the right thorax corresponding to the lesions seen on CT. ^{11}C -5-hydroxy-tryptophan-PET (12) showed high focal tracer uptake corresponding to the two lesions depicted by CT but not elsewhere in the body (Fig. 1, lower part).

Clinical course

After referral the patient was started on bisphosphonates and continued calcium–vitamin D supplementation. Treatment with ketoconazole at a low dose (200 mg bid) was given once the laboratory investigations were completed, and halted 6 days later when an opportunity rose to perform BIPSS. No ketoconazole was given during the 2 weeks preceding the BIPSS. On the day of the procedure, the ACTH and cortisol levels were in the same range as repeatedly found at investigations prior to ketoconazol.

Ketoconazole was restarted after BIPSS, and after 3 weeks a dose of 800 mg controlled the hypercortisolism. The patient underwent surgery and the middle lobe was resected. Two tumors 3 cm apart were found, measuring 1.2 and 1.4 cm in diameter respectively. There was about 2 cm resection margin and no lesions in the regional lymph nodes. After surgery, ACTH levels were below the lower limit of detection and the patient received standardized hydrocortisone replacement. Twelve months post surgery, the patient was well with remission of cushingoid features, normal testosterone levels and libido, and a normal blood pressure. Bone mineral density was improved; the T score had increased from -3.3 to -2.0 in the lumbar region and from -2.8 to -2.3 in the hip. The cortisol response at an ACTH stimulation test was still subnormal and a low dose of hydrocortisone (10 mg) replacement therapy was given.

Table 2 Bilateral inferior petrosal sinus sampling.

Level	P-ACTH (pmol/l)				Central/peripheral quotient ^a
	−2 min	0 min	CRH +2 min	CRH +5 min	
V. cava inf	34	—	—	—	
Right atrium	35	—	—	—	
Peripheral vein	36	36	36	38	
Right spi ^b	37	39	38	41	1.1
Left spi ^b	41	41	100	180	4.7

S-Cortisol 624 nmol/l and CRH <1.0 (ref. <5) pmol/l at time of investigation.
^aQuotient ≥3 after CRH stimulation is considered to predict a pituitary production of ACTH.
^bspi = inferior petrosal sinus. P-ACTH ref. range 2.0–10.0 pmol/l, Immulite, DPC, Los Angeles, CA, USA.

Histological and immunohistochemical examinations

Both tumors had the same histological appearance, growing in strands and nests. The atypia was mild and mitoses rare. Proliferation index measured by the Mib-1 antibody (Ki-67) was very low, below 1%. Immunohistochemical staining for synaptophysin (Fig. 2, left) and ACTH (Fig. 2, right) showed diffuse and strong positivity in all tumor cells. Both tumors were classified as typical carcinoids. There were no tumorlets or endocrine cell hyperplasia in the resected tissue.

Discussion

The clinical presentation of prodigious hypercortisolism with marked elevations of ACTH levels in a man with a pulmonary nodule at chest X-ray is highly suggestive of an ectopic ACTH syndrome. The present case, however, presented ambiguous results at further work-up; a paradoxical increase in cortisol in response to dexamethasone, a BIPSS pointing to a pituitary origin of ACTH, a normal MRI of the pituitary gland, and two oval-shaped lesions in the middle lobe of the lung at a CT scan. Both were positive at somatostatin receptor

Figure 1 Transaxial CT chest (upper) and corresponding ¹¹C-5-HPT-PET images (lower) displaying two pathological lesions (thick arrows) in the middle lobe of the lung measuring 1.3×2 cm (more centrally located) and 1.3×1.8 cm (more peripherally located). Physiological tracer accumulation is generally seen in the esophagus (thin arrows) and in bone (arrowheads) represented by a vertebral body (left) and the sternum (right).

Figure 2 Staining of the tumor cells with antibodies to synaptophysin (left) and ACTH (right). Original magnification $\times 100$.

scintigraphy, a finding that is compatible with, but not diagnostic for tumors, since inflammatory processes may express somatostatin receptors (13).

At this point we faced different and unusual scenarios, either a central origin of ACTH overproduction and two unrelated lesions in the lung, or ectopic ACTH production from two primary pulmonary tumors, or theoretically ectopic ACTH production of a pituitary metastasis from a neuroendocrine tumor, although it seems probable that a pituitary metastasis would have been visible on MRI. Neuroendocrine tumors have a capacity for uptake and decarboxylation of amine precursors like 5-hydroxytryptophan (5-HPT), which can be used as a tracer for PET imaging (12). Compared with CT and somatostatin receptor scintigraphy ^{11}C -5-HTP-PET has been shown to visualize more and smaller lesions (12, 14). Also, because of the biochemical pathway of 5-HPT, the nature of a lesion may be demonstrated (12, 14) and, contrary to somatostatin receptor scintigraphy, inflammatory lesions do generally not accumulate the tracer. In our case, the 5-HPT-PET showed a high tracer uptake in the two tumors in the middle lobe of the lung and no uptake elsewhere. The patient was referred to surgery and the tumors could be removed.

