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CASE REPORT

Acromegaly caused by a growth hormone-releasing hormone secreting carcinoid tumour of the lung: the effect of octreotide treatment

C.M. de Jager[1,*], L.J.M. de Heide[1], G. van den Berg[4], A. Wolthuis[2], W.D. van Schelven[3]

Departments of [1]Internal Medicine, [2]Clinical Chemistry and [3]Nuclear Medicine, Leeuwarden Medical Centre, the Netherlands, [4]Department of Endocrinology, University Medical Centre Groningen, University of Groningen, the Netherlands, [*]corresponding author (currently: Department of Internal Medicine, University Medical Centre Groningen): +31 (0)50-361 61 61, e-mail: c.c.m.de.jager@int.umcg.nl

ABSTRACT

In acromegaly, the overproduction of growth hormone is usually caused by a pituitary adenoma. We report a 74-year-old woman with acromegaly caused by ectopic overproduction of growth hormone-releasing hormone (GHRH), a rare diagnosis. The GHRH appeared to be produced by a carcinoid tumour of the lung. Treatment with monthly long-acting octreotide resulted in a reduction in the symptoms and normalisation of the insulin-like growth factor-I, which has been maintained for more than two years now. A review of literature concerning causes and treatment of ectopic GHRH-producing tumours is presented.

KEYWORDS

Acromegaly, ectopic GHRH-producing tumours, octreotide treatment

INTRODUCTION

Acromegaly is a clinical syndrome caused by overproduction of growth hormone.

The excess of growth hormone is nearly always produced by a pituitary adenoma.

In less than 1% of the cases, however, the normal pituitary is stimulated by either eutopic or ectopic overproduction of growth hormone-releasing hormone (GHRH).

Clinical, biochemical and radiological features are often indistinguishable between growth hormone-producing adenomas and ectopic GHRH-producing tumours, making it difficult for the latter to be recognised. In this case report we present a patient with a GHRH-producing carcinoid tumour of the lung, whose pituitary MRI and the presence of a lesion in the lung led us to the possibility of this rare cause of acromegaly. The response to a long-acting somatostatin analogue will be reported as well.

CASE REPORT

A 74-year-old woman was referred to the hospital with anaemia caused by iron deficiency (haemoglobin 3.6 mmol/l, normal 7.2-9.0, MCV 59 fl, normal 81-96, ferritin 2 µmol/l, normal 14-150). Further diagnostic work-up showed an adenocarcinoma of the proximal colon; a right-sided hemicolectomy was performed. Microscopic evaluation showed a $T_3N_0M_0$ tumour. On physical examination there were clear signs of acromegaly. She had coarsening of facial features, protrusion of the lower jaw and macroglossia. In retrospect these symptoms had been progressively present over approximately the last 15 years. Laboratory investigation showed a random growth hormone (GH) concentration of 85 mU/l (normal <20) and an elevated insulin-like growth factor-I (IGF-I) of 605 ng/ml (normal for age and gender <200), already confirming the clinical diagnosis of acromegaly.

The levels of the other pituitary hormones were prolactin 1795 mU/l (normal <500), luteinising hormone (LH) 2.4 U/l (normal for age and gender 20-100), follicle-stimulating hormone 5.8 U/l (normal for age and gender 30-120), thyroid-stimulating hormone 1.2 mU/l (normal 0.3-4.0). The free thyroxine (fT_4) concentration was 12 pmol/l (normal 11-24) and a random cortisol value was 312 nmol/l. After intravenous injection of thyrotrophin-releasing hormone as well as of LH-releasing hormone a more than

50% increase in growth hormone concentration was noted, a typical response of a pituitary growth hormone producing adenoma. An intravenous dose of 50 μg octreotide caused a steep decline of the growth hormone concentration from 80 mU/l to less than 5 mU/l after 90 minutes.
The MRI, however, did not show a demarcated tumour. Instead a symmetrically enlarged pituitary gland was visible (*figure 1*). This raised the possibility of a GHRH-secreting tumour leading to hyperplasia of the somatotrophic cells causing enlargement of the pituitary and overproduction of growth homone. Since our patient had had a stable solid lesion of the right lung for more than 15 years, a carcinoid tumour was considered (*figure 2*). In order to strengthen this hypothesis somatostatin receptor scintigraphy using ^{111}In pentetreotide was performed. The lesion in the right lung appeared to be the only spot with increased uptake of labelled octreotide (*figure 3*). A transthoracic cytological fine needle aspiration showed atypical cells compatable with a carcinoid tumour.

