

A Case Report of a Patient with Bronchial Carcinoid Tumour and Late Presentation of Cushing's Syndrome

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Abstract

Bronchial carcinoid tumour with ectopic adrenocorticotrophin (ACTH) production is an uncommon cause of Cushing's syndrome. In most instances, the patient presents with clinical hyperglucocorticism and a search for its underlying pathology leads to the discovery of an inconspicuous bronchial carcinoid tumour, if at all. Often the tumour is not immediately detectable. We report a patient who presented in the reverse order-she initially had a large asymptomatic bronchial carcinoid tumour that subsequently manifested as clinical Cushing's syndrome after remaining quiescent for four years.

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Key words: *Asymptomatic, Carcinoid, Ectopic adrenocorticotrophin, Quiescent*

Introduction

Cushing's syndrome is usually easy to recognise clinically. Determining the cause of non-iatrogenic Cushing's syndrome is, on the other hand, often a diagnostic enigma. Dynamic hormonal tests are crucial to differentiate between pituitary adrenocorticotrophin (ACTH)-secreting tumour, adrenal tumours and ectopic ACTH-secreting tumours. Plasma ACTH levels provide supportive value.

Imaging techniques are then applied to localise the incriminating lesion but they are not without limitations. Firstly, lesions may be too small to be picked up by imaging techniques, thus delaying surgical excision of the offending lesion. A case in point is ACTH-secreting bronchial carcinoid tumour which, being slow growing, often eludes detection for years in the face of florid clinical manifestations of the syndrome.¹ Secondly, radiologically visible lesions in the pituitary, adrenals and other sites may be non-secreting incidentalomas.

We report a patient who presented with a sizeable inactive pulmonary carcinoid that subsequently developed into full-blown Cushing's syndrome by producing ACTH four years after it was first detected. We also postulate on the possible mechanism for this mode of behaviour.

Case Report

A 57-year-old Chinese lady presented in 1996 with features of Cushing's syndrome over a 6-week period: weight gain, central obesity, moon-like facies (Fig. 1), increased facial hair, dorsal hump, supraclavicular fat pad, atrophic skin, purplish abdominal striae and proximal myopathy. Her blood pressure was 160/100 mmHg. There was no history of steroid ingestion.

Mild hypertension (blood pressure 150/90 mm Hg) was first noted by her general practitioner 10 years previously in 1986. Initial treatment with propranolol was supplemented with nifedipine in 1992, after which her blood pressure, as recorded by her GP, was stable throughout. In 1992, a chest radiograph detected a well-circumscribed coin lesion measuring 3 cm in the right lung. This was subsequently confirmed on a follow-up computerised axial tomography (CAT) scan of the thorax (Fig. 2). No action was taken with regards to this finding and the reason could not be firmly established. Upon recognition of the Cushingoid features, chest X-ray (Fig. 3) showed a lesion similar to findings of 1992 except that it had grown to 4 cm in diameter. This was also confirmed by a CAT scan (not shown).

A previous photograph of the patient taken in 1993 (a year after the initial discovery of the pulmonary lesion)

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Fig. 1. Photograph of the patient taken in 1996 (4 years after the discovery of the pulmonary lesion).

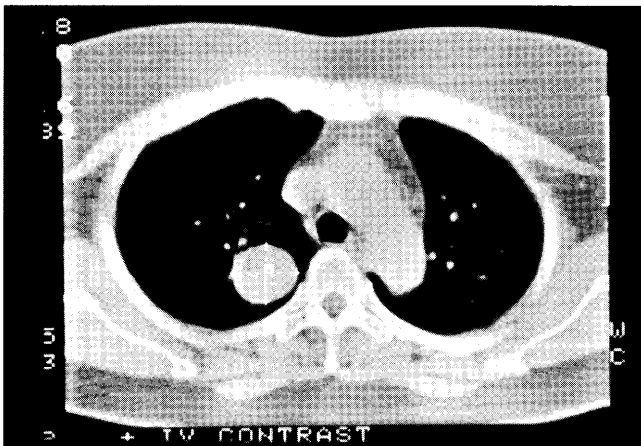


Fig. 2. Computerised axial tomography scan of the thorax done in 1992 showing a 3-cm well-circumscribed lesion in the right upper lobe of the lung.

did not reveal obvious Cushingoid features (Fig. 4). There was no history to suggest carcinoid syndrome such as episodic flushing, wheezing or diarrhoea.

