CASE REPORT

Diagnosis and radioguided surgery with $^{111}$In-pentetreotide in a patient with paraneoplastic Cushing's syndrome due to a bronchial carcinoid

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Abstract

In a 28-year-old man with Cushing's syndrome, studies investigating a hypophyseal and/or adrenal origin of the disease, including computed tomography and magnetic resonance imaging, were negative. In agreement with reports showing somatostatin receptors on the cell membrane of ectopically secreting ACTH tumours, scintigraphy was performed after intravenous injection of $111$ MBq $^{111}$In-pentetreotide (OCT). The radiolabelled OCT scan showed a small focal area of intense uptake at the inferior lobe of the right lung.

Subsequent radioguided surgery located and defined a small mass ($1.8 \times 1.4 \times 1.6$ cm). The probe pinpointed the mass to the right inferior chest lobe, with a tumour/normal tissue count ratio of $6:1$ and tumour/hilar normal lymph node ratio of $12:1$, thus permitting the complete excision of the tumour to exclude lymph node and/or parietal involvement. A lung carcinoid was diagnosed at histology. The patient is still alive and disease-free 24 months after surgery.

$^{111}$In-OCT was found to be useful for localizing the ACTH-secreting tumour and also permitted rapid non-invasive differential diagnosis between an ACTH-secreting pituitary adenoma and a malignancy causing ectopic ACTH syndrome. This study also showed the clinical usefulness of radioguided surgery in the treatment of bronchial carcinoid.

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Introduction

A differential diagnosis between adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma (ASPA) and ACTH-secreting bronchial carcinoid is very difficult. Sometimes it is possible to diagnose ASPA by measuring plasma ACTH levels in central and peripheral blood samples obtained simultaneously by venous catheterization (1, 2). Despite its usefulness in ASPA, this invasive technique rarely allows the localization of the site of ectopically secreting ACTH tumours (3).

Recently, the presence of somatostatin receptors on the cell membrane of pituitary adenomas, small lung cell carcinoma (SCLC) and carcinoids has been demonstrated (4, 5), and significant uptake of octreotide (OCT), a long-acting analogue of somatostatin, in SCLC, carcinoids and pituitary tumours other than ASPA was found (6–8).

Using these findings, a patient with ACTH-dependent Cushing’s syndrome underwent an $^{111}$In-OCT scan to discriminate between ASPA and ectopically secreting ACTH tumour, all standard diagnostic techniques being ineffective.

Case report

A 28-year-old man with asthenia, stress dyspnoea and sleepiness was admitted to our hospital. He weighed 86 kg (height 173 cm), had mild hyperpigmentation, truncal obesity, abdominal and subclavicular purple striae, facial puffiness, and hypotrophy of muscle extremities. Arterial blood pressure was 180/95 mmHg and heart rate was 78 beats/min. Blood counts, glycaemia, electrolytes and other standard biochemical parameters were in the normal range as well as serum insulinaemia, thyroid hormones, testosterone and gonadotrophin levels. A chest X-ray was negative.

In agreement with the physical examination and endocrine laboratory findings showing high mean levels
of ACTH (20.1 pmol/l; normal range 1.1–13.2 pmol/l), serum (1031.2 nmol/l; normal range 40–410 nmol/l) and urinary (2676.3 nmol/24 h; normal range 20.3–248.3 nmol/24 h) cortisol, Cushing’s syndrome was hypothesized. Nevertheless, dexamethasone tests showed partial suppression, and a significant response to metyrapone tests was also observed (Table 1). A brain magnetic resonance image (MRI) did not show any pituitary abnormality, while abdominal computed tomography (CT) demonstrated no adrenal masses and/or hyperplasia. An $^{111}$In-OCT scan was performed to evaluate the presence of an ACTH-secreting tumour.

OCT scans were performed after i.v. injection of 111 MBq of $^{111}$In-pentetreotide (OctreoScan; Mallinckrodt Diagnostic, Petten, Holland) using a large-field γ-camera (Orbiter 75; Siemens, Erlangen, Germany) equipped with a medium-energy collimator, 20% symmetrical window set to 172 KeV and 242 KeV photopeaks. Planar $256 \times 256$ matrix images on brain, thorax and abdomen were obtained at 4 and 24 h, acquiring 500 000 counts. A small focal area of intense tracer uptake at 4 and 24 h at the inferior lobe of the right lung (Fig. 1) was demonstrated. No abnormal uptake was found in other locations, including the pituitary and adrenals. A chest CT showed a 1.5 cm lesion at the site of the OCT uptake, with an intense enhancement after contrast. CT-guided biopsy was not performed because of problems related to vascularization, size and site of the lesion.

Radioguided surgery was performed 4 days after the i.v. administration of a second dose of radiolabelled OCT (111 MBq) using a hand-held γ-detecting probe (model 2, Oris, Gil-sur-Yvette Cedex, France) consisting of a cylindrical $5 \times 15$ mm sodium iodide crystal, photomultiplier and collimator connected to a proportional counter with a digital read out display.

