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Ectopic Growth Hormone-Releasing Hormone Secretion by a Neuroendocrine Tumor Causing Acromegaly: Long-Term Follow-Up Results

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Abstract Ectopic secretion of growth hormone-releasing-hormone (GHRH) is a rare cause of acromegaly—representing less than 1% of patients. A 25-year-old woman was admitted to the hospital with acromegaly and a 6×6 cm infrahepatic mass. Sellar magnetic resonance imaging indicated diffuse pituitary enlargement consistent with hyperplasia. The infrahepatic mass was resected, and the histopathological diagnosis was a well-differentiated invasive neuroendocrine carcinoma of the duodenum with metastases to local lymph nodes. The tumor cells contained cytoplasmic immunoreactivity for GHRH. Because increased IGF-1 concentrations persisted after the operation, the patient was treated with octreotide long-acting repeatable (LAR) injections of 20 mg/month. Growth hormone and IGF-1 levels normalized. After 6 years of surveillance, a left paraaortic mass was detected by uptake of indium^{111} octreotide. Surgical exploration revealed metastatic neuroendocrine carcinoma in a 2.5-cm lymph node. Postoperatively, the IGF-1 concentration was mildly elevated. Octreotide LAR therapy is being continued at 10 mg/month. This case suggests that octreotide treatment may have a beneficial effect on disease course and can be maintained for as long as 7 years in a patient with acromegaly due to a GHRH-secreting neuroendocrine carcinoma.

Keywords GHRH · ectopic acromegaly · octreotide · neuroendocrine carcinoma · recurrence

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Introduction

Ectopic growth hormone-releasing hormone (GHRH) secretion is a rare cause of acromegaly, representing less than 1% of acromegalic patients [1–3]. In the majority of cases, the cause is a GHRH-secreting neuroendocrine tumor. Bronchial carcinoids are the most common cause, followed by pancreatic and gastrointestinal neuroendocrine tumors [1–3]. To date, more than 66 patients have been previously reported [3, 4].

We report the laboratory and clinical findings of a patient with ectopic GHRH production by a gastrointestinal endocrine tumor treated with surgery and a somatostatin analog for 7 years.

Case Report

A 25-year-old woman was admitted to the hospital with iron deficiency anemia in September 2001. She complained of headache, arthralgia, and profuse sweating. Physical examination revealed significant acral enlargement and multinodular goiter with a dominant nodule on the right thyroid lobe. Laboratory findings indicated severe iron deficiency anemia, secondary hyperparathyroidism, and increased basal growth hormone (GH) and insulin-like growth hormone-1 (IGF-1) concentrations (Table 1). Her prolactin concentration was increased, but regular menstrual bleeding was reported to occur. Oral glucose tolerance test failed to suppress GH concentrations (Table 1). Fine-needle aspiration biopsy of the dominant right and left thyroid nodules measuring 15×11 and 9×11 mm, respectively, revealed benign follicular epithelial cells. Upper gastrointestinal endoscopy identified a duodenal ulcer and antral gastritis. Her serum gastrin concentration was mildly increased at 124 pmol/L (normal, 35–114). Abdominal ultrasonography revealed a 6×6 cm infrahepatic mass near the pancreatic head. Urinary 5-hydroxyindolacetic acid concentration was within normal limits at 4.0 mg/24 h (normal, 2–10). Sellar magnetic resonance (MR) imaging indicated pituitary enlargement without obvious evidence of a pituitary adenoma. Under computed tomography guidance, a diagnostic through-cut biopsy of the abdominal mass was performed, and histopathology yielded a diagnosis of well-differentiated neuroendocrine tumor. The neoplastic cells were immunoreactive for pancytokeratin, chromogranin A, CD57, and synaptophysin. The patient was started on short-acting octreotide 3×100 μg/day and subsequently underwent abdominal exploration in December 2001. Before the operation, serum prolactin concentration was 89 ng/mL, GH 3.9 ng/mL, and IGF-1 175 ng/mL. During the operation, a 3-cm tumor mass originated from the first part of the duodenum, and a second tumor mass of 5×5×2.5 cm adjacent to the duodenum was identified. Gastric and duodenal resections were performed. Histopathology confirmed the diagnosis of well-differentiated neuroendocrine carcinoma of the duodenum with invasion of tunica muscularis and metastases to nine lymph nodes, the largest representing the 5×5×2.5 cm mass seen intraoperatively (Fig. 1). In addition to general neuroendocrine markers, the neoplastic cells exhibited cytoplasmic immunoreactivity for GHRH (Fig. 2). The Ki-67 labeling index was 3%. The patient did not receive octreotide for 2 months after the operation. During that time, the IGF-1 concentration was high (485 ng/mL; normal range 116–358 ng/mL), and basal GH was 5.1 ng/mL. Octreotide long-acting repeatable (LAR) treatment was started at 20 mg/month. Her secondary hyperparathyroidism and iron deficiency anemia improved after appropriate therapies. Six months after initiation of octreotide LAR treatment, sellar MR indicated involution of the gland (Fig. 3). Her IGF-1 concentration was within normal limits, and oral glucose tolerance test (OGTT) revealed normal suppression of GH (Table 2) during octreotide LAR treatment. Abdominal MR revealed no evidence of recurrence 6 months after the operation. Octreotide therapy was continued, and the patient was followed with serial abdominal and sellar MR evaluation and octreotide scintigraphies. In May 2002, the octreotide LAR dose was decreased to 10 mg/month. After cessation for a 3-month-period, the IGF-1 concentration rose slightly to 388 ng/mL (normal range 117–329 ng/mL);

