An unusual cause of acromegaly

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ABSTRACT

We report a rare case of acromegaly due to a growth hormone releasing hormone–secreting bronchial carcinoid tumour. A 40-year-old man initially presented with acromegalic features, and was subsequently found to have a large lung mass in the right lower zone on chest X-ray. Right lower lobectomy was performed, and the tumour was confirmed to be a bronchial carcinoid tumour on histology. Resection of the tumour led to normalisation of serum insulin-like growth factor 1 level and growth hormone responses to an oral glucose tolerance test.

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Case report

In September 2010, a 40-year-old man presented to a general practitioner with multiple skin tags and acanthosis nigricans. He was noted to have acromegalic features, including prominent supraorbital ridge, prognathism, and spade-like hands. He was referred to Tseung Kwan O Hospital medical out-patient clinic. In the interim, he visited a private endocrinologist. Investigations demonstrated that his serum insulin-like growth factor 1 (IGF-1) level was markedly elevated, being 719 (reference range, 101-267) ng/mL, and his serum growth hormone (GH) levels were not suppressed following an oral glucose tolerance test (OGTT) with a trough GH level of 9.9 ng/mL, which confirmed the diagnosis of acromegaly. Magnetic resonance imaging (MRI) of the pituitary gland (Fig 1a and b) revealed a bulky pituitary gland with a 1.3 x 1.0 x 1.1 cm (transverse x height x anteroposterior dimensions) subtle roundish area in the central anterior part of the gland. Transsphenoidal resection of the pituitary macroadenoma was planned. However, preoperative chest X-ray (Fig 2a) showed a large mass at the right lower zone. Thus, the operation was cancelled and computed tomography (CT) thorax showed a well-defined lobulated mass (Fig 2b and c), measuring 8.6 x 7.4 x 7.1 cm (lateral x anteroposterior x craniocaudal dimensions), at the basal region of the right lower lobe. Fluorodeoxyglucose-positron emission tomography (FDG-PET) of the whole body suggested that the mass was consistent with a primary lung cancer; there were no intrapulmonary or distant metastases. Right lower lobectomy was performed by a private cardiothoracic surgeon in October 2010. Histology confirmed the tumour to be an atypical bronchial carcinoid. He was first seen by us in November 2012. Evaluation showed that his IGF-1 level and GH response after having an OGTT had normalised. Repeat MRI of the pituitary gland 17 months after the lobectomy (Fig 1c and d) showed that the gland had decreased in size compared with its earlier size and the previously noted structural lesion had vanished. In light of the co-existence of bronchial carcinoid and a history of a pituitary lesion, multiple endocrine neoplasia type 1 (MEN-1) syndrome was suspected, but genetic testing could not detect any mutations. Although growth hormone–releasing hormone (GHRH) level was not available, the patient most likely suffered from a GHRH-secreting bronchial carcinoid as suggested by the presence of a histologically confirmed bronchial carcinoid tumour, and normalisation of serum IGF-1 level and normal GH response following an OGTT upon complete removal of his lung tumour.

Discussion

Acromegaly is due to sustained and unregulated hypersecretion of GH. It develops insidiously and progresses slowly, and typically remains undiagnosed for about 10 years.[1] More than 95% of cases are caused by autonomous secretion of GH from anterior pituitary tumours and result in clonal expansion of somatotrophs. Less than 1% are due to ectopic GHRH production, with bronchial carcinoids being the most common cause (70%) followed by pancreatic islet cell carcinoids.[2]

Since the majority of bronchial carcinoids arise in the proximal airways, patients usually present with pulmonary symptoms,[3] including cough, shortness of breath, wheeze, haemoptysis, chest pain, or recurrent pneumonia in the same pulmonary segment or lobe (due to bronchial obstruction). Although many of

肢端肥大症的異常病因

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本文報告一個因支氣管類癌分泌生長激素釋放激素所引起的肢端肥大症的罕見病例。一名四十歲的男病人出現了肢端肥大症的症狀，及後在肺部X光檢查中發現一個體積頗大的腫瘤在其右下肺葉。經手術切除後，這腫瘤被確定為支氣管類癌。手術後，病人血液中的類胰島素生長因子濃度和生長激素在口服葡萄糖耐量試驗的反應均回復正常。