Baseline and dynamic endocrine studies are as shown in Table I. In essence, the patient had hypokalaemia, mild alkalosis, mild hyperglycaemia and elevated glucocorticoid secretion insuppressible by high dose dex-

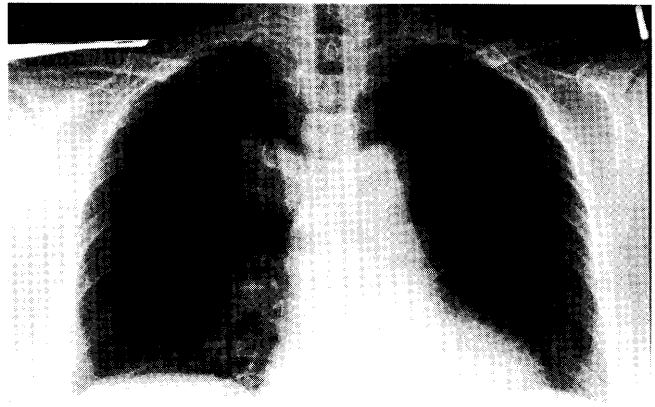


Fig. 3. Chest radiograph in 1996 showing a right pulmonary lesion similar to that in 1992 (see Fig. 2).



Fig. 4. Photograph of the patient taken in 1993 (a year after the discovery of the pulmonary lesion).

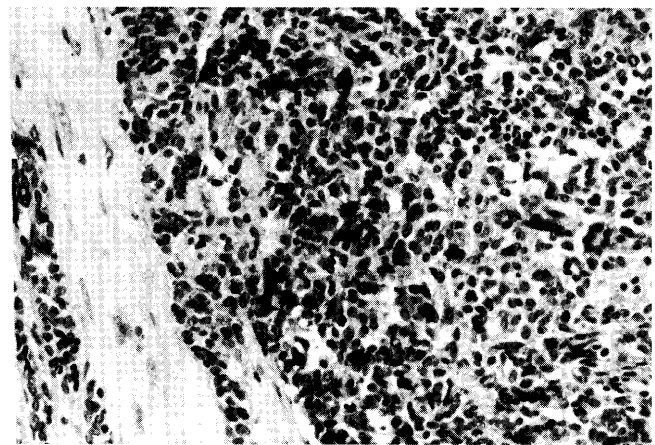


Fig. 5. The histology was that of a bronchial carcinoid composed of anastomosing trabeculae and clusters of polygonal cells with fairly uniform oval nuclei and granular, lightly eosinophilic cytoplasm, supported by a fine fibrovascular stroma. No mitoses or areas of necrosis were present. Immunohistochemistry showed the cells to be positive for chromogranin and synaptophysin. Some of the tumour cells express ACTH (immunoperoxidase stain $\times 200$).

amethasone, in association with elevated plasma ACTH. The urinary excretion of 5-HIAA was within normal limits. The cause of the Cushing's syndrome was thus

TABLE I: BASELINE AND DYNAMIC ENDOCRINE EVALUATIONS

Tests (figures in parenthesis indicate normal range or values)	Results (Percentage change compared with baseline)
Serum potassium (3.3 to 4.9 mmol/L)	2.9 mmol/L
Serum sodium (135 to 145 mmol/L)	143 mmol/L
Random plasma glucose range	5.7 to 11.8 mmol/L
HbA1c (4.6% to 6.4%)	6.5%
Serum bicarbonate (19 to 31 mmol/L)	33.7 mmol/L
8 am serum cortisol (193.2 to 579.6 nmol/L)	1457.7 nmol/L
8 am serum ACTH (10.0 to 40.0 ng/L)	50.1 ng/L
Serum cortisol after overnight 1 mg dexamethasone suppression test (<69.0 nmol/L)	1170 nmol/L
24-hour urinary cortisol (220 to 400 nmol)	3720 nmol
24-hour urinary 17 hydroxycorticosteroid (17 OHCS) (17 to 55 µmol)	80.0 µmol
Post Liddle's high dose dexamethasone suppression*	
24-hour urinary cortisol (nmol)	6730 nmol (+180%)
24-hour urinary 17 OHCS (µmol)	30 µmol (-62%)
Serum cortisol (nmol/L)	964.7 nmol/L (-33%)
24-hour urinary hydroxyindoleacetic acid (5 HIAA) (15.1 to 65.6 µmol/day)	29.2 µmol

* Oral dexamethasone 2 mg 6 hourly for 2 days. See text for interpretation of results.
ACTH: adrenocorticotrophin

linked to the pulmonary lesion, hitherto of unconfirmed pathology.

