Clinical case

Ectopic secretion of GHRH by a pancreatic neuroendocrine tumor associated with an empty sella

Sécrétion ectopique de GHRH par une tumeur neuroendocrine pancréatique associée à un syndrome de la selle turcique vide

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Résumé

L’acromégalie est habituellement en rapport avec une hypersécrétion d’hormone de croissance (GH) par un adénome hypophysaire ; très rarement, l’acromégalie est due à une sécrétion ectopique de GHRH. Nous rapportons le cas d’une patiente de 60 ans présentant une acromégalie par sécrétion ectopique de GHRH due à une tumeur pancréatique. Le diagnostic d’acromégalie a été confirmé par les dosages hormonaux. L’IRM hypophysaire a montré une selle turcique partiellement vide, sans adénome. Une échographie abdominale, réalisée devant des douleurs abdominales, a révélé une volumineuse masse infrahépatique hétérogène et calcifiée. Le scanner abdominal a montré une tumeur hétérogène de la tête du pancréas de 10 cm de diamètre. Le dosage plasmatique de GHRH a montré un taux élevé à 604 ng/L (taux normal : 10–60), faisant ainsi retenir une sécrétion ectopique de GHRH en rapport très probablement avec la tumeur pancréatique. La patiente a subi alors une duodénopancréatectomie céphalique. L’examen anatomopathologique a révélé une tumeur bien circonscrite, de structure organoïde. L’étude immuno-histochimique a montré une fixation pour la chromogranine A, la neurone specific enolase et la synaptophysine et un marquage négatif avec l’anticorps anti-prolactine, anti-GH et anti-sérotonine. Le diagnostic d’une tumeur neuroendocrine bien différenciée du pancréas fut ainsi retenu. L’évolution postopératoire était marquée par une nette amélioration des signes acromégaliques avec normalisation des concentrations de GHRH et de GH.

Abstract

Acromegaly is usually the result of a pituitary growth hormone cell-adenoma or is more rarely due to ectopic secretion of growth hormone releasing hormone (GHRH). We report the case of a 60-year-old woman with acromegaly due to a GH-RH-secreting pancreatic tumor. Laboratory evaluation confirmed the diagnosis of acromegaly. Magnetic resonance imaging revealed a partial empty sella with no signs of adenoma. Ultrasound sonography performed for abdominal pains showed a calcified large heterogeneous infrarenal mass. Computed tomography scan discovered a heterogeneous pancreatic head mass with a diameter of 10 cm. Measurement of fasting plasma GHRH was performed showing a high concentration of 604 ng/L (normal 10–60). We therefore concluded that the acromegaly was caused by ectopic overproduction of GHRH likely due to the pancreatic tumor. The patient underwent a cephalic duodenopancreatectomy. Histology revealed a well-circumscribed tumor with organoid architecture. Immunohistochemistry demonstrated diffuse positivity for chromogranin A, neuronal specific enolase and synaptophysin and negative immunoreactivity for prolactin, GH and serotonin. These features were concordant with a well-differentiated neuroendocrine tumor of the pancreas. Surgical resection of this pancreatic tumor was followed by significant amelioration of acromegalic signs and normalization of GHRH and GH levels.

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1. Introduction

Acromegaly is a systemic disorder caused by sustained hypersecretion of growth hormone (GH). It is nearly always caused by a pituitary adenoma [1]. However, approximately 1% of the cases are due to eutopic or ectopic growth hormone-releasing hormone (GHRH) hypersecretion [2,3]. The clinical features and hormone alterations in ectopic GHRH induced acromegaly is not different from that of classic acromegaly, making it difficult for the former to be recognized [2]. Here, we describe a patient with ectopic acromegaly secondary to a pancreatic neuroendocrine tumor, and who had an empty sella on pituitary magnetic resonance imaging (MRI).

2. Case report

A 60-year-old woman was referred to our department of endocrinology for suspected acromegaly. She had three pregnancies; she had a ten-year history of diabetes mellitus; and she underwent unilateral decompression of median nerve because of carpel tunnel syndrome 6 years ago and surgery for breast neoplasia 3 years ago.

On examination, there were classical features of facial changes and acral enlargement with increase in hand and shoe size; high blood pressure, obesity; she had no visual disturbance, no headaches and no galactorrhea.

Laboratory investigations were as follows: Blood glucose level: 9.6 mmol/L, hematocrit: 42%, WBC count: 7600/mm$^3$, blood urea nitrogen: 6.4 mmol/L, serum creatinine: 87 μmol/L, serum Na$: 141$ mmol/L, serum K$: 4.3 mmol/L, serum Ca$^{2+}$: 2.32 mmol/L (2.25–2.65), IGF-1: 494 ng/mL (63–380), GH: 57.2 ng/mL (<5), PRL: 63 ng/mL (5–20), LH: 9.7 IU/L, FSH: 15.6 IU/L, thyroid-stimulating hormone (TSH): 1.5 mU/L (0.3–4.0), free thyroxine (FT4): 13 pmol/L (11–24) and a random cortisol value 204 ng/mL. After intravenous injection of thyrotrophin-releasing hormone (TRH) a more than 50% increase in GH concentration was noted, a typical response of a pituitary growth hormone producing adenoma.

Magnetic resonance imaging (MRI) of pituitary gland revealed a partial empty sella without obvious evidence of a pituitary adenoma (Fig. 1). The patient was then lost to follow-up.

One year later, ultrasound sonography performed for abdomen pains showed a calcified large heterogeneous infrahepatic mass. Computed tomography scan of the abdomen discovered a voluminous pancreatic head mass as large as 10 cm in diameter, which contained necrotic and hemorrhagic islets (Fig. 2).

