CASE REPORT

'Open-and-close' pituitary surgery in an acromegalic man presenting with excessive sweatiness

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SUMMARY

Ectopic-acromegaly is rare. Diagnosing ectopic-acromegaly is challenging given that the clinical and biochemical manifestations can be almost indistinguishable from those of patients with growth hormone secreting pituitary adenomas. This case report highlights the importance of clinical vigilance in differentiating between the two conditions. A 41-year-old Caucasian man presented with typical features of acromegaly with an enlarged pituitary and a lung lesion. Although excision of the lung mass showed a carcinoid tumour, normalisation of growth hormone factors did not occur soon enough. This led to a presumed diagnosis of a pituitary adenoma. However, no pituitary tumour was identified during trans-sphenoidal surgery. Postoperatively, the patient improved clinically and biochemically. Retrospective histological examination of the excised lung lesion showed a small proportion of tumour cells containing growth hormone releasing hormone (GHRH), suggesting ectopic-GHRH production from the lung neuroendocrine tumour. An open-and-close trans-sphenoidal surgery could have been avoided in this patient with ectopic-GHRH acromegaly.

BACKGROUND

The incidence of acromegaly is ~3–4 cases per million and the prevalence is about 60 cases per million.¹ Less than 1% of these cases are caused by ectopic secretion of growth hormone (GH) releasing hormone (GHRH) from non-pituitary neuroendocrine tumours (NETs), and only 99 of such cases have been reported in the literature. Most ectopic-GHRH cases are due to lung carcinoid tumours, leading to hyperplasia of the pituitary and the resulting hyper-secretion of GH. Of all these cases, the mean age at diagnosis was 41 years, and 2/3 were female, similar to acromegaly caused by GH-secreting pituitary tumours.² Failure to distinguish between pituitary and ectopic-acromegaly can lead to unnecessary major neurosurgery. In many reported cases, the diagnosis of ectopic-acromegaly was later confirmed during diagnostic work up or post unsuccessful pituitary surgery for acromegaly. The pitfalls and difficulties lie in the fact that most patients with ectopic-acromegaly have pituitary hyperplasia visible on imaging that is radiologically difficult to distinguish from pituitary adenoma. Of the reported cases of ectopic-acromegaly, pituitary enlargement was noted in 75% of the cases and 1/3 of the patients underwent trans-sphenoidal surgery for presumed GH-secreting pituitary adenoma.² Also, the time it takes for insulin-like growth factor-1 (IGF1) to normalise after resection of the

GHRH-secreting tumour is unknown. Some normalised as early as 1 month postoperatively, while others took longer.³

CASE PRESENTATION

A 41-year-old Caucasian man presented with a 2-year history of hyperhidrosis. Physical examination revealed typical features of acromegaly including acral and soft tissue overgrowth, with enlarged hands and feet. He had no visual field defect and no galactorrhoea. Serum IGF1 was 719 ng/mL (age-specific reference range: 101–267 ng/mL). Pituitary-dedicated MRI showed a 1.3×1×1.1 cm bulky pituitary gland with a subtle roundish hypoenhancing area in its anterior part, suggestive of a macroadenoma (figure 1A). Trans-sphenoidal surgery was planned, and during the preoperative work up, an incidental lung shadow was found on chest radiograph. CT of the thorax showed a well-defined 8.6×7.5×7.1 cm lobulated mass at the basal region of right lower lobe with coarse, contrast-enhancing calcified foci (figure 2). Whole body trunk positron-emission-tomography scan showed only abnormal increased metabolic activity in this right lung mass. The patient proceeded to have a right lower lobectomy. Histology of the lung lesion revealed an atypical carcinoid tumour (figure 3A). Five days of somatostatin analogue (Sandostatin 100 µg 3 times/day subcutaneous) prior to the lobectomy was given, followed by one dose of long-acting somatostatin analogue (Sandostatin LAR 20 mg intramuscular) right after the thoracic surgery. IGF1 dropped significantly to 256 ng/mL at 1 month and 199 ng/mL at 2 months, but rose to 276 ng/mL at 5 months postoperatively. A pituitary-dedicated MRI repeated at 5 months postlobectomy showed a reduction in size of the anterior pituitary gland. However, a mildly hypoenhancing 2.4×7.1 mm area was still present, making it suspicious for residual tumour (figure 1B). The initial fall of IGF1 was attributed to the somatostatin analogue the patient had received. With the residual pituitary tumour and a rebound of IGF-1, pituitary acromegaly was suspected. Trans-sphenoidal surgery was attempted, but ended up only open-and-close, as there was no identifiable pituitary adenoma during the operation.

