DETECTION OF AN ACTH-SECRETING BRONCHIAL CARCINOID TUMOUR EIGHTEEN MONTHS AFTER ADRENALECTOMY FOR CUSHING'S SYNDROME

By
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ABSTRACT

A patient is described in whom an ACTH-producing bronchial carcinoid tumour was found eighteen months after bilateral adrenalectomy for Cushing's syndrome. A critical review is given of laboratory methods used in the differential diagnosis of ectopic Cushing's syndrome. Finally a course of action is suggested by which such unnecessary ablative surgery might be avoided.

In the majority of cases the so-called ectopic Cushing's syndrome is caused by a highly malignant tumour, usually a pulmonary oat-cell carcinoma (O'Riordan et al. 1966), and can be diagnosed before the development of clinical signs of hyperadrenocorticism. The chance of a permanent cure by resection of such a tumour is however very small.

Benign ACTH-secreting tumours are less frequently found and may remain hidden until after adrenalectomy, which should of course not have been performed.

Such a situation is particularly apt to occur in patients with bronchial carcinoid tumours which are either benign or of a low-grade malignancy. In the literature the association of bronchial carcinoid with Cushing's syndrome has been described in 18 cases (O'Riordan et al. 1966; Christy 1961; Cohen et al. 1960; Escovitz & Reingold 1961; Gabrilove et al. 1969; Jones et al. 1969; Lipsett 1964; Morse et al. 1967; Prunty et al. 1968; Sobota & Reed 1964; Steel et al. 1967; Strott et al. 1968; Harrison et al. 1957; Perrault et al. 1968; Riggs &
Sprague 1961; Williams & Celestin 1962) in 13 of which ACTH secretion by
the tumour has definitely or very probably caused the hyperadrenocorticism
(O'Riordan et al. 1966; Christy 1961; Cohen et al. 1960; Escovitz & Reingold
1961; Gabriove et al. 1969; Jones et al. 1969; Lipsett 1964; Morse et al. 1967;
Prunty et al. 1963; Sobota & Reed 1964; Steel et al. 1967; Strott et al. 1968). In
6 of these cases the tumour was only found after ablative surgery for Cushing's
syndrome.

In this paper a case is presented in which the tumour was found eighteen
months after bilateral adrenalectomy. A review of the literature is given, with
special reference to diagnostic procedures by which such unnecessary surgery
could be avoided.

MATERIAL AND METHODS

Urinary 17-hydroxycorticosteroids (17-OHCS) were determined by the method of
Appleby et al. (1955). Urinary 17-ketosteroids (17-KS) were measured by the method,
recommended by the British Medical Research Council Committee on Clinical Endo-
crinology (1963). Plasma 11-OHCS were determined by the method of Mattingly (1962).
The cortisol production rate (CPR) was determined using a slight modification (Thijssen et al. 1967) of the method of Cope & Black (1958). ACTH in plasma was determined,
using a slight variation of the method of Landon & Greenwood (1968). ACTH-activity
of tumourous extracts was measured in hypophysectomized rats according to the method

Case report

A man born in 1947 was seen for obesity in another hospital in 1965. At that time, the
excretion of 17-KS and 17-OHCS in the urine was slightly elevated. His reaction to me-
tarpane was judged to be normal (Table 1). The patient was put on a reducing diet.
In 1967 he entered military service. By this time a moonface, buffalo hump, broad livid
striae in both axillae, on the chest and on the thighs, central obesity, bruising, plethora,
acne and osteoporosis had developed. The blood pressure was 190/130 mm Hg; height
1.70 m; weight 77 kg. On X-ray examination the skull and thorax were normal. Dexam-
ethasone given daily in doses of 2 and 8 mg did not bring about a decrease of the 17-
OHCS-excretion in the urine (Table 1). The patient was transferred to our department.
The cortisol production rate was 56 mg/24 h. On presacral oxygen insufflation the right
adrenal gland appeared to be enlarged and of irregular shape. The left adrenal could
not be visualized.

