

Metastatic Pancreatic Neuroendocrine Tumor that Progressed to Ectopic Adrenocorticotrophic Hormone (ACTH) Syndrome with Growth Hormone-releasing Hormone (GHRH) Production

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Abstract

The patient was a 61-year-old woman who had a well-differentiated pancreatic neuroendocrine tumor (PNET) with lymph node metastasis. After 15 months of octreotide treatment, glucose control deteriorated and pigmentation of the tongue and moon face developed, leading to the diagnosis of ectopic adrenocorticotrophic hormone (ACTH) syndrome. An abnormal secretion of growth hormone (GH) was identified, and the plasma growth hormone-releasing hormone (GHRH) level was elevated. A tumor biopsy specimen positively immunostained for ACTH and GHRH. Ectopic hormone secretion seems to have evolved along with the progression of the PNET.

Key words: GHRH, ACTH, ectopic hormone secretion, PNET

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Introduction

Pancreatic neuroendocrine tumors (PNETs) are derived from neuroendocrine cells of the pancreas. Tumors that synthesize and secrete biologically active hormones are called functional neuroendocrine tumors and all others are called non-functional neuroendocrine tumors (1). An epidemiological study conducted in Japan revealed the prevalence of PNET to be 2.23 per 100,000 people. Non-functional tumors were the most frequent, constituting 47.4% of all cases (2). The most frequent functional PNETs were insulinoma (38.2%) and gastrinoma (7.9%); glucagonoma and somatostatinoma were rare, with frequencies of 2.6 and 0.7%, respectively (2). Ectopic adrenocorticotrophic hormone (ACTH)-producing and growth hormone-releasing hormone (GHRH)-producing tumors are both very rare types of PNET.

We herein report a case of ACTH and GHRH producing

PNET presenting as Cushing's syndrome and an abnormal secretion of growth hormone (GH), following an initial diagnosis of a non-functional neuroendocrine tumor.

Case Report

The patient was a 61-year-old woman who became aware of abdominal pain in September 2009. A mass measuring 6 cm in diameter was noted in her pancreas (Fig. 1A). A biopsy of the pancreas was performed, and the diagnosis of a well-differentiated neuroendocrine tumor was made (Fig. 2A). The percentage of Ki67-positive cells was 11.5% (Fig. 2B), and these findings were consistent with the diagnosis of NET G2 (3). Since symptoms suggesting excessive hormone secretion, such as hypoglycemia, were lacking and the serum levels of insulin, gastrin and glucagon were all within the normal reference ranges (17.4 μ IU/mL, 80 pg/mL, and 130 pg/mL, respectively), the patient was diagnosed as having a non-functional PNET. The results of other

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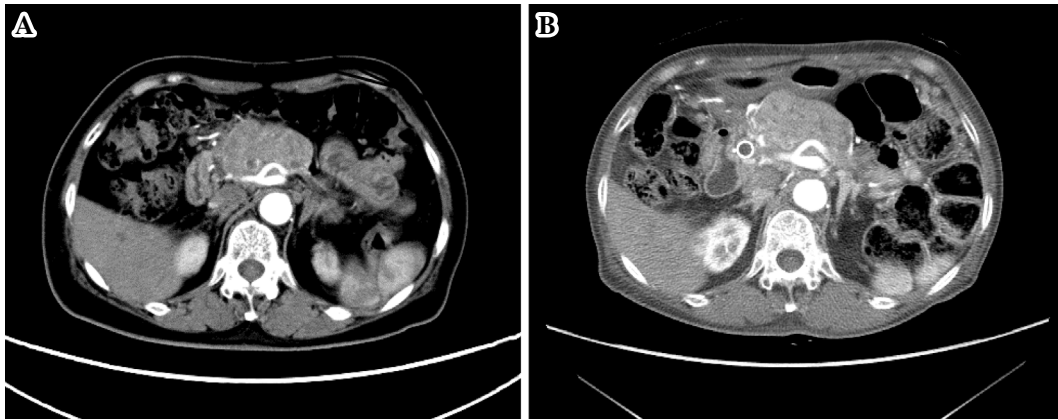


Figure 1. Computed tomography of the abdomen. An enhanced pancreatic tumor with metastasis to the para-aortic lymph nodes was demonstrated. A) Beginning of December, 2009. B) End of September, 2011.