Preoperative treatment with nifedipine 10 mg tds and ketoconazole 200 mg tds for 3 weeks normalised serum potassium to 3.7 mmol/L and the blood pressure. Thoracotomy was then performed to enucleate the pulmonary lesion, a yellowish nodule 4 cm in diameter located at the periphery of the lung, abutting on the pleural surface. The resected tumour was confirmed histologically to be a carcinoid tumour (Fig. 5) with positive ACTH immunocytochemical staining.

Three weeks after the tumour was removed, serum potassium was 4.2 mmol/L and serum sodium 138 mmol/L without potassium supplement or anti-steroidogenesis drugs. Blood pressure was 120/80 mm Hg on nifedipine 10 mg bd. Attempts to withdraw antihypertensive therapy without causing a rebound of hypertension were unsuccessful. Presenting features of glucocorticoid excess, in particular the proximal myopathy, the moon-facies and the striae, resolved progressively after surgery. Weight reduction of 4 kg was achieved two and a half months post-surgery. At that stage the 24-hour urine free cortisol was 106 nmol/day [normal range (NR) 30 to 150 nmol/day, urine volume 1000 ml] while the 24-hour urine total cortisol was 472 nmol/day (NR 220 to 400 nmol/day, urine volume 1000

ml). Plasma cortisol at 9 am was 403 nmol/L (NR 193 to 579 nmol/L).

A year after surgery her blood pressure was maintained at 120/70 mm Hg with Adalat LA 60 mg and Atenolol 100 mg daily despite complete regression of her Cushingoid features.

Discussion

The conglomeration of initial clinical and biochemical manifestations, such as weight gain, central obesity, proximal myopathy, alkalosis, and hypokalaemia was classical of Cushing's syndrome. Hypokalaemia is consistent with the mineralocorticoid activity of excess glucocorticoids on the renal tubules. This is commonly noted in patients with ACTH-secreting bronchial carcinoids.¹ The markedly elevated baseline serum cortisol, and the failure to suppress serum cortisol with overnight 1 mg dexamethasone, confirmed the diagnosis of Cushing's syndrome.²

Elevated serum ACTH (though not extremely high) pointed to ACTH dependent hypercortisolaemic state. It was noted by previous investigators that not all patients with corticotrophin-producing bronchial carcinoid tumours had extreme elevation of ACTH levels.' With high dose dexamethasone, 24-hour urinary cortisol showed a paradoxical rise while 24-hour urinary 17-hydroxycorticosteroid (17OHCS) and serum cortisol were both only partially suppressed. (Adequate suppression is defined by a decrease in 24-hour urinary cortisol of ≥90%,³ a decrease of 24-hour urinary 17OHCS of ≥64%³ and a fall in serum cortisol of ≥50%.⁴) The patient's pattern of response to high dose dexamethasone is compatible with non-pituitary ACTH-dependent Cushing's syndrome.

The 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) was within normal range indicating that the lesion was not secreting any 5-hydroxytryptamine-related metabolites.

Bronchial carcinoid tumours with ectopic ACTH production account for up to 40% of ACTH-dependent Cushing's syndrome. The local literature after 1970 however has only one recent report of this condition occurring in a 17-year-old girl whose rapid onset of ACTH-dependent hypercortisolism was caused by an 8 x 8 x 8 cm atypical bronchial carcinoid.⁵ There is however no mention, in this report, of how long the carcinoid existed prior to presentation of Cushing's syndrome or a discussion of late transformation from an inert to an ACTH-producing state.