Table 1 Laboratory findings of the patient on admission (September 2001)

Test	Value	Reference range
Hemoglobin (g/dL)	6.9	(12–14)
Creatinine (mg/dL)	0.6	(0.6–1.4)
Calcium (mg/dL)	8.1	(8.5–10.5)
Alkaline phospatase (IU/L)	868	(90–260)
Albumin (g/dL)	4.0	(3.5–5.0)
PTH (pg/mL)	559	(10–65)
25 (OH) vitamin D (ng/mL)	<5	>30
Urinary calcium (mg/24 h)	59	(100–350)
Basal cortisol (μg/dL)	23	>14
Prolactin (ng/mL)	110	<20
Free T4 (pmol/L)	14	10–22
TSH (μU/mL)	0.3	0.2–4.2
Basal GH (ng/mL)	27	<2
IGF-1 ng/mL	>600	116–358
Calcitonin (pg/mL)	3.7	0–30
Fasting insulin (μU/mL)	9.9	1–25
Fasting glucose (mg/dL)	98	60–100
OGTT		
Glucose (mg/dL)		
0 min	102	
30 min	116	
60 min	148	
90 min	158	
120 min	174	
GH (ng/mL)		
0 min	27	
30 min	43	
60 min	50	
90 min	46	
120 min	42	

PTH parathyroid hormone, *GH* growth hormone, *IGF-1* insulin-like growth factor-1, *OGTT* oral glucose tolerance test

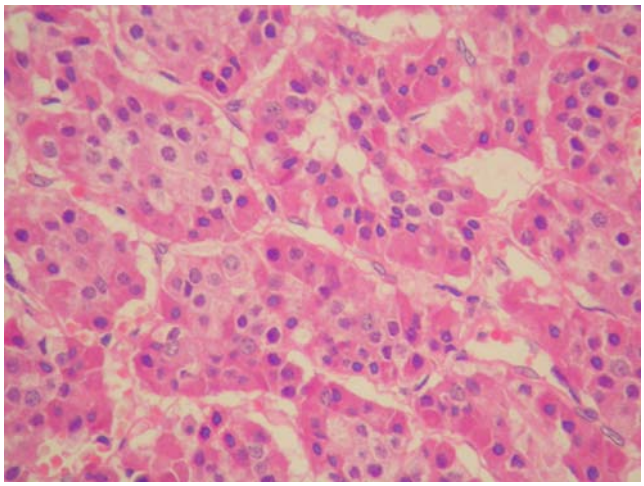

Fig. 1 Uniform neoplastic cells with organoid and trabecular pattern (H&E)

therefore, the treatment was restarted. The patient remained stable on octreotide treatment until 2007 when a left paramedian mass measuring 2 cm in diameter was identified (Fig. 4). Octreotide scintigraphy showed left paraaortic uptake of indium^{111} octreotide. (Figure 5) The patient underwent a second abdominal operation on September 2007. A mass measuring 2.5×1.5×1.4 cm was excised from the left paracaval region and was diagnosed as a lymph node containing a well-differentiated neuroendocrine carcinoma (Fig. 6). Three months after the operation, while the patient was not receiving octreotide, the IGF-1 concentration was mildly elevated (366 ng/mL; normal range, 115–307). Sellar MR revealed no change. Abdominal and thoracic MR and octreotide scan revealed no residual or new masses. A lower dose of octreotide LAR (10 mg/month) treatment was started and continued. One