OUTCOME AND FOLLOW-UP

The patient's symptoms improved with much reduction in hyperhidrosis. IGF1 was normalised at 189 ng/mL. An extended oral glucose tolerance test (EOGTT) showed normal physiological suppression of GH confirming that his acromegaly was in remission. Repeated pituitary-dedicated MRI

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Figure 1 Pre-trans-sphenoidal surgery pituitary-dedicated MRI showing a 1.3×1×1.1 cm bulky pituitary gland with a subtle roundish hypoenhancing area in its anterior part (A). Six months after the presentation, the anterior pituitary gland had decreased in size, but a mildly hypoenhancing area 2.4×7.1 mm was still present (B). After lobectomy of the atypical carcinoid tumour, post-trans-sphenoidal surgery pituitary-dedicated MRI shows only a slightly bulky pituitary gland with a residual 2.0×2.0 mm hypo-enhancing area of unknown significance (C).

showed a slightly bulky gland, which had significantly reduced in size, with a residual 2.0×2.0 mm hypoenhancing area of unknown significance (figure 1C). The latest CT of the thorax showed only postoperative changes in the right lower lobe with no suspicious residual tumour. The endocrine nature of the atypical carcinoid tumour of the right lung was then revisited. GHRH was present in a small proportion of the tumour cells (<1%, figure 3B–E), suggesting the source of GHRH might have originated from this atypical carcinoid tumour.

DISCUSSION

Our patient presented with typical acromegalic features, suspicious pituitary macroadenoma and an incidental lung mass. The diagnosis turned out to be acromegaly secondary to the ectopic secretion of GHRH from atypical carcinoid tumour of the lung. He was misdiagnosed to have a GH-secreting pituitary macroadenoma based on the initial limited investigation together with sluggishly normalised IGF1 and pituitary-dedicated MRI findings. These resulted in an unnecessary open-and-close trans-sphenoidal surgery, which carried risks to the patient. In retrospect, a ‘wait-and-observe’ approach in the follow-up of this patient after the lobectomy to allow a longer period of observation of IGF1 to normalise would have proven invaluable, as the possibility of ectopic-GHRH acromegaly would have been proposed. Investigation of the lung NET might have been extended to a wider panel of immunohistochemical staining for various

hormones. Also, if a normal postlobectomy EOGTT GH response and/or GHRH level were to have been documented, this neurosurgery could have been avoided.

As in our patient, most ectopic-GHRH cases are due to lung carcinoid tumours, leading to hyperplasia of the pituitary and the resulting hyper-secretion of GH. Clinical presentations of ectopic-acromegaly are similar to pituitary-dependent disease. Some patients present only with acromegalic features, as did our patient. In other cases, signs and symptoms might be related to the underlying tumours, such as cough/wheezing in the lung carcinoid, or jaundice in pancreatic NETs causing obstruction of the biliary tract. Attention has to be paid towards watching out for other endocrinopathies such as: pituitary tumour, pancreatic tumour and/or primary hyperparathyroidism, since as many as 25% of the patients with ectopic-acromegaly have been shown to be associated with multiple-endocrine-neoplasm1 (MEN1),¹ suggesting that the underlying genetic pathogenesis might be common for these two diseases. Further molecular analysis of the MEN1 gene mutation detection in this patient was negative, ruling out the possibility of associated MEN1.

