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CASE REPORT

Acromegaly secondary to an incidentally discovered growth-hormone-releasing hormone secreting bronchial carcinoid tumour associated to a pituitary incidentaloma

E. Verrua · C. L. Ronchi · E. Ferrante · D. I. Ferrari · S. Bergamaschi · S. Ferrero · M. C. Zatelli · V. Branca · A. Spada · P. Beck-Peccoz · A. G. Lania

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Abstract In this report we emphasize the opportunity of considering the uncommon causes of chronic GH-excess in the initial diagnostic process, such as GHRH hypersecretion, especially in the presence of ambiguous pituitary neuroimaging. This topic may have an important clinical significance in order to plan the most cost-effective diagnostic procedures and management and to avoid unnecessary pituitary neurosurgery.

Keywords Acromegaly · Carcinoid tumour · Pituitary incidentaloma

Patient consent has been received for publication of the case details and the figures.

E. Verrua · C. L. Ronchi · E. Ferrante · D. I. Ferrari · S. Bergamaschi · A. Spada · P. Beck-Peccoz · A. G. Lania (✉)
Unit of Endocrinology, Department of Medical Sciences, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, University of Milan, Via F. Sforza 35, 20122 Milan, Italy
e-mail: andrea.lania@unimi.it

S. Ferrero
Pathology Unit, Department of Medicine, Surgery and Dentistry, AO San Paolo and Fondazione Ospedale Maggiore IRCCS, Milan, Italy

M. C. Zatelli
Section of Endocrinology, Department of Biomedical Sciences and Advanced Therapies, University of Ferrara, Via Savonarola 9, 44100 Ferrara, Italy

V. Branca
Department of Diagnostic and Interventional Neuroradiology, IRCCS Maggiore Hospital, Mangiagalli and R. Elena Foundation, University of Milan, Milan, Italy

Introduction

Acromegaly is prevalently due to GH-secreting pituitary adenomas, while an increased hypothalamic or ectopic growth hormone releasing factor (GHRH) secretion accounts for <1% of total cases of this disease. About 50 cases of ectopic GHRH-dependent acromegaly have been so far described in the literature [1–3].

The classical clinical features of acromegaly in patients with the ectopic GHRH syndrome are usually indistinguishable from those of patients with the more frequent GH-secreting pituitary adenoma [4].

This report describes a case of a non-functioning pituitary incidentaloma associated to acromegaly related to ectopic GHRH secretion, secondary to a large bronchial carcinoid, incidentally discovered at the radiological thoracic imaging and successfully treated.

Case report

A 55-year-old caucasian woman was referred to our Institution with complaints of progressive enlargement of hands and feet, macroglossia and snoring. On physical examination there were clear signs of acromegaly. She had coarsening of facial features, protrusion of the lower jaw and macroglossia. She did not complain of headache, arthralgia, galactorrhea. She also had hypertension, diagnosed 7 years before and treated with angiotensin converting enzyme inhibitors. There was not a familial history of cancer.

Laboratory investigation showed increased growth hormone (GH) concentration (mean of three blood samples), failure to suppress GH level after oral glucose tolerance test (OGTT, with 75 g of glucose) and high insulin-like

Table 1 Clinical and biochemical parameters at diagnosis and after 2 months from surgical treatment for bronchial carcinoid

Test	Before surgery	After surgery	Normal range
BMI (kg/m^2)	22.7	23.4	20–25
SBP/DBP (mmHg)	**145/90**	**130/85**	<120/80
Serum GH (μg/l)	**3**	1.4	<2.5
Nadir GH (μg/l) during OGTT	**2.2**	0.31	<1.0
Plasma GHRH (pg/ml)	**13.86**	0.46	<3.0
Serum IGF-1 (ng/ml)[a]	**593**	216	81–225
Fasting glycemia (mg/dl)	**108**	95	<100
Two hours post-OGTT glycemia (mg/dl)	**174**	132	<140
Plasma ACTH (ng/l)	14.8	29.7	3–60
Serum cortisol (nmol/l)	250	478	140–700
Cortisol peak (nmol/l)[b]	604	–	>500
TSH (mU/l)	1.7	0.95	0.26–4.2
FT4 (pmol/l)	12.2	11.8	9–20
FT3 (pmol/l)	5.8	4.1	3.8–8.0
PRL (mU/l)	**544**	277	<500
Chromogranin A (U/l)	**49.4**	10.9	<36
Gastrin (pg/ml)	41.0	51.2	<108
Insulin (mU/l)	8.7	2.5	5–25

[a] Normal range gender and age matched

[b] Cortisol peak after stimulation test after Synacthen 250 μg e.v.

Bold font indicates out of range values

growth factor type-1 (IGF-1) levels adjusted for sex and age, thus confirming the diagnosis of acromegaly (Table 1).

Other biochemical investigations measured by standard procedures showed mild hyperprolactinemia and impaired carbohydrate tolerance. All the remaining pituitary functions and haematological parameters were in the normal range, while the plasma Chromogranin A levels were slightly elevated (Table 1). On further work-up, cardiac echo-colour-doppler and thyroid ultrasound were normal, while abdominal ultrasound revealed a slight liquid left pleural effusion.