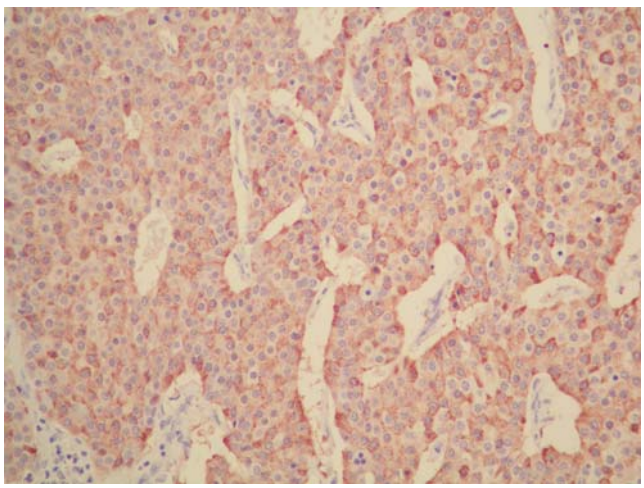

Fig. 2 Cytoplasmic immunoreactivity to GHRH antibody

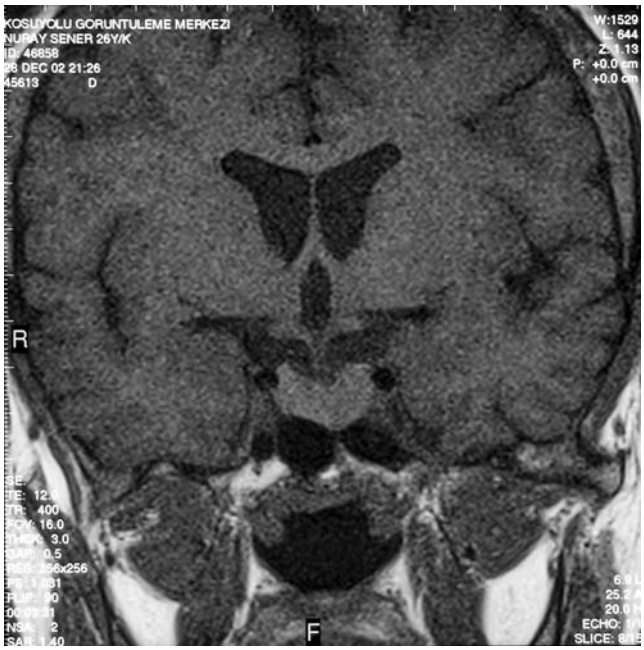

Fig. 3 Sellar magnetic resonance imaging of the patient, showing no clear-cut evidence of pituitary adenoma responsible for acromegaly

year later, the patient remains well with no evidence of residual tumor or recurrence on imaging. Her last endocrine profile is reported in Table 3. During follow-up, her prolactin concentrations remained between 50 and 100 ng/mL with normal menstrual cycles. No macroprolactinemia was evident. Her parathyroid hormone (PTH) concentration normalized after vitamin D supplementation. The patient's hemoglobin concentration was within normal limits after

Table 2 Laboratory findings of the patient (September 2002)

Test	Value	Normal range
IGF-1 ng/mL	134	117–329
OGTT		
Glucose (mg/dL)		
0 min	91	
30 min	182	
60 min	125	
90 min	66	
120 min	55	
GH (ng/mL)		
0 min	0.740	
30 min	13.2	
60 min	3.03	
90 min	1.25	
120 min	0.538	

IGF-1 insulin-like growth factor-1, *OGTT* oral glucose tolerance test, *GH* growth hormone

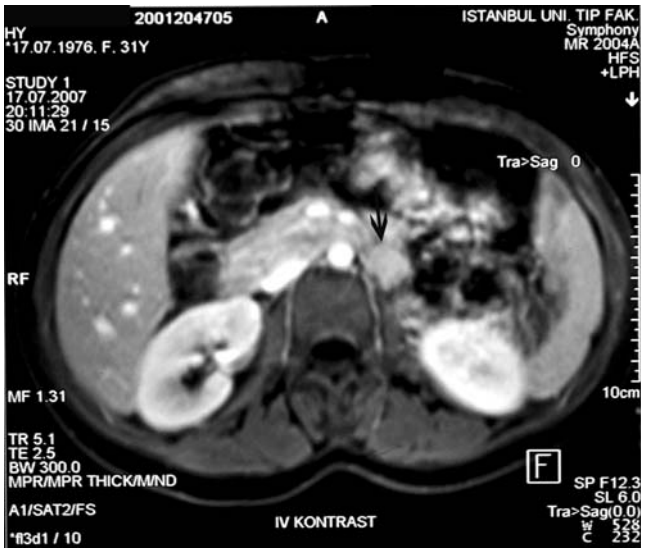

Fig. 4 Abdominal magnetic resonance imaging of the patient indicating a left paramedian mass measuring 2 cm in diameter (with contrast)

gastrectomy and parenteral vitamin B_{12} injections. There has been no evidence of other endocrine tumors that might suggest a diagnosis of multiple endocrine neoplasia type 1 syndrome (MEN-1).