More typically, bronchial carcinoid tumours are small in size, averaging 0.3 to 1.3 cm. Despite their usually small size, carcinoids may be endocrinologically active enough to cause the myriad of features of Cushing's syndrome. This property, coupled with their slow growth

makes bronchial carcinoids difficult to localise. Therefore, even upon presentation of overt clinical Cushing's syndrome, only about 55% of patients with bronchial carcinoids have a pulmonary nodule or mass noted on chest radiography.⁶ Although the advent of CAT scan of the thorax has greatly improved the success of identifying the lung lesion when it is still small or located at sites difficult to pinpoint on the plain chest radiography,⁷ there have been reports of patients with Cushing's syndrome from secretory bronchial carcinoids which cannot be localised until 10 years later.⁷

Hence it is noteworthy that in one report of patients with Cushing's syndrome due to bronchial carcinoids where the site of the primary tumour was not apparent initially, at least half of them underwent adrenalectomy and/or hypophysectomy to alleviate the primary endocrine symptoms and signs, several months to even years before the eventual discovery and removal of the carcinoid tumour in question.⁷

Our patient is unusual in that her clinical presentation was in the reverse order of the commonly described sequence of events. She was found to have a 3-cm asymptomatic right lung nodule in 1992. A portrait of her taken in 1993 did not reveal obvious cushingnoid features. It took another 3 years before she manifested gross features of hyperglucocorticism from a histologically-proven highly active ACTH-producing carcinoid. Over 4 years, the carcinoid had enlarged by only 1 cm. We believe that the carcinoid tumour was either endocrinologically dormant or of low secretory capacity previously. Subsequently, some trigger had unmasked or enhanced its ACTH secretion. Hence, the biological behaviour of bronchial carcinoid could be more varied than we had previously believed.

Although much work has been done on the molecular mechanisms of neoplastic transformation, the pathogenesis of the ectopic ACTH syndrome remains unknown. Two plausible mechanisms based on the known molecular biology of normal and abnormal expression of ACTH secretion could be advanced to explain our patient's mode of presentation.

The neoplastic cells possess and express the pro-opiomelanocortin (POMC) gene.⁸ This peptide pro-hormone, POMC, is processed by proteolytic cleavage to ACTH, beta lipotropin (LPH), and an amino-terminal peptide.⁹ The ACTH molecule may in turn be cleaved to form smaller peptides such as corticotropin-like intermediate lobe peptide (CLIP) and alpha melanocyte stimulating hormone (MSH).⁹ If the tumour was initially extremely efficient in cleaving the ACTH into CLIP and MSH, ACTH may not be produced sufficiently to cause Cushing's syndrome. It is conceivable that subsequently, the tumour may lose its ability to cleave the ACTH molecules rapidly enough to prevent a rise in the plasma

ACTH levels, hence resulting in a state of hyperglucocorticism.

An alternative explanation is based on the "dysdifferentiation hypothesis" proposed by Baylin and Mendelsohn.¹⁰ In their theory, cells responsible for ectopic hormone production are believed to represent primitive cells which have been prevented from differentiating to mature endocrinologically inert progeny. Our patient's carcinoid tumour cells may initially be well differentiated enough not to produce ACTH. Further neoplastic changes could then have occurred to "dysdifferentiate" the lesion and allow a clone of the cells to revert to their primitive behaviour and start producing and secreting ACTH. Admittedly, these proposals to explain our patient's presentation are largely speculative and await further studies to confirm.

Benign ACTH-secreting tumours, particularly carcinoids, have a good prospect of cure after surgical excision. Up to 81% of patients with localised disease are reported to be cured after surgery.¹¹ All 10 patients with ectopic ACTH-secreting tumours in the series studied by Howlett et al¹² were cured after surgical treatment. Of these, 2 had bronchial carcinoids with micrometastases to the hilar lymph nodes; they remained in remission after postoperative radiotherapy to the mediastinum. In another 19 patients with ectopic ACTH syndrome from the National Institutes of Health (NIH), 6 of the 9 who were cured had bronchial carcinoid tumours and amongst them, 4 had histologically proven metastatic disease to the lymph nodes.⁷ Complete normalisation of the serum cortisol, ACTH and 24-hour urinary free cortisol can occur as early as the first 10 days after surgery with dramatic improvement of all Cushingnoid features at 6 months postoperatively. Indeed in our patient, all the features of Cushing's syndrome abated except hypertension. This, however, is not surprising in view of the long duration of antecedent hypertension.

In conclusion, although carcinoid tumour destined to cause Cushing's syndrome is well known to present initially with paraneoplastic endocrine syndrome while remaining elusive to localisation, it may also "start life" as an asymptomatic recognisable lesion only to manifest the syndrome of hyperglucocorticism many years later. Our patient's unusual presentation in the latter manner has broadened our understanding of the biological behaviour and endocrine manifestations of bronchial carcinoid tumours.

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