Because suppression could not be achieved the presence of either an adrenal tumour
or an ectopic ACTH producing tumour was considered. Further X-ray examination of
the chest and abdominal organs failed to show a neoplasm. On surgical exploration bi-
lateral adrenal hyperplasia was found and both adrenals were removed. They weighed
10 and 16 g respectively, the right adrenal showing hyperplasia of the zona fasciculata.
the left marked hyperplasia of both the zona fasciculata and the zona reticularis.

For the following eighteen months the patient felt well on 37.5 mg of cortisone daily.
Gradually pigmentation of the face, the handlines and the surgical scars developed, and this progressed notwithstanding an increase in the cortisone-dosage to 50 mg a day.

In November 1968 X-ray examination of the chest showed a tumour in the left lingula. Apart from a slight cough the patient felt well. In retrospect there were no symptoms pointing to the existence of a carcinoid syndrome. The ACTH level of the plasma was tested preoperatively on 4 occasions with and without corticosteroid substitution (Table 2). Values higher than 1000 pg/ml (corresponding to more than 14 mU/100 ml) were found. Unfortunately these titres were higher than expected and no plasma was left for determination in higher dilution.

On thoracotomy the tumour was found to measure about 1.5 cm in diameter. An enlarged lymph node was found behind the pulmonary artery and resected.

On microscopic examination fields of epithelial cells of a pale pink colour were seen. There were few mitotic figures and scanty stroma. Occasionally a thin-walled blood-vessel was seen. The lymph gland contained metastases of the tumour. The diagnosis was made of malignant bronchial carcinoid.

Part of the tumour immediately after removal was frozen in liquid nitrogen and tested for its ACTH-content, which was 0.5 IU/g frozen tissue. Three weeks after the operation the plasma-ACTH-level was 75 pg/ml. The pigmentation gradually disappeared. At the present time the patient feels well on 37.5 mg of cortisone daily and 25 mg of deoxycorticosterone-trimethyl-acetate given every three weeks. Up to the present (19 months after thoracotomy) no signs of recurrent malignancy are detectable.

**DISCUSSION**

There is no reasonable doubt that the bronchial tumour in our patient caused Cushing's syndrome. The disappearance of cutaneous pigmentation and the sharp decrease in plasma ACTH after removal of the tumour, as well as the finding of ACTH activity in the tissue itself confirm that this was a neoplasm producing considerable quantities of corticotrophin. The symptoms of Cushing's syndrome probably started in 1965; in February 1967 no pulmonary tumour could be detected notwithstanding intensive investigations. In November 1968 the tumour was clearly visible on thoracic X-ray examinations and on removal it weighed about 7 g. We are bound to assume that in 1965 it was much smaller but nevertheless gave rise to rapidly progressing hyperadrenocorticism. This would point to a very high production of ACTH per gram of tumour tissue. The finding of high plasmalevels (more than 14.0 mU/100 ml) and a moderate ACTH content of the tumour (0.5 IU/g) indicates a high secretion rate of ACTH by the tumour with little storage. Similar data were reported by Strott et al. (1968), who found a tumour of only 600 mg capable of producing Cushing's syndrome. It is evident that such a small tumour may be missed even by meticulous clinical investigation. The question then arises as to which laboratory procedures would enable the clinician to save the adrenals of the patient.

The key position of laboratory diagnostics is held by the dexamethasone suppression test as introduced by Liddle (1960). Unfortunately this test too is not infallible. Non-suppressibility of the steroid excretion has not only been found
Table 1.
Essential laboratory data.

