Lung carcinoid related Cushing’s syndrome: report of three cases and review of the literature

K M A Amer, N B N Ibrahim, C P Forrester-Wood, R A Saad, M Scanlon

Abstract

Three patients with lung carcinoid related Cushing’s syndrome (LCRCS) treated at Frenchay Hospital, Bristol between January 1984 and January 1994 are described. The first patient presented with hyperpigmentation 13 years after bilateral adrenalectomy. The second patient had no recurrence or metastases 14 years after removal of a typical carcinoid tumour. The last patient survived nine years after diagnosis of liver metastasis. The possibility of LCRCS should be considered in every patient proved to have Cushing’s disease and bilateral adrenal enlargement on abdominal computed tomography. Biochemical sets of investigation (for example, adrenocorticotrophic hormone (ACTH) stimulation, dexamethasone suppression, and metyrapone response) could be misleading and should not be relied upon solely. Search for an ectopic ACTH source should be called off only when ACTH has been demonstrated in the surgically removed specimen, and most importantly, when the serum ACTH concentration returns to normal after surgery. Lung carcinoid tumours are compatible with long survival, and liver metastasis could prove indolent and slowly growing.

Keywords: lung carcinoids; Cushing’s syndrome; ectopic ACTH syndrome; adrenocorticotrophic hormone

Ninety patients were operated upon for lung carcinoid tumour at Frenchay Hospital in Bristol between January 1984 and January 1994, of these, three were found to have Cushing’s syndrome. Sections from the paraffin blocks were stained with haematoxylin and eosin, neurone specific enolase (NSE), protein gene product (PGP) 9.5, chromogranin A, and for adrenocorticotrophic hormone (ACTH). The clinical presentation, investigations, treatment, and follow up are briefly discussed.

The association between lung carcinoids and Cushing’s syndrome has been referred to in the past as “ectopic ACTH syndrome” and Cushing’s syndrome caused by “non-endocrine” tumours.1 Besides ACTH, these tumours were shown to secrete a number of biologically active hormones and precursors, that could cause Cushing’s syndrome. Corticotrophin releasing hormone, corticotrophin-like intermediate lobe peptide, ACTH precursors, and pro-opiomelanocortin were among the described factors.2-5 We therefore opted to refer to the condition as lung carcinoid related Cushing’s syndrome (LCRCS) in this report.

Case reports

CASE 1

A 54 year old woman presented in June 1980 with generalised fatigue, muscle weakness, and weight gain. She showed classical Cushing’s habitus including “moon face”, abdominal striae, and hirsuitism. Blood biochemical data are summarised in tables 1 and 2. Abdominal computed tomography showed bilateral adrenal hyper trophy. Skull radiography and cerebral computed tomography were normal, yet she was diagnosed as pituitary dependent Cushing’s disease and underwent transphenoidal hypophysectomy. Histology of the removed pituitary failed to demonstrate an adenoma. Symptoms persisted and three months later the same set of biochemical investigations remained unchanged. She then underwent bilateral adrenalectomy, and her symptoms were cured. Thirteen years later (September 1993) she presented with increasing skin pigmentation. She was found to have an ACTH concentration of 491 pmol/l (reference range 2.2–17.6 pmol/l) and a suspicious shadow in a routine chest radiograph. In retrospect, the same shadow was present, unchanged in her 1980 films. Computed tomography of the chest demonstrated a 3 cm diameter mass in the left upper lobe, which was removed by lobectomy. Histology showed atypical carcinoid tumour with trabecular and focally insular pattern; a few areas were showing a marked degree of nuclear pleomorphism and hyperchromasia that is associated with the presence of mitotic figures (up to six per 10 high power fields). Immunohistochemistry stains were positive for NSE, PGP 9.5, chromogranin A, and ACTH. The hilar lymph nodes were free from tumour. In May 1997, she suffered an anterior myocardial infarction and a brain stem stroke, but made a good recovery. At six years follow up she was slightly short of breath on exertion but her skin pigmentation had disappeared. Her ACTH was still undetectable.

Table 1  Case 1. Biochemical data on first presentation in 1980: diurnal rhythm

<table>
<thead>
<tr>
<th>Time</th>
<th>Cortisol (nmol/l)</th>
<th>ACTH (pmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00 am</td>
<td>986</td>
<td>42.0</td>
</tr>
<tr>
<td>Midnight</td>
<td>807</td>
<td>11.2</td>
</tr>
</tbody>
</table>

1 Besides ACTH, these tumours were shown to secrete a number of biologically active hormones and precursors, that could cause Cushing’s syndrome. Corticotrophin releasing hormone, corticotrophin-like intermediate lobe peptide, ACTH precursors, and pro-opiomelanocortin were among the described factors.2-5 We therefore opted to refer to the condition as lung carcinoid related Cushing’s syndrome (LCRCS) in this report.

