

## Ectopic Acromegaly Secondary to Bronchial Tumour: A Case Report of Rare Occurrence

Sara Sohail<sup>1</sup>, Waqas Shafiq<sup>1</sup>, Kashif Sajjad<sup>2</sup>, Umal Azmat<sup>1</sup>,  
Muhammad Atif Naveed<sup>3</sup>

<sup>1</sup>Department of Internal Medicine, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan, <sup>2</sup>Department of Internal Medicine, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Peshawar, Pakistan, <sup>3</sup>Department of Radiology, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan

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### Correspondence:

Waqas Shafiq, 7A Block R-3,  
Phase 2, M.A. Johar Town,  
Lahore, Punjab 54782, Pakistan.  
E-mail: waqasshafiq@skm.org.pk

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### Abstract

**Introduction:** Acromegaly is caused due to the unregulated and sustained overproduction of growth hormone (GH). The majority of the cases are caused by autonomous secretion of GH from anterior pituitary tumours. Nonetheless, in <1% of the cases, the cause of autonomous secretion is secondary to ectopic GH-releasing hormone (GHRH) production. Bronchial carcinoids are the most common cause of ectopic GHRH production. **Case Description:** A 32-year-old female presented to the clinic with a history of cough, haemoptysis and undocumented weight loss for 4 years. Initial workup showed a large right main stem endobronchial mass. Transbronchial biopsy of the mass revealed a Grade I neuroendocrine tumour (NET). During NET workup, a large sellar mass was incidentally found on cross-sectional imaging. The hormonal profile revealed markedly elevated insulin-like growth factor-1 (IGF-1) and mildly raised prolactin. The magnetic resonance imaging (MRI) brain study revealed pituitary macroadenoma measuring 2 cm × 1.2 cm × 1.5 cm. The patient underwent bronchial carcinoid tumour resection, which led to normalisation of serum IGF-1 and GH response to an oral glucose tolerance test. Subsequent MRI brain revealed complete resolution of previously noted sellar mass. **Practical Implications:** This case highlights the importance of differentiating acromegaly secondary to pituitary adenoma and ectopic acromegaly. This case emphasises the importance of keeping rare entities in the differential while assessing patients with pituitary macroadenoma.

**Key words:** Acromegaly, bronchial tumour, ectopic acromegaly, neuroendocrine tumour

### Introduction

Acromegaly is a chronic disorder caused by the hypersecretion of growth hormone (GH). Hypersecretion of GH leads to excess production

of insulin-like growth factor-1 (IGF-1), leading to a multisystem disease characterised by somatic overgrowth, multiple comorbidities, premature mortality and physical disfigurement. The diagnosis of acromegaly should be suspected in individuals

who present with an enlarged jaw and enlarged hands and feet, which results in increasing shoe and ring size. The facial features become coarse with an enlarged nose, tongue and protrusion of the lower jaw. The rate of this change is so slow that only a few patients report a difference in their appearance. The prevalence of acromegaly is estimated to range from 38 to 80 cases per million population, and the annual incidence of new patients is 3–4 cases per million.<sup>[1]</sup>

In more than 95% of acromegaly patients, the underlying cause of GH hypersecretion is a pituitary adenoma. Other causes include excess secretion of GH-releasing hormone (GHRH) by hypothalamic tumours, ectopic GHRH secretion by neuroendocrine tumours (NET) and ectopic secretion of GH by NET.<sup>[2-4]</sup> Ectopic acromegaly caused by NET is caused by bronchial, pancreatic or gastrointestinal carcinoids,<sup>[5]</sup> with bronchial carcinoids being the most common cause (70%) followed by pancreatic islet cell carcinoids.<sup>[6]</sup> Bronchial NETs have been linked to hormone secretion in up to 30% of the cases. They can present with clinical features of Cushing's syndrome, syndrome of inappropriate antidiuretic hormone secretion and acromegaly.<sup>[7]</sup>

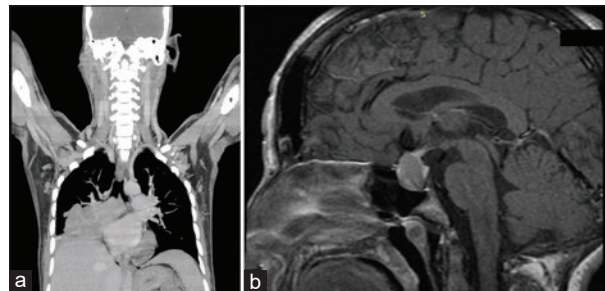
This is a clinical case report of a patient with acromegaly due to paraneoplastic GHRH secretion mediated by a bronchial NET. The waiver of informed consent to publish this case report was obtained from the local Institutional Review Board (EX-24-10-19-02).

### Case Presentation

A 32-year-old female presented to the pulmonology clinic with cough, haemoptysis and weight loss for 4 years. The computed tomography of the chest showed a large right main stem endobronchial mass. Transbronchial biopsy of the endobronchial mass revealed NET Grade I. During tumour staging workup, a large sellar mass was incidentally noted, which prompted a referral of the patient to the endocrine clinic for further assessment.