Diagnosing ectopic-acromegaly is challenging, given that the clinical and biochemical manifestations can be almost indistinguishable from those in patients with GH-secreting pituitary adenomas. Diagnostic criteria include those for diagnosing acromegaly plus evidence of GHRH secretion from an ectopic tumour by immunofluorescence staining or GHRH-mRNA expression, elevation of plasma GHRH levels, abnormal uptake on somatostatin-receptor-scintigraphy (SRS) and/or complete recovery of the above after resection of the ectopic tumour. In a French series with 20 cases of acromegaly induced by ectopic secretion of GHRH from identifiable tumours, 16 tumours were histologically confirmed to be GHRH-secreting, while the remaining tumours were considered GHRH-secreting based on elevated plasma GHRH and abnormal uptake of SRS.³ Our patient had high IGF1 at presentation, which was slow to but did eventually normalise after resection of the lung carcinoid tumour. In addition, the tumour stained positive for GHRH on immunofluorescence staining. Taken together, the clinical presentation, progress and histology support a diagnosis of ectopic-acromegaly derived from the GHRH-secreting lung carcinoid tumour.

Managing ectopic-acromegaly is more straightforward than making the diagnosis. It consists of resection of the primary tumour and documentation of biochemical normalisation of the hormone levels. Surgical resection can be curative if no metastasis is present. In patients with unresectable tumours or metastases, medical treatment with somatostatin analogue therapy and adjuvant chemotherapy and/or radiotherapy can be of use. In 90

Figure 2 Prelobectomy CT of the thorax shows a well-defined 8.6×7.5×7.1 cm lobulated mass at the basal region of right lower lobe, with coarse calcified foci that enhanced heterogeneously with contrast at presentation.

Figure 3 Tumour at the right lower lobe is an atypical carcinoid tumour consisting of trabecules of cuboidal cells with ovoid nuclei containing fine chromatin ((A) $\times 100$ H&E stain). Growth hormone releasing hormone (GHRH) was demonstrated in only a small proportion of the tumour cells ((B) arrow, $\times 50$) by immunofluorescence stain with anti-GHRH (1:800, Abcam AB8899, pseudocoloured red). Nuclei were counter-stained with DAPI (pseudocoloured blue). Higher power view of this GHRH+ tumour cell cluster ((C) $\times 400$) shows granular cytoplasm signals in some of the tumour cells (arrows, composed image in (C), grey scale image of anti-GHRH signals in (D), counter stain of nuclear signals shown as grey scale image in (E)).

reported cases of ectopic-acromegaly, lymph node or distant metastases were documented in 39 cases. Tumour resection was performed in 55 cases, somatostatin analogue therapy was given in 13 cases, and adjuvant chemotherapy and radiotherapy were used in 2 cases. Of these, 44% showed complete remission, 31% showed partial improvement, 5% did not show any improvement and 10% died.² Antiangiogenic drugs and tyrosine kinase inhibitors are currently being investigated as potential treatments for NETs by inhibiting tumour growth.^{4 5} Overall, GHRH-producing NETs have a favourable prognosis, provided that the right diagnosis is made early followed by prompt surgical resection.

Learning points

Open-and-close trans-sphenoidal surgery can potentially be avoided in patients with ectopic growth hormone releasing hormone (GHRH) acromegaly, if the following are considered:

- ▶ including rare conditions in the differential diagnoses particularly in the presence of a co-existing lung lesion;
- ▶ a longer period of observation of IGF1 trend although the length of this is unknown; and
- ▶ measurement of plasma GHRH level before/after the lobectomy, or prompt demonstration of the presence of GHRH of the resected lung mass.

In summary, acromegaly caused by ectopic-GHRH-secreting lung carcinoid tumour is a rare clinical entity. We report a patient in whom open-and-close trans-sphenoidal surgery could have been avoided. Accumulation of more experiences using standardised management protocol is needed in future to help define the average time for IGF1 to normalise after complete resection of an ectopic-GHRH-releasing tumour. Coupled with the wider use of GHRH immunofluorescence stain and/or GHRH measurements in appropriate clinical settings, these efforts would guide clinicians in better management of these rare cases of ectopic-GHRH-secreting tumours.

Contributors KKTC managed the patient in the clinic, made substantial contributions in drafting the manuscript, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. FCCC managed the patient in the clinic, revised the manuscript critically for important intellectual content, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AWIL made substantial contributions toward the investigation of the pathology, developed the immunofluorescence test for GHRH and histopathology review, revised the manuscript critically for important intellectual content, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All three authors participated sufficiently in the work to take public responsibility for appropriate portions of the content and have given final approval of the version to be published.

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