Keywords: lung carcinoids; Cushing’s syndrome; ectopic ACTH syndrome; adrenocorticotrophic hormone.
Table 2  Case 1. Biochemical data on first presentation in 1980: 24 urine steroid studies

<table>
<thead>
<tr>
<th></th>
<th>Cortisol derivatives (mmol/mol creatinine)</th>
<th>Cortisol precursors (mmol/mol creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>23.59</td>
<td>0.75</td>
</tr>
<tr>
<td>Low dose dexamethasone 0.5 mg 6 hourly</td>
<td>14.15</td>
<td>4.27</td>
</tr>
<tr>
<td>High dose dexamethasone 2 mg 6 hourly</td>
<td>5.08</td>
<td>0.45</td>
</tr>
<tr>
<td>On metyrapone</td>
<td>4.00</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>Basal 6.26</td>
<td>Basal 35.36</td>
</tr>
<tr>
<td></td>
<td>After 15.3</td>
<td>After 65.97</td>
</tr>
</tbody>
</table>

Table 3  Case 3. Biochemical data on first presentation in 1983: diurnal rhythm

<table>
<thead>
<tr>
<th></th>
<th>Cortisol (normal = 130–600 nmol at 9:00 am)</th>
<th>ACTH (normal &lt; 17.6 pmol at 9:00 am)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00 am</td>
<td>760</td>
<td>24.2</td>
</tr>
<tr>
<td>Midnight</td>
<td>615</td>
<td>37.4</td>
</tr>
</tbody>
</table>

CASE 2

A 62 year old woman presented in early 1984 with polyuria, polydipsia, and hypertension. Maturity onset diabetes was diagnosed and she was controlled on oral hypoglycaemics. Despite good control of her diabetes, she complained of fatigue and weight loss. Investigations showed a persistent hypokalaemic alkalosis. The blood cortisol concentration was high (994 nmol/l at 9:00 am), whereas ACTH was normal (8.8 pmol/l at 9:00 am). Routine chest radiograph and subsequent computed tomography revealed a 2 cm diameter shadow in the right middle lobe, which was removed by lobectomy. Histology confirmed a typical carcinoid tumour having prominent trabecular pattern, without lymph node involvement. The tumour cells stained positively for NSE, PGP 9.5, chromogranin A, and ACTH. After 14 years of follow up (October 1998) there were no signs of recurrence or metastases and her diabetes remained under control.

CASE 3

Details of this case have been published previously.6 The patient was a 15 year old girl who presented in 1983 with a 14 month history of Cushing’s syndrome with polyuria, polydipsia, and hypertension. Investigations showed a persistent hypokalaemic alkalosis. The blood cortisol concentration was high (994 nmol/l at 9:00 am), whereas ACTH was normal (8.8 pmol/l at 9:00 am). Routine chest radiograph and subsequent computed tomography revealed a 2 cm diameter shadow in the right middle lobe, which was removed by lobectomy. Histology confirmed a typical carcinoid tumour having prominent trabecular pattern, without lymph node involvement. The tumour cells stained positively for NSE, PGP 9.5, chromogranin A, and ACTH. After 14 years of follow up (October 1998) there were no signs of recurrence or metastases and her diabetes remained under control.

Table 4  Case 3. Biochemical data on first presentation in 1983: 24 urine steroid studies

<table>
<thead>
<tr>
<th></th>
<th>Cortisol derivatives (normal = 1.0–3.8 mmol/mol creatinine)</th>
<th>Cortisol precursors (normal = 0.2–0.6 mmol/mol creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>13.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Low dose dexamethasone 0.5 mg 6 hourly</td>
<td>14.7</td>
<td>0.5</td>
</tr>
<tr>
<td>High dose dexamethasone 2 mg 6 hourly</td>
<td>6.2</td>
<td>0.4</td>
</tr>
<tr>
<td>On metyrapone 750 mg 4 hourly</td>
<td>15.7</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Basal 15.7</td>
<td>Basal 0.4</td>
</tr>
<tr>
<td></td>
<td>After 28.0</td>
<td>After 17.7</td>
</tr>
</tbody>
</table>

Discussion

The syndrome of “ectopic ACTH” secretion, which relates to sources other than the pituitary or adrenals, is a rare disease. W H Brown first described it in 1928 as “diabetes of bearded women” in a patient suffering from oat cell carcinoma of the lung and bilateral adrenal enlargement.7 The definition of the syndrome was established by Meador and Liddle in 1962 who were the first to demonstrate biologically active ACTH in a lung carcinoid tumour.1