The endocrine evaluation revealed a pertinent history of amenorrhoea for 1 year. There was no history of galactorrhoea, headaches or visual disturbances. The patient did not report any changes in facial features. However, the family said that they noted a gradual change in her face's shape. The clinical examination revealed subtle acromegalic features with prominent supraorbital ridges, enlarged nose and dry skin. The visual field examination of this patient was normal.

The magnetic resonance imaging (MRI) brain scan revealed pituitary macroadenoma measuring 2 cm × 1.2 cm × 1.5 cm extending into the suprasellar region, causing mild-to-moderate optic pathway compression [Figure 1]. The hormonal profile showed markedly elevated IGF-1 1018 ng/ml (115–307 ng/ml) and mildly elevated prolactin levels 136 ng/ml (1.9–25 ng/ml). The morning cortisol was 8.82 ug/dl (4.3–22.4 ug/dl), thyroid stimulating hormone (TSH) was 0.742 Uiu/ml (0.4–4 Uiu/ml), free thyroxine (free T4) was 1.5 ng/dl (0.89–1.76 ng/dl), follicle-stimulating hormone (FSH) was 3.15 mIU/mL (2.8–11.3 mIU/mL) and luteinising hormone (LH) was 0.559 mIU/mL (1.1–11.6 mIU/mL). An oral glucose tolerance test (OGTT) was not done at that time.



**Figure 1:** (a) Pre-operative contrast-enhanced computed tomography thorax in coronal view shows large endobronchial mass involving the right main stem bronchus and right lower lobar bronchus. (b) Sagittal post-gadolinium with fat saturation T1-weighted magnetic resonance image is showing pituitary macroadenoma measuring approximately 2 cm × 1.2 cm × 1.5 cm (anteroposterior × transverse × craniocaudal) occupying the sella and suprasellar cistern

The coexistence of bronchial carcinoid and a pituitary lesion was suggestive of the presence of multiple endocrine neoplasia type 1 syndrome. The patient underwent an additional workup, which was representative of a raised serum parathyroid hormone level of 122.5 pg/mL (18.5-88 pg/mL), normal serum calcium level and 25-hydroxyvitamin-D level of 12.16 ng/mL (30-100 ng/mL). These results were conclusive for secondary hyperparathyroidism. Similarly, the CT triphasic abdomen scan did not reveal any pancreatic lesion.

### Diagnosis and Management

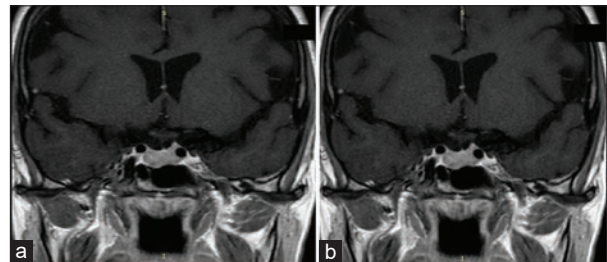
Based on the history, clinical examination and radiological and pathological findings, a diagnosis of GH-secreting pituitary macroadenoma with bronchial carcinoid tumour was made. Following the discussion in a multidisciplinary team meeting, it was decided to proceed with right-sided pneumonectomy followed by reimaging the pituitary lesion and trans-sphenoidal resection.

The histopathology of the resected pulmonary mass revealed NET Grade II. The sample was positive for synaptophysin and anti-cytokeratin (CAM 5.2) stains. The proliferative ki67 index of the sample was 1%.

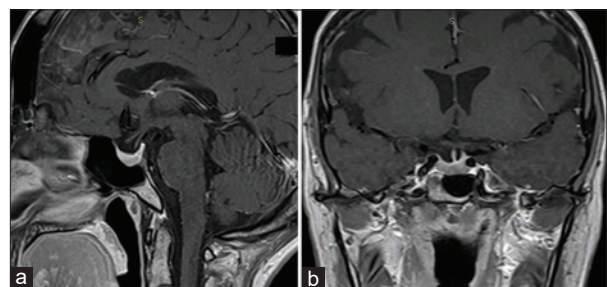
Four months post-surgery, the patient reported a normal menstrual cycle. Her hormonal profile normalised with IGF-1 levels of 116 ng/ml from 1018 ng/ml (115 to 307 ng/ml), and prolactin levels reduced to 44.4 ng/ml from 136 ng/ml (1.9 to ng/ml). Morning cortisol, TSH, FT4 FSH and LH were all within the normal physiological range. The OGTT showed appropriate suppression of the GH. Repeat MRI brain revealed a significant interval decrease in the size of large pituitary macroadenoma with residual mass measuring 1.6 cm × 1.3 cm × 0.8 cm [Figure 2a] against the initial measurement of 2 cm × 1.3 cm × 1.8 cm [Figure 2b]. This case was rediscussed in MDT. Based on the improving pathological markers and reducing the size of the pituitary adenoma, it was

decided to use a wait-and-watch approach and defer the trans-sphenoidal resection.