Discussion

We report a case of ectopic secretion of GHRH by a duodenal endocrine carcinoma with a relatively benign course and prolonged response to somatostatin analogues. Different biological behavior of the neuroendocrine tumors originated from duodenum were reported previously compared with pancreatic endocrine tumors [5, 6]. Although approximately two thirds of duodenal neuroendocrine tumors were reported to be duodenal gastrinomas, our patient did not have clinical and laboratory findings indicating a hormonal syndrome such as gastrinoma/carcinoid syndrome other than GHRH-induced acromegaly. Tumors originated from duodenum were reported to have frequent (40–60%) metastases to regional lymph nodes at an early stage, but—in contrast to pancreatic neuroendocrine tumors—liver metastases appeared as a late event [5, 6]. The 5-year survival rate for patients with well-differentiated duodenal carcinomas was reported as 72%, significantly lower than that found for well-differentiated duodenal neuroendocrine tumors [6]. These tumors were not associated with a functional syndrome in 90% of cases [6]. Therefore, it is highly rare for a doudenal neuroendocrine well-differentiated carcinoma causing acromegaly by GHRH secretion. Although data about clinical course of GHRH-secreting duodenal neuroendocrine carcinomas is limited, we think that occult metastases that could not be identified by current diagnostic methods could be responsible for increased GH and IGF-1 concentrations after octreotide withdrawal, but they could be easily controlled until present time under octreotide treatment without clinical or radiological appearance.

Although we could not measure serum GHRH concentrations, all of the evidence supports the diagnosis of ectopic GHRH excess. We cannot exclude a pituitary

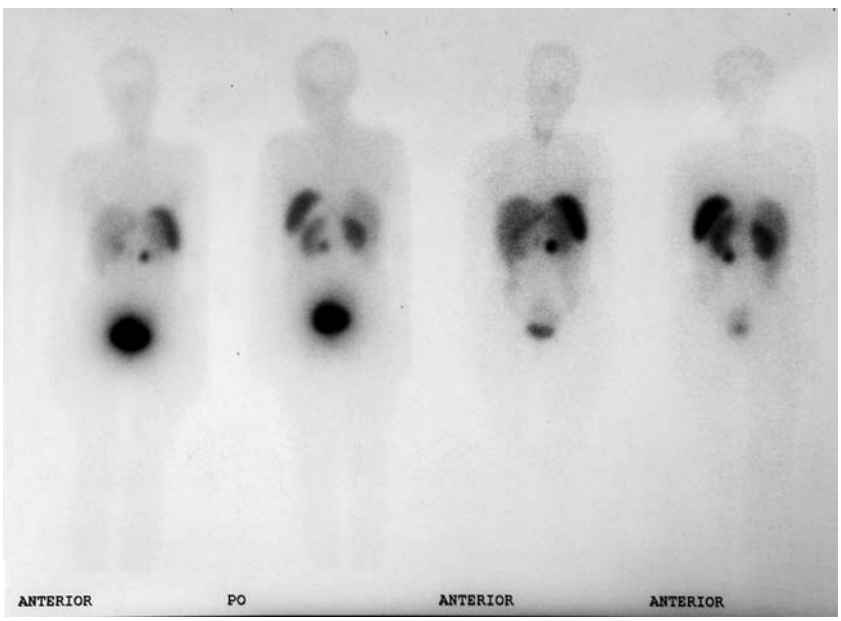

Fig. 5 Octreotide scan of the patient indicating uptake of radionuclide on the left paraaortic region

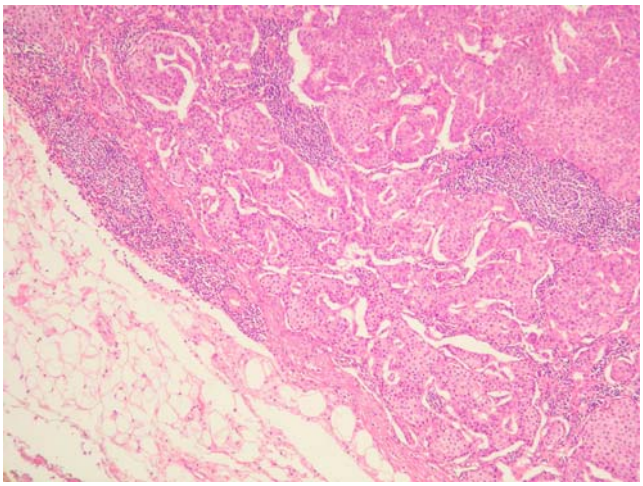

Fig. 6 Lymph node metastasis of the well-differentiated endocrine carcinoma (H&E)