The true incidence of LCRCS is not known. Review of the literature in the UK and Ireland revealed 16 individually reported cases (table 5). Mason et al in 1972 published the largest series of seven cases collected from six different UK institutions.12 World wide, the largest number of cases was 15 patients described separately by Pass et al and Limper et al.13 14 We encountered three cases of LCRCS among 90 resected lung carcinoid tumours, over a 10 year period. This is in keeping with data obtained from the University Hospital of Wales in Cardiff, where four cases of LCRCS were...
reported among 80 cases of lung carcinoid tumours removed over a period of 20 years (M Scanlon, Professor of Endocrinology, University of Wales; unpublished observation). In sharp contrast, previously published series of operated lung carcinoids in the UK and Ireland do not report a single case of LCRCs. On the other hand, the incidence of lung carcinoid tumours as the cause of “ectopic ACTH syndrome” is variable. Limper et al reported only 1% of Cushing’s syndrome was attributed to a lung or bronchial tumour. Riggs and Sprague investigated 232 cases of Cushing’s syndrome, and found only 22 cases associated with ectopic ACTH, of which only a single case was attributed to a lung carcinoid.

Analysis of the 19 cases reported in UK and Ireland (including this report) show an equal sex distribution, and a mean age at presentation of 43 years. Chest symptoms were absent in our three patients, which is usually the case with LCRCs, in contradistinction to oat cell carcinoma. This finding is in keeping with cases reported by others. Hypertension, cushinoid habitus, muscle weakness, and hypokalaemic alkalosis were the main presenting features (fig 1). Skin pigmentation is a relatively uncommon presentation in patients with LCRCs. Four out of 19 cases (21%) presented with generalised skin pigmentation appearing after bilateral adrenalectomy. Skin pigmentation significantly faded from three cases and failed to disappear in one patient, who continued to have high concentrations of serum ACTH as a tumour marker to predict early recurrence.

Our first case is very unusual in that there were 14 years between diagnosis of Cushing’s disease and clinical hyperpigmentation. The longest latent period reported previously was 10 years.

Nine patients (47.4%) were alive and well at one year follow up. Three patients (15.8%) died in the perioperative period after bilateral adrenalectomy. Subsequent postmortem examination showed these patients to have lung carcinoid tumours. The commonest operation performed before lung surgery was bilateral adrenalectomy (42.1%), followed by hypophysectomy (10.5%). O’Riordan et al described a patient who had four adrenal operations before lung surgery.

Older biochemical investigations were frequently unhelpful in distinguishing between pituitary dependent Cushing’s syndrome and LCRCs. Fifty per cent of patients with LCRCs demonstrate suppression by high dose dexamethasone (8 mg daily). Eighty per cent have an unexpected positive Synacthen stimulation test, and 36% show a positive metyrapone response. In our third case dexamethasone suppression and metyrapone response were positive, suggesting a pituitary tumour, so much so that the pulmonary lesion was initially thought to be coincidental. In our second case, despite the resected tumour staining strongly for ACTH, the patient had an unexplainable normal blood ACTH. Recently there has been a shift of practice towards routine bilateral inferior petrosal sinus sampling with and without corticotrophin releasing hormone stimulation for the differential diagnosis between pituitary and ectopic sources of ACTH in patients with hypercortisolism.

There is no single foolproof imaging technique for lung carcinoid tumours. Computed tomography remains the gold standard of demonstrating abnormal masses in the chest. In addition, 80% of lung carcinoids demonstrated somatostatin receptors, and scintigraphy using labelled octreotide (a somatostatin analogue) can be very helpful indeed in detecting such tumours. The role of positron emission tomography has yet to be determined.

Surgical removal of the lung carcinoid tumour should aim at “anatomic resection” rather than “parenchyma saving” surgery. Search for involved mediastinal lymph nodes should be rigorous, and a low threshold for clearing lymph nodes should be adopted. Failure to remove all involved lymph nodes could lead to persistence or recurrence of the syndrome, and diminishes the chances of long term survival.

Liver metastases proved compatible with long survival in our third case. Selective venous catheterisation is indicated to confirm hepatic source of ACTH secretion. Hemihepatectomy could be considered for solitary hepatic metastases. In selected patients with slowly growing multiple hepatic secondaries, liver transplantation may be regarded as an adequate therapeutic procedure, provided extrahepatic spread had been excluded by peritoneoscopy. All patients should be followed up by yearly check of serum ACTH as a tumour marker to predict early recurrence.

We wish to thank Professor C Mott for allowing us to include his patient in this series, and Professor J Farndon for providing valuable follow up information about the same patient.
Lung carcinoid related Cushing’s syndrome

1. Foster-Carter AF. Bronchial adenoma.


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Postgrad Med J 2001 77: 464-467
doi: 10.1136/pmj.77.909.464

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