The incidence of CS in subjects with bronchial carcinoids is around 1% (15). Bronchial tumorlets are multiple small nests (≤ 5 mm in greatest dimension) of endocrine cell hyperplasia, disseminated in the lung parenchyma or in close proximity to a carcinoid tumor (16–18). The tumorlets are often seen in association with chronic inflammatory conditions such as bronchiectasis (19). It has been hypothesized that the small nests represent precursor lesions to pulmonary carcinoids, or intramucosal metastatic dissemination from a tumor. However, in subjects who had both a carcinoid tumor and tumorlets the two types of lesions had discordant genotypes arguing against the latter hypothesis (20). Occasional case reports on CS due to tumorlets have been published (21–24), whereas CS caused by more than one carcinoid tumor (i.e. tumor dimension > 5 mm) is very rare without a concomitant presence of multiple tumorlets. To our knowledge, there

is only one such previous case report (25). This patient had three bronchial adenomas of which at least one was a carcinoid. In a large series of 294 patients with pulmonary tumorlets and/or carcinoid tumors evaluated at the Mayo Clinic Rochester, 28 patients were found to have multiple lesions, either at imaging or at pathological examination post surgery. Out of these, the majority had multiple tumorlets. Five patients, all middle-aged or elderly women, had two carcinoid tumors. Two out of the 28 patients with multiple lesions had CS and it was not specified whether these patients had multiple tumorlets or two carcinoid tumors (18).

A paradoxical increase in serum and urine cortisol levels on a low-dose dexamethasone suppression test, as seen in the present case, has previously been reported in CD, in patients with ectopic ACTH production (26–29), and in primary pigmented nodular adrenocortical dysplasia (30). Several of these responses have occurred in patients with cyclic CS and were thought to be merely coincidental with periods of increased endogenous tumor activity (25, 26). Consistent paradoxical responses upon repeat tests as reported in a case with CD (31) argue, however, against such findings as being serendipitous. There are examples of abnormal responses to exogenous steroids in patients with ACTH-dependent CS. No suppression of ACTH in response to dexamethasone, although intact response to i.v. hydrocortisone, have been described in two case reports (32, 33). An apparent feed-forward regulation by glucocorticoids of ACTH release was reported in a case with ectopic ACTH production due to a pheochromocytoma. In this case dexamethasone was *in vitro* found to induce the production of ACTH precursors (34). We speculate that an alternative explanation for a paradoxical increase in cortisol could be apoptosis in ACTH producing cells induced by dexamethasone. Glucocorticoid-induced apoptosis is a well established phenomenon in a variety of cell lines (35) and forms the basis for using steroids in the treatment of certain malignancies.

In the present case, the BIPSS wrongly indicated a pituitary source of ACTH. Few reports on a false positive

outcome in ectopic CS have been published. Some tumors co-secrete CRH which thereby could counteract a suppression of normal pituitary corticotrophs during hypercortisolism (36–40). In these reports, CRH levels in peripheral blood were found to be clearly elevated in two of the patients (38, 40) and within the normal range in one case (38). In our patient, CRH was below the detection limit in plasma at the time of BIPSS. An alternative explanation for a false finding at BIPSS could be that the investigation was not performed during hypercortisolism (11, 41). However, in the present case there was no history of periods with amelioration of symptoms during the 3 years preceding the diagnosis. Furthermore, during the period of work-up there was no occasion with UFC less than two times the ULN and plasma ACTH remained about three times above the ULN during repeat sampling. The patient had been treated with a low dose of ketoconazole for less than a week and no medication was given during the 2 weeks preceding the BIPSS. At the day of the procedure, cortisol and ACTH levels were the same as during the initial work-up. Therefore, one might suggest that stimulation with a high, unphysiologic dose of CRH, like the one used in CRH tests, may awaken dormant pituitary corticotrophs in a patient with particular sensitivity. The fact that there was no central/peripheral gradient in the basal state in spite of the markedly elevated ACTH levels argues, however, *per se* for an ectopic source of ACTH and underlines that a calculated ratio must be interpreted against the full clinical picture.

In conclusion, the present case illustrates diagnostic dilemmas sometimes encountered in the work-up of CS. The paradoxical increase in cortisol in response to dexamethasone may reflect properties of this unusual tumor, whereas the outcome at BIPSS is unlikely to be related to the bronchial carcinoids. The data caution for relying on a positive gradient at BIPSS as the sole support for a central origin of ACTH, and demonstrates the value of ^{11}C -5-HPT-PET before surgical intervention in cases where other investigations have produced ambiguous results.

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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