

# ACTH Producing Pulmonary Carcinoid and Pituitary Macroadenoma: A Fortuitous Association?

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### SUMMARY

We report a case of a 45 year-old man who presented initially with a non-functioning pituitary macroadenoma. A routine chest radiography done preoperatively revealed a right lung nodule which was confirmed by computed tomography (CT) of the thorax. Transfrontal hypophysectomy was performed while a conservative approach was taken for the lung nodule. Four years later, he presented acutely with adrenocorticotrophic hormone (ACTH) dependent Cushing's syndrome which resolved following a right lobectomy. Histological examination revealed an atypical carcinoid. To our knowledge, this is the first reported case of an ectopic ACTH secreting pulmonary carcinoid found in association with a non-functioning pituitary macroadenoma.

### KEY WORDS:

*Carcinoid tumour, Cushing's syndrome, ACTH syndrome, Ectopic, Multiple endocrine neoplasia, Pituitary neoplasms*

### INTRODUCTION

Atypical carcinoids are neuroendocrine malignant tumours that comprise almost 25% of pulmonary carcinoid tumours. It has two important endocrine relationships: a frequent association with other tumours, and secondly production of a spectrum of hormones resulting in a variety of clinical manifestations. Approximately 1% of patients with pulmonary carcinoid manifest as Cushing's syndrome characterized by ACTH production. The association of bronchial carcinoid and pituitary adenoma has rarely been described in patients with multiple endocrine neoplasia<sup>1</sup>. It is important to recognize this combination of endocrine tumours as screening for other associated endocrine neoplasms is indicated.

### CASE REPORT

A 45 year-old Chinese man presented to a neurosurgeon in 2000 with headache, visual blurring, diminished libido and impotence. Magnetic resonance imaging (MRI) of the pituitary demonstrated a large sellar mass with suprasellar extension resulting in compression of the optic chiasm. A diagnosis of a clinically non-functioning pituitary macroadenoma was made and he was operated on via the transfrontal route. Chest radiography preoperatively showed a lung nodule which was confirmed by CT thorax. It measured 3cm in diameter in the right upper lobe. The patient refused further assessment of the nodule. He required

hydrocortisone, thyroxine and testosterone replacement postoperatively.

The patient was closely followed-up by a physician. He was asymptomatic until 2004 when his physician noted a rapid change in the patient's appearance which was consistent with Cushing's syndrome. Further questioning disclosed a two month history of recurrent visual blurring, hyperpigmentation, oedema and weakness. He denied flushing, gastrointestinal symptoms or wheeze. He was a non-smoker. His family history was unremarkable for any multiple endocrine neoplasia (MEN) related conditions. He was hypertensive and his random blood sugar was persistently above 12 mmol/L although his HbA1c was only 5.3% suggesting recent onset of glucose intolerance. Abnormal biochemical findings were as follows; sodium 159 mmol/L (135-150 mmol/L), potassium 1.8 mmol/L (3.5-5.0 mmol/L), thyroid stimulating hormone 0.17 uIU/ml (0.32-5.00 uIU/ml), free thyroxine 9.68 pmol/L (9.10-23.80 pmol/L), 5- hydroxyindoleacetic acid (5 HIAA) 88 µmol/24 hr (<48 µmol/24 hr).

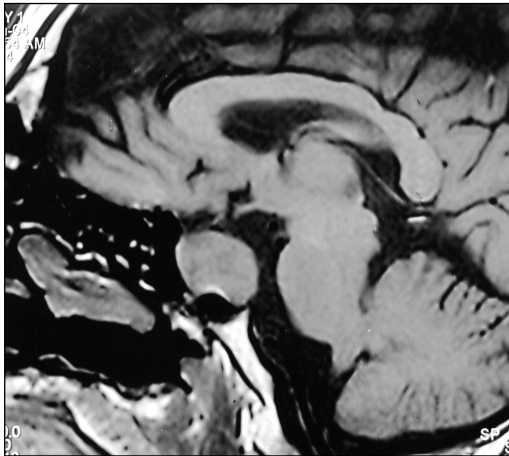
His morning cortisol and ACTH without hydrocortisone replacement were elevated at 1225 nmol/L (68-469 nmol/L) and 311 pg/ml (0-46 pg/ml) respectively suggesting ACTH dependent Cushing's syndrome. Overnight and low dose dexamethasone suppression test failed to suppress his cortisol. He was treated with gliclazide, amlodipine, ketoconazole, spironolactone and potassium supplement. MRI pituitary revealed a recurrence of macroadenoma (Figure 1). Patient underwent transphenoidal hypophysectomy to relieve his visual symptoms. Histopathology of the tumour showed no mitotic figures and no expression of pituitary hormones indicative of a non-functioning pituitary adenoma. He was referred to our hospital for further management of Cushing's syndrome.

Physical examination revealed a man who was darker for his race. He had subtle signs of Cushing's syndrome; there were increased pigmentation of the palmar creases and acne. His blood pressure was 140/80 mmHg. Visual field assessment revealed left temporal hemianopia. The remainder of the physical examination was unremarkable.