The subsequent magnetic resonance imaging (MRI) of the sellar region showed an hyperplasic pituitary gland with a convex superior outline and enlarged peduncle, with a slightly appreciable alteration of the contrast enhancement, suggesting the uncertain presence of a focal lesion (Fig. 1a). The patient was then referred to the Neurosurgeon to perform the trans-naso-sphenoidal adenoma removal.

During the pre-operatory workout, a routine chest X-ray demonstrated the presence of a large thickening in the left lung (Fig. 1b), that a subsequent thorax computerized tomography (CT) scan revealed to be a mass of $60 \times 84 \times 50$ mm^3 in contact with pulmonary hilum. Due to the suspect of a carcinoid lesion, an octreoscan (^{111}In pentatreotide) was then performed. The lesion in the left lung appeared to be the only spot with increased uptake of labelled octreotide (Fig. 1c).

Finally, histological examination carried out from broncoscopy permitted to classify the mass as a bronchial carcinoid tumour. The possible association between the bronchial carcinoid and acromegaly was then confirmed by the observation of increased plasma GHRH levels (13.86 pg/ml, n.v. < 3.0 pg/ml). The GHRH levels were measured using a RIA kit (Phoenix Pharmaceuticals Inc., Phoenix Europe GmbH, Karlsruhe, Germany), as previously described [5].

The patient was successfully operated on by resection of the superior left pulmonary lobe, associated with lymphadenomectomy and removal of pulmonary artery tract. Histological examination of the resected tissue confirmed the diagnosis of a typical well differentiated bronchial carcinoid tumour (Grade I), characterized by mitosis $<1 \times 10$ HPF and absence of necrosis, infiltrating into pulmonary artery. Lymphonodes were devoid of metastases. Immunoreactivity demonstrated a positivity for GHRH, synaptofisin, chromogranin A and CD 56 as marker of neuroendocrine tumour (Fig. 1d).

Two months after surgery, a complete hormonal and clinical remission of acromegaly was observed. In fact, "safe" basal GH levels normally suppressed after OGTT and normal IGF-1 concentrations, along with the improvement of acromegaly related signs and symptoms, were observed (Table 1). A normal tolerance to carbohydrate was restored and blood hypertension slightly improved after operation. Plasma cromogranin A and GHRH levels reversed to normal 2 months after the excision of the neoplasm. The MRI demonstrated the normalization of the pituitary gland size and morphology, while the presence of a focal lesion was confirmed.