Based on the presumptive diagnosis of acromegaly secondary to ectopic GHRH secretion, measurement of fasting plasma GHRH was performed showing a high concentration of 604 ng/L (normal 10–60) [4]. We therefore concluded that the acromegaly was caused by ectopic overproduction of GHRH likely due to the pancreatic tumor.

The patient underwent a cephalic duodenopancreatectomy. Macroscopically, the tumor, measuring $13 \times 9 \times 8$ cm and weighing 670 g, was well encapsulated and contained hemorrhage and calcifications. Duodenum and gastric antrum were without any injury.

Light microscopic examination of the pancreas revealed a well-circumscribed tumor, organized in organoid architecture. It was composed of monomorphous proliferation of small cuboidal and polygonal cells with mild nuclear atypia and rare mitosis (Fig. 3). Neither lymph node metastasis nor vascular invasion was observed. Moreover, there were scattered calcified foci and
focal hemorrhage. Fundal, antral, and duodenal mucosae were without any injury. Immunohistochemistry demonstrated diffuse positivity for general neuroendocrine markers (chromogranin A, neuronal specific enolase and synaptophysin). There were focal positivity for ACTH and gastrin but immunostaining for prolactin, GH and serotonin were negative.

These features were concordant with a well-differentiated neuroendocrine tumor of the pancreas. Three months after surgery, a significant amelioration of acromegalic signs with desinfiltration, depression of diabetic drugs and normalization of blood pressure were observed. IGF1 levels were normal (115 ng/mL) and mean GH levels of four blood drawings in the morning were lower (0.74 ng/mL, range, 0.26–1.75) than in the presurgical condition. GHRH level decreased considerably (32 ng/L). During follow-up, prolactin concentrations remained between 40 and 61 ng/mL. Ten years after the operation, the patient is alive and well, IGF1 levels are normal and no CT evidence of recurrence is detectable.

3. Discussion

Ectopic GHRH secretion is a rare cause of acromegaly, representing less than 1% of acromegalic patients [2,3,5]. To date, only about 67 patients have been previously reported in the literature [6].

In the majority of cases, the cause is a GHRH-secreting neuroendocrine tumor [6]. Carcinoids, especially of the lung and gastrointestinal tract, constitute about two-thirds of all cases reported so far [2]. Less frequently, pancreatic islet cell tumors, thymic tumors, tumors associated with multiple endocrine neoplasia type I (MEN-1) syndrome, small cell lung cancer, adrenal adenoma or pheochromocytoma have been reported to cause acromegaly due to GHRH secretion [2,6–9].

The criteria for demonstration of ectopic extracranial GHRH-induced acromegaly include the presence of high circulating concentration GHRH, presence of GHRH in the tumor, presence of hormone-specific mRNA in tumor tissue, a significant arteriovenous gradient across the suspected tumor and the reversibility of acromegaly after complete removal of the ectopic-hormone producing tumor [7,10]. Two criteria at last are needed for diagnosis [10].

In our case, elevated GHRH level in peripheral blood samples before surgery in conjunction with clinical improvement of acromegalic features and normalization of GH levels after removal of the tumor led to the definitive diagnosis of ectopic GHRH production.

The clinical symptomatology in ectopic GHRH-induced acromegaly is not different from that of pituitary GH-producing adenoma apart from symptoms due to the underlying neoplasm or the effect of cosecreted hormones [2,3,6–8].

Biochemically, there is no specific test. Dynamic pituitary tests are not helpful in distinguishing acromegalic patients with pituitary tumors from those harboring extrapituitary tumors [7]. In both cases, most patients show a paradoxical response (more than 50% increase from basal value) to TRH and mostly a blunted response to exogenous GHRH administration [2,3,6–8]. Plasma GHRH levels are usually elevated in patients with peripheral GHRH-secreting tumors, and are normal or low in patients with pituitary acromegaly. Measuring GHRH plasma levels therefore provides a precise and cost-effective test for the diagnosis of ectopic acromegaly [8].

On pituitary imaging using MRI, there is also a wide range of abnormalities, ranging from a normal pituitary gland, to hyperplasia or adenoma. GHRH could exhibit chronic hyper-stimulation on somatotroph cells leading to hyperplasia or even development of adenomas [7].

MRI of our patient showed partial empty sella. To our knowledge, this is the second report of ectopic GHRH syndrome coexisting with primary empty sella [11]. This association appears to be fortuitous and could be linked to the high frequency of empty sella mainly in women aged more than 50 years [11].

In addition, in some of the reported cases, as observed in our case, hyperprolactinemia was evident. It has been reported that GHRH also stimulates pituitary lactotrophs [12].

In our patient, hyperprolactinemia may also be explained by the empty sella; in fact high prolactin levels persisted after the removal of pancreatic tumor.

Surgical removal of the tumor secreting ectopic GHRH should be the logical approach to a patient with ectopic GHRH syndrome [3,13,14]. Somatostatin analogs have been used in the treatment of ectopic acromegaly and they seem to be able not only to control the endocrine hypersecretion but also tumor proliferation [13,14]. Therefore, they are now preferred as a second-line therapy especially in patients with recurrent disease [8].

In conclusion, acromegaly caused by ectopic production of GHRH is a rare syndrome that must be recognized because its treatment differs from classic acromegaly. Measurement of
plasma GHRH is a reliable method for detection of this particular entity and should be performed in all patients with proved acromegaly but no clear evidence of pituitary adenoma. This strategy allows avoiding unnecessary pituitary surgery.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References