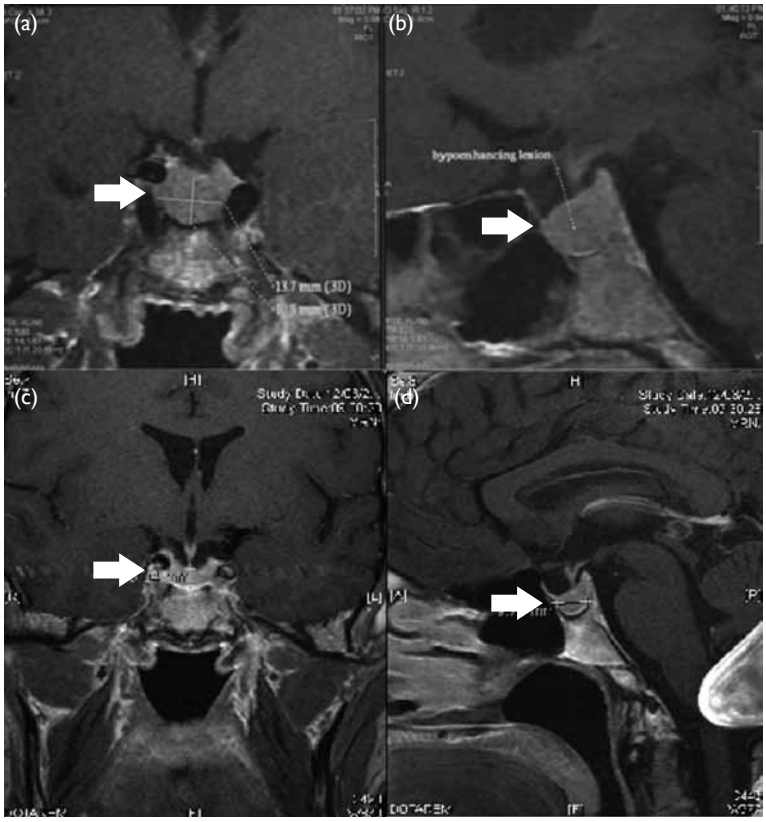

FIG 1. (a, b) T1-weighted magnetic resonance imaging (MRI) of the pituitary gland shows a 1.3 x 1.0 x 1.1 cm (transverse x height x anteroposterior) lesion in the central anterior part of the gland (arrows). (c, d) Repeat MRI of the pituitary gland 17 months after the right lower lobectomy shows that the gland has decreased in size (arrows) compared with the previous one with no more structural lesion

the tumours express immunoreactive GHRH, most patients with bronchial carcinoid are not clinically acromegalic. The first case of a bronchial carcinoid causing acromegaly was reported in 1958.[4] Despite the large size and central location of his tumour, our patient did not have any chest symptoms; instead he came to medical attention because of prominent acromegalic features.

The clinical manifestations of acromegaly in patients with the ectopic GHRH syndrome are indistinguishable from those of any GH-secreting pituitary adenoma.[5] Similarly, regardless of the cause, serum GH and IGF-1 levels are invariably elevated and GH levels fail to suppress (<1 ng/mL) during OGTT in all forms of acromegaly.[6] No dynamic tests are helpful in differentiating the causes.[7] Among all, plasma GHRH is the most precise and cost-effective test for the diagnosis of ectopic GHRH causing acromegaly. Plasma GHRH levels are usually elevated in patients with peripheral GHRH-secreting tumours, and are normal or low in patients with pituitary acromegaly.[8] Regrettably, before the operation plasma GHRH level was not checked in our patient as this test was not available in most of the local hospitals. The presence of positive staining for GHRH could also provide direct evidence of the diagnosis.

Bronchial carcinoids are usually picked up easily on chest X-rays and by CT thorax. Compared with chest X-rays, CT delineates the extent of the tumour and its location better as well as the presence of any mediastinal lymphadenopathy. In our patient, the bronchial carcinoid was visualised by FDG-PET. However, FDG-PET yields conflicting results when it comes to identifying bronchial carcinoids, probably because of their small size and hypometabolic nature. In a retrospective review of 16 patients with surgically resected bronchial carcinoids, preoperative PET detected only 12 (75%).[9] The use of other PET tracers, such as 11C-L-DOPA and 11C-5-hydroxytryptophan, improves the sensitivity for imaging neuroendocrine tumours.[10] Approximately 80% and 60% of typical and atypical bronchial carcinoids express somatostatin receptors by immunohistochemistry, respectively. They may also be imaged with octreoscan.[11] However, specificity is limited because scintigraphy is positive in many other tumours, and not all carcinoid tumours that express somatostatin receptors by immunohistochemistry test positive with octreoscan.