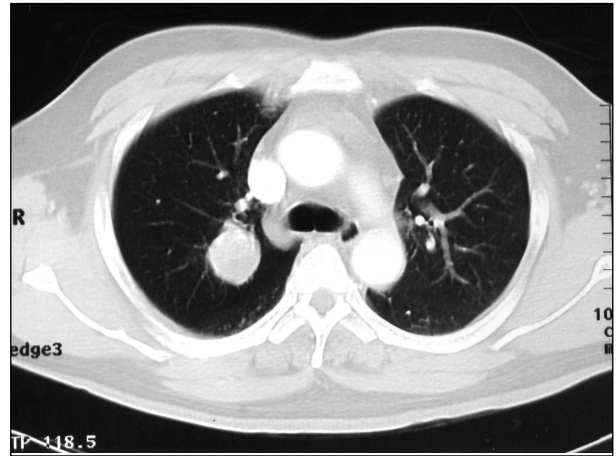
His CT thorax showed the lung nodule had increased in size (Figure 2). There was no radiological evidence of hilar, mediastinal or aortocaval lymphadenopathy. A metastatic workup including CT abdomen was negative. A CT guided

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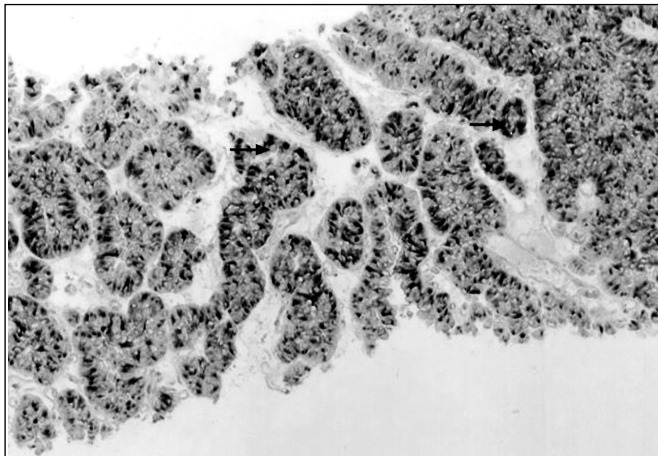
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**Fig. 1:** Magnetic resonance imaging scan showing pituitary adenoma



**Fig. 2:** Computed tomography scan showing a well defined nodule measuring 3.5 x 3.7 x 3.0cm in the apico-posterior segment of the right upper lobe.



**Fig. 3:** The neoplastic cells show positivity towards chromogranin A.

biopsy of the right lung nodule was consistent with a diagnosis of carcinoid tumour and right upper lobectomy was performed.

Histopathology showed a mass composed of neoplastic cells consistent with carcinoid morphology. Mitotic figures were 6/10 high power fields. Necrosis was scanty. Immunohistochemically, the cells were positive for neurone specific enolase, chromogranin A, synaptophysin and cytokeratin and negative for ACTH and other pituitary hormones (Figure 3). A diagnosis of atypical carcinoid tumour was made.

Postoperatively, his morning cortisol level was low at 47 nmol/L and he was replaced with hydrocortisone. Hypokalemia normalized without potassium supplement and hypertension and diabetes resolved. He was referred for lung and pituitary radiotherapy. At three months follow-up his skin pigmentation had decreased, ACTH was undetectable and continued to require steroid replacement therapy.

**DISCUSSION**

This patient was diagnosed to have ectopic ACTH-producing atypical carcinoid on the basis of elevated serum ACTH, cortisol, urinary 5-HIAA and the histopathological findings. The short history of hyperpigmentation, hypokalaemia, diabetes and hypertension further supports the diagnosis. It is unlikely the pituitary adenoma was the source of ACTH because four years ago he was not cushingoid and he required hydrocortisone replacement. The resolution of symptoms and signs together with the undetectable ACTH level after lobectomy is highly predictive that the carcinoid was the source of ACTH although immunohistochemically it stained negatively for ACTH. We speculate that the acute presentation of Cushing's syndrome could be as a result of transformation of a non-producing carcinoid tumour to one that secretes either ACTH or its precursors.

Pulmonary carcinoid tumours have been recognized 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 are among the described hormones<sup>2</sup>.

High molecular weight forms of ACTH were found in extracts from ectopic tumour in 1971. Subsequently, the presence of pro-opiomelanocortin (POMC) and pro-ACTH in plasma of patients with ectopic ACTH syndrome have been described<sup>3</sup>. Therefore, the failure to detect ACTH with immunohistochemical staining could be due to the carcinoid producing ACTH precursors like POMC and pro-ACTH which are not detected routinely in our laboratory<sup>4</sup>. The elevated level of ACTH detected in the periphery could be explained by the cleavage of POMC to ACTH.

Pulmonary carcinoid in the presence of a non-functioning pituitary adenoma is a rare but strong association that has been described in MEN type 1<sup>1</sup>. Inactivation of the MEN 1 gene mutation has been reported in isolated atypical carcinoid. In the absence of a family history, it is likely that he may have acquired mutations of the tumour suppressor gene, MENIN gene. The mutations of this gene in MEN 1 are

usually dominantly inherited although up to 10% of cases the mutation can arise de novo. This hypothesis, however cannot be confirmed because genetic study is not available locally. To the best of our knowledge, this is the first described case of an ACTH secreting pulmonary carcinoid found in association with a pituitary macroadenoma. It is important to recognize this combination of endocrine tumours as screening for other associated endocrine neoplasms is indicated. Currently our patient is normocalcaemic and his CT scan of the abdomen has so far yielded a normal looking pancreas.

## REFERENCES

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