microadenoma concurrently secreting GH; however, regression of sellar hyperplasia during follow-up and absence of pituitary uptake of indium^{111} octreotide after primary tumor removal make this possibility highly unlikely. It is reported that failure to down-regulate GH secretion during long-term GHRH stimulation is responsible for the typical clinical and laboratory findings of acromegaly in association with pituitary hyperplasia—even adenomatous transformation—in GHRH-producing tumors [7, 8].

Long-acting somatostatin analogs have been previously shown to be effective for inducing clinical and biochemical remission in ectopic acromegaly [3, 4, 9–11]. The effect of somatostatin analogs on GH secretion was reported to be greater than the effect on GHRH secretion, indicating a direct influence on the pituitary [9, 12]. Recently, van Hoek et al. [13] indicated suppressive effects of somatostatin analogs on GH and GHRH levels in bronchial carcinoid tumor, both in vivo and in vitro.

In our case, cessation of a relatively low dose of octreotide resulted in a slight increase in IGF-1 concentrations which may indicate disease activity. This could be due to an occult focus of endocrine carcinoma which could not be detected by imaging procedures. Biermasz et al. [3] evaluated three patients with GHRH-secreting endocrine tumors. In patients 2 and 3, GHRH concentrations remained elevated after tumor removal. In the second patient, persistent elevation was thought to be the result of a liver metastasis. In case 3, after the removal of the GHRH-secreting lung carcinoid, GHRH concentrations remained slightly elevated. Both of the patients were treated with octreotide. Suspect liver images remained stable in patient 2. In the third patient, a small metastasis in the superior mediastinum was identified approximately 9 years after tumor removal. In our case, first relapse occurred 6 years after the diagnosis. We suggest that octreotide treatment may lead to a delay in tumor growth as well as in clinical and radiological diagnosis of recurrence and may have a beneficial effect on disease course. In vitro studies indicated that somatostatin analogs and native somatostatin were able to suppress GHRH secretion from bronchial carcinoid [1, 14] and pancreatic tumor [15]. An in vitro study by Zatelli et al. [1] indicated a reduction in carcinoid cell viability by somatostatin analogs, although decreases did not reach statistical significance. Barkan et al. [16] and Van Den Bruel et al. [10] reported significant shrinkage of GHRH-secreting carcinoid tumor masses. In their study however, the GHRH concentration in serum remained elevated. A recent unpublished study (PROMID) also indicated that, in patients with newly diagnosed, treatment-naïve, locally inoperative or metastatic well-differentiated functional or nonfunctional midgut neuroendocrine tumors, octreotide LAR significantly increased time to tumor progression compared with placebo (median, 14.3 vs 6.0 months, $p<0.001$) [17].

In some of the reported cases—as observed in our case—hyperprolactinemia was evident. It has been reported that GHRH also stimulates pituitary lactotrophs [8, 9]. Although frequent association of GHRH-secreting endocrine tumors with MEN-1 was reported, no evidence indicating multiple tumor syndrome was developed during follow-up in our patient [18].

In conclusion, the follow-up of our patient suggests that octreotide treatment may have a beneficial effect on disease course and lead to a delay in tumor recurrence in ectopic acromegaly due to a GHRH-secreting endocrine carcinoma.

Table 3 Last laboratory profile of the patient (September 2008)

Test	Value	Normal range
Hemoglobin (g/dL)	12.5	(12–14)
Creatinine (mg/dL)	0.7	(0.6–1.4)
Calcium (mg/dL)	9.4	(8.5–10.5)
Alkaline phospatase (IU/L)	220	(90–260)
Albumin (g/dL)	4.0	(3.5–5.0)
PTH (pg/mL)	60	(10–65)
25 (OH) vitamin D (ng/mL)	28	>30
Prolactin (ng/mL)	58	<20
Free T4 (pmol/L)	14.8	10–22
TSH (μU/mL)	0.3	0.2–4.2
IGF-1 (ng/mL)	132	115–307
Calcitonin (pg/mL)	2.05	0–10
Fasting insulin (μU/mL)	1.9	1–25
Fasting glucose (mg/dL)	85	60–100

PTH parathyroid hormone, *IGF-1* insulin-like growth factor-1

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