Pituitary gland MRI is necessary to verify the presence and size of a pituitary lesion, even when the diagnosis of ectopic GHRH syndrome has been established. In contrast to patients with classical acromegaly, no pituitary tumour but an enlargement of the sella is detected in the majority of such patients.[12] The first MRI of the pituitary gland in our patient suggested the presence of an anterior pituitary macroadenoma, which is unexpected in patients with GHRH-secreting bronchial carcinoid. Thus, three other issues need to be considered. First, the co-existing carcinoid tumour and possible pituitary adenoma alerted us to the possibility of MEN-1. Second, the bronchial carcinoid might have metastasised to the pituitary gland. Third, the

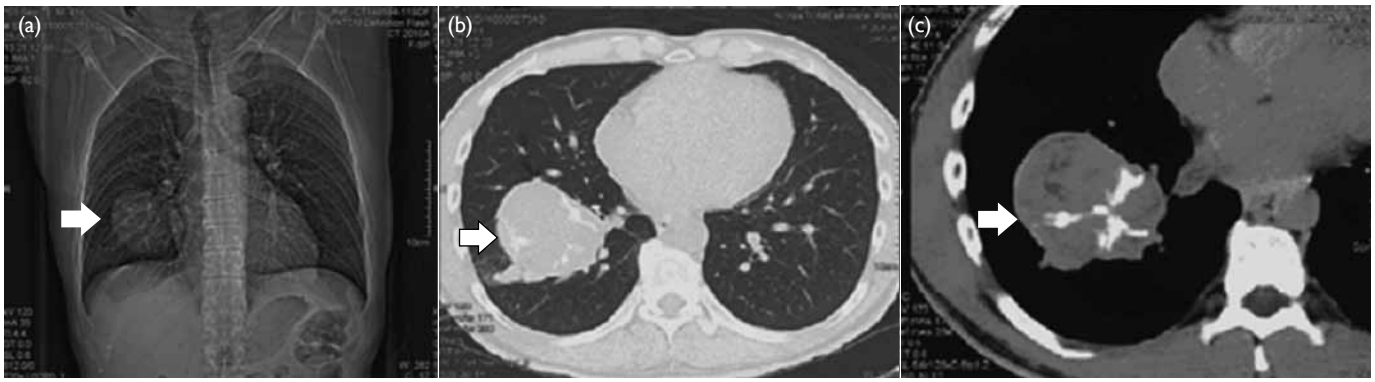

FIG 2. (a) A chest X-ray shows a large lung mass at the right lower lobe (arrow). (b) Non-contrast computed tomography thorax shows a well-defined, lobulated mass, measuring 8.6 x 7.4 x 7.1 cm (lateral x anteroposterior x craniocaudal) at the basal region of right lower lobe (arrow). Elongated coarse calcified foci are seen at the peripheral and central part of the lesion. (c) After contrast injection, heterogeneous enhancement is seen in the lesion (arrow). It also contains non-enhanced low-density area suggestive of cystic change of necrosis

acromegaly really was due to the pituitary tumour producing excessive amounts of GH, and that its auto-infarction leads to normalisation of IGF-1, a normal GH response after an OGTT and shrinkage of the tumour on subsequent MRI. The absence of an MEN-1 mutation and hyperparathyroidism, and the resolution of pituitary lesion after lobectomy make the first possibility unlikely. Although we did not have any histology from the pituitary, again, disappearance of the lesion after the lobectomy also makes the second possibility unlikely. Regarding the third possibility, it cannot be proved or disproved in the absence of a plasma GHRH level and tumour histology. Nevertheless, we have to follow the patient closely to obtain the final answer.

Surgical resection of the bronchial carcinoids offers the best chance of cure, the prognosis of following resection of a typical carcinoid is excellent, with reported 5-year survival rates of 87% to 100%. While for atypical carcinoid, 5-year survival of 30% to 95% has been reported.[3,13] Chemotherapy and radiotherapy are generally not effective. For those with non-resectable, disseminated tumours; who refuse surgery; or who are unsuitable because of medical co-morbidities, long-acting somatostatin analogues provide an effective option to control symptoms, and according to some studies, may also slow tumour progression.[14]

Conclusions

Ectopic GHRH acromegaly is so rare that routine screening would have a very low yield. Instead, clinicians should bear this diagnosis in mind, and search for an extrapituitary source of GH excess in those with unexpected clinical features (eg breathlessness, wheeze, or facial flushing), absence of a pituitary tumour on imaging, and the presence of tumours known to be associated with extrapituitary acromegaly. Measurement of plasma GHRH is the most cost-effective means of arriving at a diagnosis, but is not widely available. Chest X-ray, CT thorax and abdomen could be performed, if plasma GHRH testing is not available. A correct diagnosis is important, as the primary treatment for extrapituitary acromegaly entails surgical removal of the underlying tumour. Long-acting somatostatin analogues might be used to control symptoms, if resection is incomplete or not feasible.

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Answers to CME Programme
Hong Kong Medical Journal June 2014 issue

Hong Kong Med J 2014;20:187–93

I. Characteristics and outcomes of patients with percutaneous coronary intervention for unprotected left main coronary artery disease: a Hong Kong experience

A	1. False	2. True	3. False	4. True	5. False
B	1. True	2. False	3. True	4. True	5. False

Hong Kong Med J 2014;20:241–50

II. Current status of robot-assisted surgery

A	1. True	2. True	3. True	4. True	5. False
B	1. True	2. True	3. False	4. False	5. False