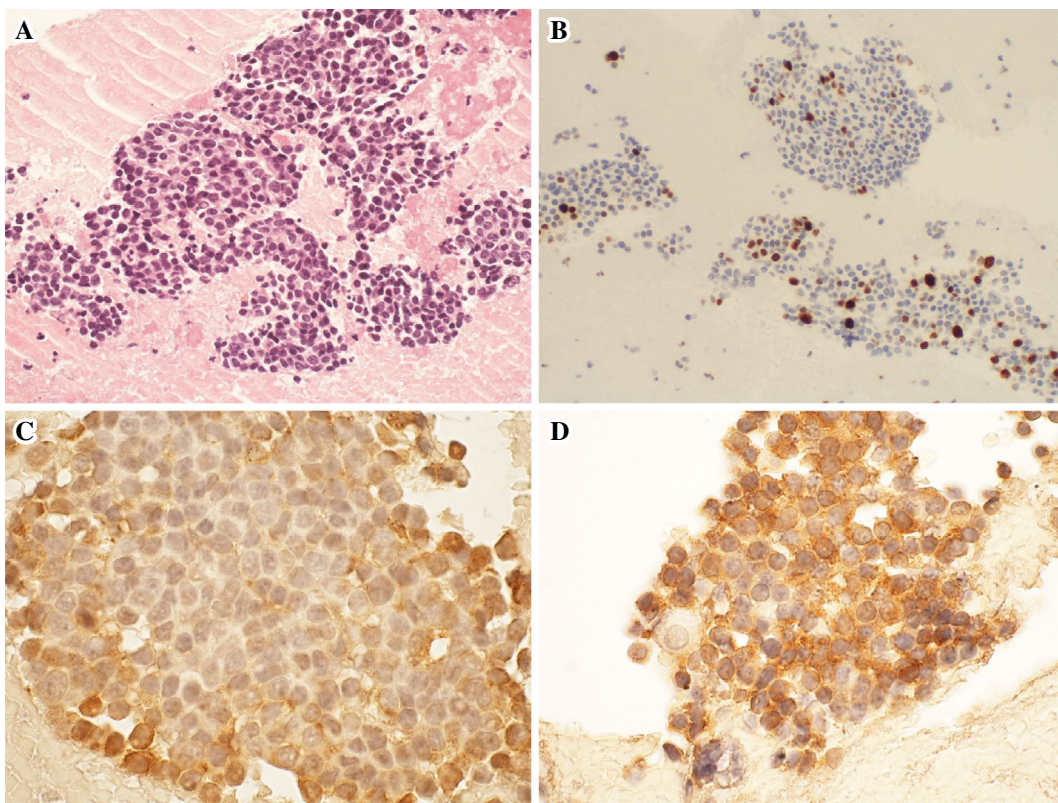


Figure 2. Pathological examination of the pancreatic tumor. A) Well-differentiated neuroendocrine tumor (Hematoxylin and Eosin staining). B) The percentage of Ki67 positive cells was 11.5%. C) Positive immunostaining for ACTH. D) Positive immunostaining for GHRH. ACTH: adrenocorticotrophic hormone, GHRH: growth hormone-releasing hormone

blood examinations were as follows: leukocyte count 4,700/ μ L, eosinophil fraction 0%, lymphocyte fraction 33%, serum potassium level 3.8 mEq/L, and serum albumin level 4.1 g/dL. Although the eosinophil fraction was found to have decreased, the overall results, along with a lack of Cushingoid features on physical examination, were not indicative of hypercortisolemia. Due to the presence of distant lymph node metastases, surgery was not indicated, and instead, treatment with octreotide LAR 20 mg/month was initiated and continued.

In March 2011, the patient was admitted to our hospital to be treated for diabetes mellitus (HbA1c 9.9%). The plasma level of ACTH (192.9 pg/mL; reference range, 7.2-63.3) was elevated, but the serum levels of cortisol (10.4 μ g/dL; 4.5-21.1), GH (0.99 ng/mL; \leq 3.61), and insulin-like growth factor-1 (IGF-1) (85 ng/mL; 37-150) were within the normal reference ranges. In April 2011, the patient developed pigmentation of the tongue, and then moon face in the following month, leading to the suspicion of Cushing's syndrome. In September 2011, levels of ACTH, cortisol, GH

Table 1. General Laboratory Data.