At surgery the probe pinpointed the mass to the right inferior chest lobe, with a tumour/normal tissue count ratio of 6 : 1 and tumour/hilar normal lymph node ratio of 12 : 1. No increased uptake at lymph nodes or elsewhere in the surgical field was observed. The probe was useful for locating and defining the small mass to exclude lymph node and/or parietal involvement, thus allowing accurate and complete excision of the tumour. After surgical exeresis, an ex vivo tumour/normal lung tissue count ratio of 18 : 1 and tumour/lymph node ratio of 30 : 1 were measured.

The tumour size was $1.8 \times 1.4 \times 1.6$ cm. At histology, a bronchogenic carcinoid without lymph node involvement and no neoplastic extension to surrounding tissues, as defined by the nuclear probe, was diagnosed. Immunohistochemistry was positive for ACTH, neuron-specific enolase, chromogranin, S-protein and cytokeratin. It was negative for neurofilament and carcinoembryogenic antigen.

Two months after surgery, plasma ACTH and serum and urinary cortisol levels returned to the normal range. At present, 24 months after surgery, the patient is alive and disease-free.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Dexamethasone test</th>
<th>Metyrapone test</th>
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<tbody>
<tr>
<td></td>
<td>Overnight test</td>
<td>Two day test</td>
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<td></td>
<td>Low-dose test</td>
<td>Standard dose</td>
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<tr>
<td></td>
<td>(1 mg at 2300 h)</td>
<td>(2.5 g at 2400 h)</td>
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<td></td>
<td>High-dose test</td>
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<td></td>
<td>(8 mg at 2300 h)</td>
<td>(2.5 g at 2400 h)</td>
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<td>Serum cortisol (nmol/l)</td>
<td>Before After</td>
<td>Before After</td>
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<td></td>
<td>996.0 712.9</td>
<td>1051.0 507.6</td>
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<tr>
<td>Urinary cortisol (nmol/day)</td>
<td>Before After</td>
<td>Before After</td>
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<tr>
<td></td>
<td>2676.0 176.0</td>
<td>3035.0 93.8</td>
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<tr>
<td>ACTH (pmol/l)</td>
<td>Before After</td>
<td>Before After</td>
</tr>
<tr>
<td></td>
<td>20.1 17.6</td>
<td>19.9 17.2</td>
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<td>17α-hydroxyprogesterone (nmol/l)</td>
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<td>Androstenedione (nmol/l)</td>
<td>12.2 12.2</td>
<td>10.5 12.2</td>
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<tr>
<td>11-Deoxycortisol (nmol/l)</td>
<td>15.3 /</td>
<td>14.4 /</td>
</tr>
</tbody>
</table>

Table 1 Serum and urinary hormones levels before and after dexamethasone screening tests and overnight single-dose metyrapone test.

**Figure 1** Anterior 24 h octreotide planar scan showing a small focal area of intense tracer uptake at the inferior lobe of the right lung.
Discussion
In a patient with hypercortisolism and high plasma ACTH levels, the absolute resistance to glucocorticoid negative feedback and reduced ACTH response to falling sFa suggest a tumour causing ectopic ACTH syndrome (9). Our patient showed a good response to dexamethasone and metyrapone tests, thus suggesting an ASP A. Nevertheless, brain MRI was unable to show the presence of a pituitary tumour. Moreover, circadian rhythm of ACTH and cortisol were absent.

Therefore we postulated the use of radiolabelled OCT to localize the site of the tumour and to discriminate between ASP A and ectopically secreting ACTH tumour. The premise for our attempt was based on recent reports showing in vivo uptake of radiolabelled OCT in a large percentage of bronchial and abdominal carcinoid as well as in SCLC and other neuroendocrine tumours (10, 11).

In fact, after the observation of Philpnonneau et al. (12) reporting the case of a 6mm ACTH-secreting bronchial carcinoid visualized with OCT scan, this procedure has been utilized in the differential diagnosis of Cushing’s syndrome and in localizing ACTH-secreting tumours. In one series, the tumour was successfully found in eight of ten patients with ectopically secreting ACTH malignancies (13). In four of them, scintigraphy revealed a tumour that could not be localized with standard imaging techniques. Conversely, none of the pituitary adenomas of eight patients with Cushing’s disease was seen using OCT scintigraphy.

In our patient, OCT scintigraphy revealed a small focal area of intense accumulation at the inferior lobe of the right lung. This finding allowed us to target the chest CT scan which also showed a small lesion. This lesion was identified as a bronchial carcinoid at histology. The finding confirms that a bronchial carcinoid should be considered even when responses to metyrapone and dexamethasone suggest pituitary Cushing’s disease (14). Moreover, this study confirms that an OCT scan should at present be the first choice diagnostic step. This technique is simple and non-invasive, more rapid and less expensive than selective catheterization, and more effective for accurately localizing the tumour site.

Finally, tumour OCT uptake was the premise for radioguided surgery, which was to our knowledge the first performed successfully on a bronchial carcinoid. This technique was shown to be useful at the thoracic level where it effectively guided surgical resection, helped to define tumour borders, and to investigate parietal and lymph node involvement. The absence of significant blood pool activity allowed the determination of higher tumour/background ratios than other radioguided approaches to surgery utilizing radiolabelled antibodies, thus ensuring the complete excision of the tumour.

References

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