Similarly, repeat MRI brain studies at 8 and 18 months post-resection showed a significant shrinkage in tumour size [Figure 3]. At an 8-month follow-up, her IGF-1 levels were within the normal physiological range. At her 3-year follow-up, she remains well and asymptomatic.



**Figure 2:** (a) Coronal post-gadolinium with fat saturation T1-weighted magnetic resonance (MR) image shows sellar and suprasellar mass measuring approximately 2 cm × 1.2 cm × 1.5 cm (anteroposterior × transverse × craniocaudal) and causing mild-to-moderate mass effect in the optic chiasm. (b) Coronal post-gadolinium T1-weighted MR image 4 months after the resection of the neuroendocrine tumour shows homogeneously enhancing large sellar mass with significant interval decrease in size compared to one in A. The residual enhancing tumour process currently measures 1.6 cm × 1.3 cm × 0.8 cm against the prior measurement of 2 cm × 1.3 cm × 1.8 cm (anteroposterior × transverse × craniocaudal)



**Figure 3:** Sagittal (a) and coronal (b) T1-weighted post-gadolinium magnetic resonance images, 18 months post-resection of bronchial carcinoid tumour, show normalised pituitary glands with normal enhancement. There is complete resolution of previously noted mass in the pituitary gland before the resection of the right lung endobronchial tumour. No lesion is seen in the pituitary gland in the current study

## Discussion

In this case, a large pituitary mass was found on early radiological imaging, which was initially considered a pituitary macroadenoma. However, resection of bronchial carcinoid tumour leads to normalisation of IGF-1 and GH levels on OGTT, with complete resolution of the enlarged pituitary gland in 18 months, suggesting the possibility of pituitary hyperplasia secondary to ectopic secretion of GHRH. Although GHRH levels were not available, the patient most likely suffered from a GHRH-secreting bronchial carcinoid. This was suggested by the presence of a histologically confirmed diagnosis of bronchial carcinoid tumour, and normalisation of serum IGF-1 level, and normal GH response following an OGTT post-complete resection of lung tumour.

NETs constitute 2% of all lung cancers.<sup>[7,8]</sup> One-fourth of all NETs are located in the respiratory tract, making them the most frequent extraintestinal site for NET.<sup>[9]</sup> The reported annual incidence of pulmonary NET is about 1.35 in every 100,000 cases.<sup>[10]</sup>

Patients with bronchial carcinoids usually have a tumour in proximal airways and present with cough, shortness of breath, wheeze, haemoptysis or recurrent chest infection secondary to bronchial obstruction.<sup>[11]</sup> The clinical features of patients with ectopic acromegaly are indistinguishable from GH-secreting pituitary adenoma.<sup>[12]</sup> Similarly, serum GH and IGF-1 levels are elevated, and GH levels fail to suppress during OGTT in both acromegaly forms.<sup>[13]</sup> Plasma GHRH levels can differentiate between the two entities. It is normal or low in patients with pituitary driven acromegaly and elevated in ectopic GHRH-secreting tumours.<sup>[14]</sup> GHRH levels are not only a reliable marker for the diagnosis of ectopic acromegaly but it is also an indicator of disease activity following surgical treatment.<sup>[15]</sup>

Ectopic acromegaly and pituitary related acromegaly are challenging to differentiate on pituitary imaging. On pituitary imaging using MRI,

findings vary from a normal pituitary gland to global pituitary hyperplasia or adenoma. In a case series of 63 patients with ectopic acromegaly, 12 subjects had a normal brain MRI scan, 13 subjects had a pituitary adenoma and 38 cases had pituitary hyperplasia.<sup>[15]</sup>

This case report's limitation is that the GHRH levels were not checked; neither GHRH staining was done on histopathology due to these modalities' non-availability in the country. However, normalisation of IGF-1 levels, suppression of GH on OGTT and complete resolution of pituitary mass following pneumonectomy suggest that ectopic GHRH production from the bronchial NET was the most likely diagnosis.

The overall prognosis for such patients is favourable, following surgical removal of the responsible tumour. In a series of 23 cases, a cure rate of 87% was reported after a median follow-up of 2 years,<sup>[16]</sup> while a French series of 21 cases stated a survival rate of 85% after a 5-year median follow-up.<sup>[17]</sup> This patient has had a successful outcome post-resection of bronchial carcinoid tumour after a follow-up period of 3 years.

Ectopic acromegaly diagnosis is pivotal for the patient's management, as complete excision of the responsible tumour is usually curative. This will avoid unnecessary interventions such as pituitary surgery. Ectopic acromegaly should be considered in patients with acromegaly clinical features where pituitary imaging does not demonstrate a discrete adenoma and in patients with resistant acromegaly despite multimodality treatment. This case adds to the existing literature of clinical cases of ectopic acromegaly, in particular, and highlights the diagnostic challenges encountered in clinical practice; it also highlights the importance of keeping ectopic origin in the differential diagnosis.

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#### Authorship Contributions

Conceived and designed the analysis; SS and WS. Collected the data; SS, WS, KS and MAN. Contributed data or analysis tools; WS, UA and MAN. Performed the analysis; SS, KS and UA. Wrote the paper; SS, WS, KS, UA and MAN.