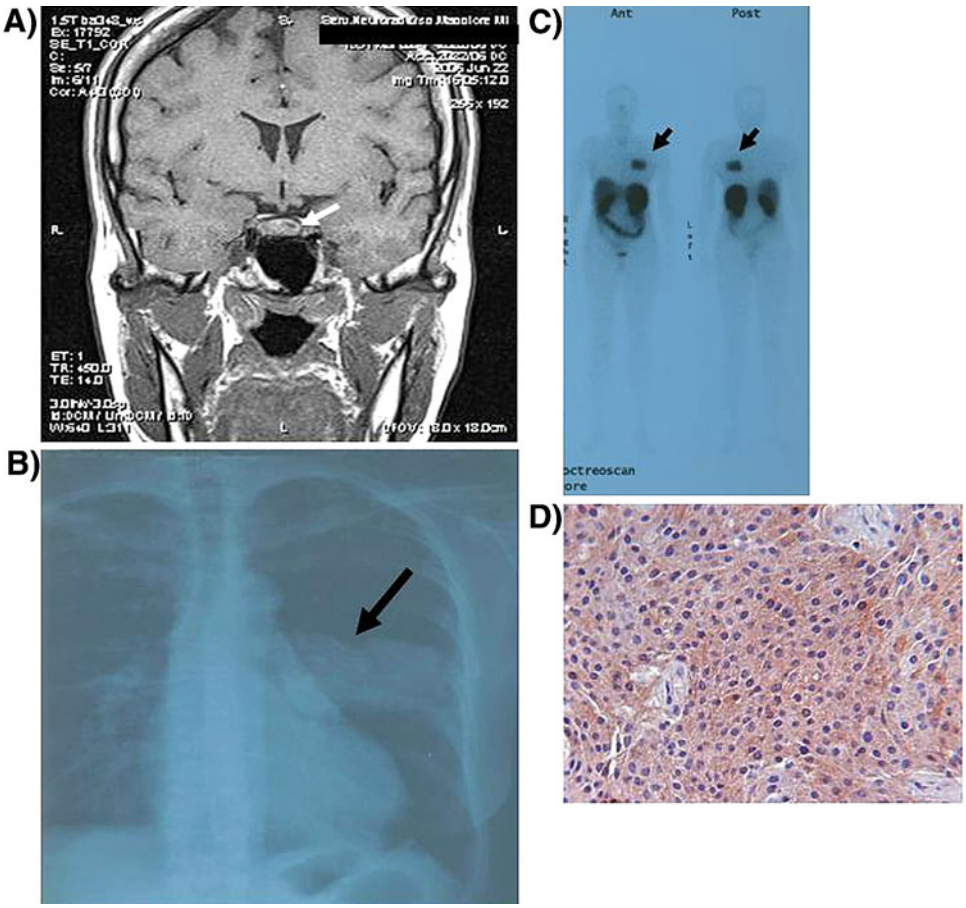

Fig. 1 **a** Magnetic resonance imaging of the sellar region at the diagnosis showing an hyperplasic pituitary gland with a convex superior outline and enlarged peduncle. An alteration of the contrast enhancement located in the left side of the gland was observed, suggesting the presence of a microadenoma. **b** Routine chest X-ray (*front view*) demonstrating the presence of a large mass in the left lung. **c** Whole-body ^{111}In-DTPA-octreotide scan showing an area of intense radiotracer uptake (*arrow*) in the superior left lung; anterior and posterior whole-body scans were obtained 4 and 24 h after the radiotracer administration. **d** Immunostaining for GHRH performed in carcinoid tissue surgically removed by acromegalic patients; the immunoreactivity was visualized by diaminobenzidine, positive cells giving a *brown colour* at the site of reaction. All photomicrographs are shown at ×25

Discussion

Neuroendocrine tumours represent a heterogeneous group of neoplasm that originate from glands as well as endocrine cells and demonstrate a wide range of morphologic, functional and neoplastic characteristics. In general, they grow slowly and preserve the ability to differentiate, but, occasionally, some may show very aggressive behaviour. The diagnosis depends on recognition of characteristic clinical and/or morphological features and on presence of markers indicative of neuroendocrine differentiation.

Ectopic GHRH-secreting tumours, such as bronchial or pancreatic carcinoids, account for <1% of all cases of acromegaly. Clinical as well as biochemical features of GH-producing pituitary adenomas and GHRH-producing tumours are often indistinguishable, making the differential diagnosis difficult. In fact, regardless of the cause, GH and IGF-1 concentrations are invariably elevated and GH levels are not suppressed after an oral glucose load. It has been described that dynamic testing of GH secretion may reveal significant differences between different forms of acromegaly. In fact, patients with the ectopic GHRH syndrome are more likely than patients with "classic" acromegaly to have a paradoxical rise (>50% of baseline) in GH level after TRH and glucose load, contrary to what observed in our patient. Moreover, they frequently show a normal GH response (>100% of baseline) after insulin-induced hypoglycaemia [4]. Hyperprolactinemia is also more commonly found in GHRH-dependent form of acromegaly, probably due to the sustained exposure to GHRH that can boost prolactin secretion through stimulation of mammosomatotrophs [6]. In fact, it has been well shown that mice transgenic for human GHRH develop hyperplasia of pituitary somatotrophs and mammosomatotrophs, cells capable of producing both GH and prolactin, by 8 months of age, providing conclusive evidence that protracted stimulation

of secretory activity can cause proliferation, hyperplasia and adenoma of adenohypophysial cells [7].

As Frohman predicted, demonstration of circulating GH-releasing activity could be and indicator of the ectopic origin a acromegaly [8]. Indeed, from a biochemical view point only patients with hypothalamic or peripheral GHRH-secreting tumours show elevated circulating plasma GHRH levels, that may provide a precise and cost-effective diagnosis even if available only in few centres [9]. Moreover, markers of neuroendocrine tumours, such as chromogranin A (or gastrin), may be helpful to suspect an extra-hypothalamic source of GHRH [10].

Similarly, pituitary imaging may be unreliable. In fact, even though in patients with ectopic GHRH syndrome the pituitary gland frequently shows evidence of diffuse enlargement, reflecting somatothoph hyperplasia, an adenoma may also occasionally occurs [11]. This was the case of our patient. In fact, after carcinoid resection and GH secretion normalization, MRI showed the disappearance of pituitary hyperplasia, while the lesion compatible with microadenoma was still present, probably being a non-functioning pituitary incidentaloma.

Nowadays, the complete surgical resection remains the only curative therapy in the majority of patients. Parenchyma-sparing resections are indicated whenever possible. Overall survival after surgery is excellent (5-years rate, 87–100%), with low recurrence rate (2–11%), while *N*-status and type of resection seem not to affect prognosis [12, 13].

However, the diagnosis is frequently not established until the disease is metastatic and therefore surgical cure is often impossible. Long-acting somatostatin analogues (octreotide or lanreotide) can represent a first-line therapy, since they may control the endocrine hypersecretion and tumour proliferation, but experience is still limited [1, 2].

Conclusions

This report emphasizes the importance of considering the uncommon causes of acromegaly in the initial diagnostic process, especially in the presence of ambiguous pituitary imaging or not clearly suggestive clinical features. Considering that the measurement of plasma GHRH levels is carried out in very few laboratories, we suggest the introduction of affordable and available examinations, such as thorax X-ray and/or abdomen ultrasound, in the routine screening process. This topic may be particularly relevant in order to plan the most cost-effective diagnostic procedures and management and to avoid unnecessary pituitary neurosurgery.

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