<table>
<thead>
<tr>
<th>Date</th>
<th>17-OHCS urine mg/24 h</th>
<th>17-KS urine mg/24 h</th>
<th>11-OHCS plasma 8.30 a.m.</th>
<th>11-OHCS plasma 4.30 p.m.</th>
<th>CPR mg/24 h</th>
<th>ACTH plasma pg/ml</th>
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</thead>
<tbody>
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<td>6/65</td>
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<tr>
<td></td>
<td>metyrapone test</td>
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<td></td>
<td>before</td>
<td>20.3</td>
<td>37.1</td>
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<td></td>
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<tr>
<td></td>
<td>during (1 g every 6 h)</td>
<td>25.9</td>
<td>52.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>after</td>
<td>16.9</td>
<td>19.7</td>
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<td></td>
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<tr>
<td>11/66</td>
<td>till 1/67</td>
<td>31.4</td>
<td>23.7</td>
<td>26.9</td>
<td>37.1</td>
<td>56.0</td>
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<tr>
<td></td>
<td>overnight dexamethasone</td>
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<td>suppression test (1 mg) (performed 4 times)</td>
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<td></td>
<td>dexamethasone 0.5 mg</td>
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<td>every 6 h</td>
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<td></td>
<td>day 1</td>
<td>27.4</td>
<td>23.0</td>
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<tr>
<td></td>
<td>day 2</td>
<td>28.2</td>
<td>24.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>day 3</td>
<td>31.0</td>
<td>28.0</td>
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<tr>
<td></td>
<td>dexamethasone 2 mg</td>
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<td>every 6 h</td>
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<td></td>
<td>day 1</td>
<td>29.6</td>
<td>24.9</td>
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<tr>
<td></td>
<td>day 2</td>
<td>27.2</td>
<td>24.0</td>
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<tr>
<td></td>
<td>day 3</td>
<td>34.4</td>
<td>28.0</td>
<td></td>
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<tr>
<td>Date</td>
<td>Procedure</td>
<td>ACTH Plasma (pg/ml)</td>
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<td>------------------------------------------------</td>
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<tr>
<td>2/2/67</td>
<td>Bilateral total adrenalectomy</td>
<td>&gt; 1000</td>
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<td></td>
<td>on 37.5 mg of cortisone daily</td>
<td>&gt; 1000</td>
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<td></td>
<td>on 2 mg of dexamethasone daily</td>
<td>&gt; 1000</td>
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<td></td>
<td>after withdrawal of steroids:</td>
<td>&gt; 1000</td>
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<td></td>
<td>day 1</td>
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<td></td>
<td>day 2</td>
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</tr>
<tr>
<td>11/28/68</td>
<td>Thoracotomy</td>
<td>75</td>
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<tr>
<td></td>
<td>3 weeks later (on 37.5 mg of cortisone)</td>
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</tbody>
</table>
in nodular adrenal hyperplasia (Meador et al. 1967; Mosier et al. 1960; Silverman et al. 1963) but also in a patient with diffuse bilateral hyperplasia (Harden & Forrest 1964) who is well 8 years after operation without an ectopic tumour having appeared (Harden 1970, personal communication).

Furthermore cases have been described in which 32 mg of dexamethasone was needed for suppression (Linn et al. 1967) and there is a case in which 50 mg of cortisol suppressed the plasma ACTH while 32 mg of dexamethasone failed to do so (Rayyis & Bethune 1969). In a previous paper our group reported on spontaneous hyperadrenocorticism in a dog with »non-suppressible hyperplasia« in which adrenocortical function was normalized by hypophysectomy (Rijnberk et al. 1968). Neither is suppressibility definite proof of the absence of a tumour: decrease in corticosteroid excretion has been described in a case of adrenocortical carcinoma (Kendall & Sloop 1968), in a case of thymoma (Miura et al. 1967) and in 3 of the 8 cases of bronchial carcinoid listed in Table 2.

Hormone secretion of pituitary tumours is suppressible in some instances, but not in others (Vingerhoeds et al. 1969).

There is no explanation why in some cases of Cushing’s syndrome of tumourous origin the corticoid excretion can be anomalously suppressed. If there are no other signs of tumour such a result may cause unsurmountable diagnostic difficulties.