Figure 1. *Coronal section showing a symmetrically enlarged pituitary gland*

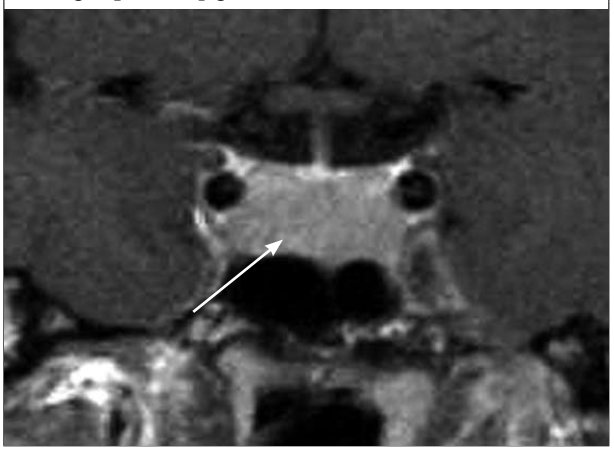


Figure 2. *Chest X-ray with a rounded-shaped tumour in right lung*

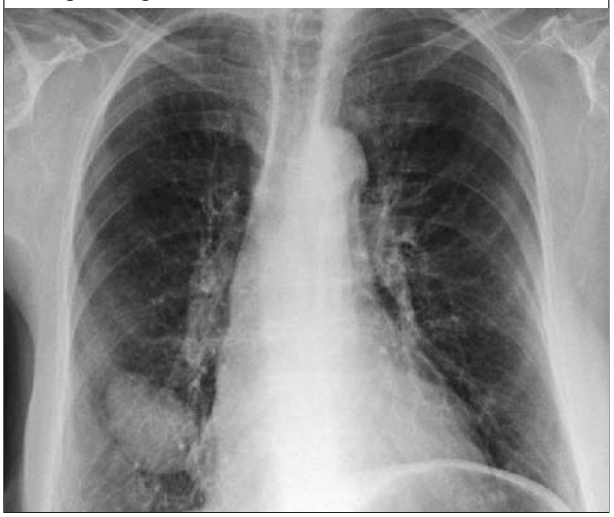
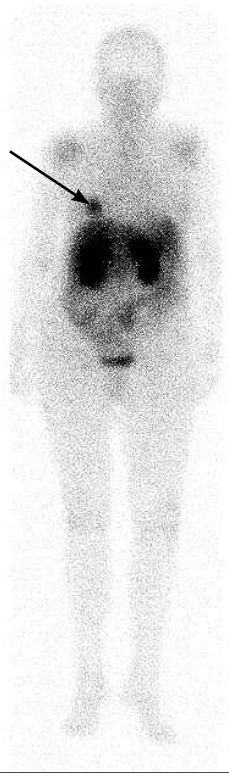


Figure 3. *^{111}In labelled pentreotide scintigraphy showing increased uptake of the radiopharmacon in a lesion in the right lung (arrow)*

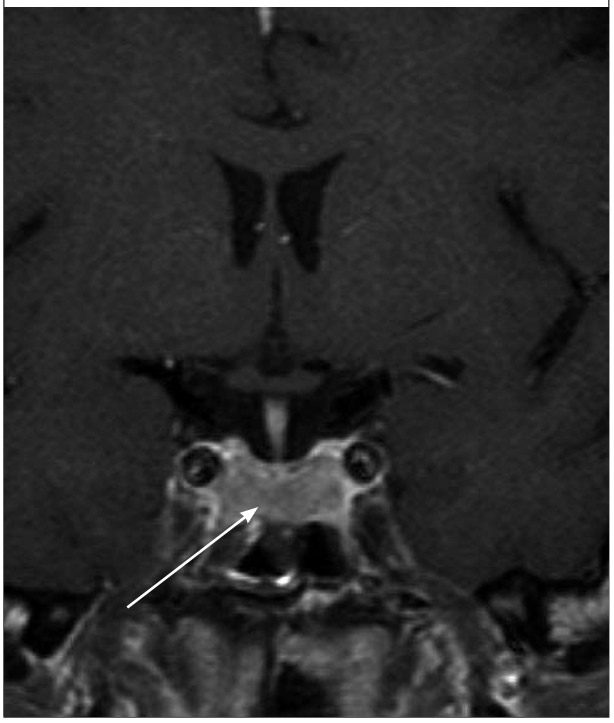


Successively measurement of fasting plasma GHRH was performed showing a high concentration of 3155 pg/ml (Quest Diagnostics, California, normal <49), as well as a simultaneously measured IGF-I level of 599 ng/ml (normal <200). We therefore concluded that the acromegaly was caused by ectopic overproduction of GHRH likely due to the carcinoid tumour of the right lung. Our patient was very reluctant to undergo surgery. We therefore started treatment using a monthly intramuscular long-acting somatostatin analogue, octreotide (Sandostatin LAR 20 mg). This led to a clinical reduction in the signs of acromegaly, a normalisation in IGF-I (177 ng/ml) and GH (2.2 mU/l) and a reduction in the fasting GHRH concentration (805 pg/ml). One year after the initiation of therapy a MRI showed a reduction in size of the pituitary gland (*figure 4*). At the moment, two years after the start of medical therapy, our patient is still being biochemically controlled with the long-acting octreotide and the lung tumour has remained unchanged in size without evidence of metastases elsewhere.