It has been held that a significant response of either plasma or urinary 17-hydroxycorticosteroids to stimulation with ACTH is characteristic of pituitary dependent hyperplasia. As Table 2 shows there was a rise in corticosteroids in all cases of bronchial carcinoid in which the test was done. Obviously the test does not distinguish between glandular and tumoural ACTH dependence. In the literature numerous cases have been reported (Nichols et al. 1968; Pennington et al. 1970) which show the same result, and even a positive adrenal response in cases of adrenocortical tumour. In our patient, the metyrapone-test was judged to be normal in another hospital where the patient was investigated for obesity in 1965. In fact there was only a significant rise in 17-KS and not in the 17-OHCS-excretion; we cannot interprete this result and have subsequently not repeated the procedure. In the literature a great variety of results with metyrapone can be found. The test has been done in 6 cases of bronchial carcinoid in three of which a normal response was found (rise in 17-OHCS excretion) (Table 2). Nichols et al. (1968) in the literature found four cases of ectopic Cushing’s syndrome in which there was a rise in the 17-OHCS excretion of at least 100 %. A rise has also been described in a case of adrenocortical adenoma (Pennington et al. 1970). It appears that the results of this test are also not dependable.

Perhaps the determination of plasma ACTH will offer a better chance of differential diagnosis, but experience with this method is at present rather limited. In cases of ectopic Cushing’s syndrome very high plasma levels of ACTH were
<table>
<thead>
<tr>
<th>Author</th>
<th>Interval between development of Cushing's syndrome and detection of the tumour</th>
<th>Results of tumour-extration</th>
<th>Dexam. suppression test</th>
<th>Metyrapone test</th>
<th>ACTH stimulation test</th>
<th>ACTH in tumour tissue</th>
<th>ACTH in plasma before operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christy (1961)</td>
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<td>+</td>
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<tr>
<td>Cohen et al. (1960)</td>
<td>a  3 a</td>
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<td>+</td>
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<td></td>
<td>b  3 a</td>
<td></td>
<td></td>
<td>+</td>
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<tr>
<td>Escovitz &amp; Reingold (1961)</td>
<td>not extirpated; died soon</td>
<td></td>
<td></td>
<td>+</td>
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<td></td>
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<tr>
<td>Jones et al. (1969)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>suppression obtained with metyrapone and dexam. together</td>
<td></td>
<td>yes</td>
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<td>Lipsett (1964)</td>
<td></td>
<td>+</td>
<td>+</td>
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<td>Morse et al. (1967)</td>
<td>9 a</td>
<td>good</td>
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<td>+</td>
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<td>yes</td>
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<td>Prunty et al. (1963)</td>
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<td>O'Riordan et al. (1966)</td>
<td>6 a</td>
<td></td>
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<td>+</td>
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<tr>
<td>Sobota &amp; Reed (1964)</td>
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<td>+</td>
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<td>Steel et al. (1967)</td>
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<td>+</td>
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<td>Strott et al. (1968)</td>
<td>a 7 a</td>
<td>good</td>
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<td>+</td>
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<td>yes</td>
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<td></td>
<td>b  1.5 a</td>
<td>good</td>
<td></td>
<td>+</td>
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<td>yes</td>
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</table>

↑: rise in 17-OHCS-excretion, plasma cortisol-level or plasma ACTH-content  
↓: decrease of 17-OHCS-excretion, plasma cortisol-level or plasma ACTH-content  
= : unchanged level of 17-OHCS-excretion.
found (Landon & Greenwood 1968; Liddle et al. 1962). Such a very high level combined with nonsuppressibility would point to ectopic Cushing's syndrome or possible to a pituitary tumour (Liddle 1969).

If in such a case extensive investigations fail to disclose a tumour, either in the pituitary or elsewhere in the body we would suggest that ablative surgery should be delayed as long as possible. Such a delay of adrenalectomy is justifiable if the symptoms of hyperadrenocorticism can be controlled by treatment with aminogluthethimide (Elipten®). This drug blocks the conversion of cholesterol to pregnenolone (Cash et al. 1967). In pituitary-dependent adrenal hyperplasia, this block is quickly overcome by a rise in pituitary ACTH-secretion (Fishman et al. 1967).

When there is no feedback system between cortisol and ACTH, as may be found in ectopic Cushing's syndrome and adrenocortical tumour, aminogluthethimide-treatment may be very successful (Schteingart & Conn 1967; McMillan & Maisey 1970). A good therapeutic response will thus also be of diagnostic significance. Of course such a delay of surgery is only permissible if an adrenal tumour has been definitely excluded and if the patient can be watched meticulously by physical and X-ray studies at regular intervals.

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