DISCUSSION

Acromegaly caused by a GHRH-secreting tumour is very rare. Only about 65 cases have been reported in the literature. Thorner measured GHRH in plasma of

Figure 4. *Coronal section showing decrease in volume of the pituitary gland one year after the start of octreotide treatment*



177 consecutive cases of acromegaly and found no cases of GHRH overproduction.[1] The frequency of GHRH excess causing acromegaly is estimated to be less than 1%.[2] Cases can be divided into eutopic and ectopic. Eutopic excess of GHRH secretion is caused by hypothalamic hamartomas, choristomas, gliomas or gangliocytomas. Ectopic causes are neuroendocrine tumours. Two-thirds are believed to be of carcinoid origin usually bronchial, but gastrointestinal and pancreatic carcinoids have also been reported. Pancreatic islet cell tumours, thymic tumours, tumours associated with multiple endocrine neoplasia type 1 (MEN-1) syndrome, small cell lung cancer, adrenal adenoma or pheochromocytoma have also been reported.[3,4-17]

Clinically and biochemically eutopic and ectopic GHRH overproduction are virtually indistinguishable from a pituitary GH-producing adenoma. Losa, however, reported that in dynamic testing all GHRH-producing tumours showed a hyperresponse (more than 50% increase from basal value) to TRH and mostly a blunted response to GHRH administration.[2] Hyperprolactinaemia is much more often present as GHRH is also known to stimulate the pituitary lactotrophic cells to increase their production of prolactin. Furthermore, in ectopic GHRH production a strikingly elevated GHRH level in peripheral blood samples is usually present, disappearing after removal of the ectopic origin.[3,18] In ectopic acromegaly there may be symptoms of mass effect of the primary tumour and in some cases of the co-secreted hormones, such as insulin, gastrin, somatostatin, glucagon, calcitonin, pancreatic polypeptide, serotonin, dopamine or norepinephrine.[5]

On pituitary imaging using MRI, there is also a wide range of abnormalities, ranging from a normal pituitary gland, to hyperplasia or adenoma.[5,19] Our patient showed both an elevated GHRH level and a symmetrical enlargement of the pituitary on MRI.

Most carcinoid tumours can be visualised with somatostatin-receptor scintigraphy. Kwekkeboom *et al.* found a sensitivity of 86% in a group of 37 patients with histologically proven carcinoid tumours.[20] ^{111}In-pentetreotide is injected intravenously and imaging is performed 24 hours later. When necessary, additional images are taken 48 hours after injection, for example if interpretation of the images of the abdomen is difficult because of physiological bowel activity. Planar images are taken routinely, single photon emission computed tomography (SPECT) can be performed for a more accurate localisation of the abnormalities. Somatostatin receptor scintigraphy can be carried out for tumour localisation or for staging purposes. Another indication is demonstration of somatostatin receptor positivity of a tumour, in order to select patients who are likely to respond favourably to somatostatin analogue therapy.[7,20]

A definitive diagnosis of ectopic GHRH production can be made either by showing an arteriovenous concentration gradient of GHRH in the region of the tumour or by normalisation of GHRH, IGF-I and GH-levels after removal of the tumour.[2] Although in our patient these conditions are not met, we feel confident with the diagnosis considering the biochemical, radiological, cytological and scintigraphic data and the response to therapy.

Surgical removal of the tumour is the usual therapy. Differentiation from pituitary adenomas is thereby essential, avoiding unnecessary pituitary surgery. Although carcinoids are believed to be slow-growing malignancies with insidious development of acromegaly over many years, by the time the diagnosis is made they have frequently metastasised, thus prohibiting curative surgery.[21] Pituitary irradiation, sometimes used in acromegaly for patients who are not cured by surgery and/or medical therapy, is of little use in ectopic GHRH-secreting tumours.

Until the end of the 1980s metastatic GHRH-producing tumours were essentially untreatable, since dopamine agonists such as bromocriptine could not suppress the GH secretion and IGF-I levels sufficiently due to a continued peripheral GHRH overproduction. The introduction of (long-acting) somatostatin analogues, octreotide and

lanreotide, suppressing both GH and the peripheral carcinoid GHRH production, changed this situation dramatically. With the start of treatment several patients experienced sudden relief of their symptoms, with a drop in GH and IGF-I levels following some months later. The effect on tumour shrinkage, also in the long term, appeared to be dose-dependent in several cases, with follow-up ranging from 3 to 120 months.[5,17,22,23]

Our patient has responded very well to the treatment and has sustained a reduction in the symptoms and acceptable biochemical marks for more than 2 years now. An MRI one year after initiation of the octreotide therapy showed regression of the size of the pituitary gland.
In conclusion, we present a patient with a very rare cause of acromegaly due to an ectopic overproduction of GHRH by a carcinoid tumour of the lung. Treatment consisted of monthly intramuscular long-acting octreotide. This induced a reduction in the symptoms with acceptable biochemical values in the follow-up of more than two years to date.

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