WBC	3,900	/ μ L	Glucagon	32	pg/mL	(50-150)
Hb	11.9	g/dL	Gastrin	313.1	pg/mL	(0-200)
Ht	34.9	%	VIP	23	pg/mL	(0-100)
PLT	150,000	/ μ L	ACTH	205.9	pg/mL	(7.2-63.3)
TP	6.6	g/dL	Cortisol	15.2	μ g/dL	(4.5-21.1)
Alb	3.7	g/dL	DHEA-S	160	μ g/dL	(12-133)
BUN	11	mg/dL	GH	4.08	ng/mL	(\leq 3.61)
UA	3.8	mg/dL	IGF-1	103	ng/mL	(37-150)
Cre	0.56	mg/dL	GHRH	9,230.4	pg/mL	(4-14)
Na	142	mEq/L	PRL	13.3	ng/mL	(3.5-32.7)
Cl	103	mEq/L	TSH	2.031	μ IU/mL	(0.30-4.5)
K	2.6	mEq/L	free T4	0.84	ng/dL	(0.7-1.8)
Ca	8.4	mg/dL	FSH	96.3	mIU/mL	(10.5-142.8)
Fasting glucose	184	mg/dL	LH	32.2	mIU/mL	(13.3-61.6)
HbA1c	9.9	%	UFC	86.1	μ g/day	(11.2-80.3)

VIP: vasoactive intestinal peptide, DHEA-S: dehydroepiandrosterone sulfate, GH: growth hormone, IGF-1: insulin-like growth factor-1, PRL: prolactin, TSH: thyroid stimulating hormone, FSH: follicle stimulating hormone, LH: luteinizing hormone, UFC: urinary free cortisol excretion

Table 2. Endocrinology Examinations.

Diurnal changes in ACTH and cortisol levels					
	Morning	11 p.m			
ACTH (pg/mL)	205.9	221.4			
cortisol (μ g/dL)	15.2	13.3			
Overnight 8mg DST					
ACTH (pg/mL)	312.8				
Cortisol (μ g/dL)	20.0				
CRH stimulation test					
	0 min	30 min	60 min	90 min	
ACTH (pg/mL)	188.2	141.4	146.9	139.3	
Cortisol (μ g/dL)	12.3	14.0	14.2	14.1	
TRH stimulation test					
	0 min	30 min	60 min	90 min	120 min
TSH (μ IU/mL)	2.36	26.84	26.74	21.62	17.86
GH (ng/mL)	4.14	22.12	13.89	8.55	5.08
PRL (ng/mL)	9.1	158.3	128.2	88.6	61.5

DST: dexamethasone suppression test, CRH: corticotrophin-releasing hormone, TRH: thyrotropin-releasing hormone

and IGF-1 were elevated to 249.1 pg/mL, 17.6 μ g/dL, 11.6 ng/mL, and 148 ng/mL, respectively. The patient was re-admitted to our department. The patient had no family history of multiple endocrine neoplasia (MEN) or any other endocrine disorders.

On admission, her height was 147.5 cm and weight 45.15 kg. Her blood pressure was 140/86 mmHg and body temperature was 36.5°C. Moon face and pigmentation of the tongue were noted. Clinical features of acromegaly were lacking. A left supraclavicular lymph node was palpable.

The patient's general laboratory data are shown in Table 1. Hypokalemia, and elevated fasting glucose and HbA1c levels were noted. Plasma ACTH was as high as 205.9 pg/mL, and the urinary excretion of cortisol had also increased.

Endocrinological examinations revealed the lack of any diurnal changes in ACTH and cortisol levels, and those levels were not suppressed in response to the overnight dexamethasone (8 mg) suppression test (Table 2). The plasma ACTH levels did not respond to an intravenous corticotrophin-releasing hormone challenge. These results were consistent with the diagnosis of ectopic ACTH-producing syndrome. The serum GH levels were modestly elevated (Table 1, 2) despite hyperglycemia, and paradoxically responded to an intravenous thyrotropin-releasing hormone (TRH) challenge (Table 2). The plasma levels of GHRH were as high as 9,230.4 pg/mL (reference range, 4 ~ 14) (4) (Table 1).

Pituitary magnetic resonance imaging (MRI) revealed no abnormalities. Computed tomography (CT) of the abdomen revealed a progressive enlargement of the pancreatic tumor with metastases to the para-aortic lymph nodes (Fig. 1B). No liver metastasis was observed, but the decrease in visceral and subcutaneous and fat area was apparent as compared to the previous CT (Fig. 1).

Re-examination of the biopsied specimen of pancreatic tissue obtained at first diagnosis revealed positive immunostaining for ACTH (Fig. 2C) and GHRH (Fig. 2D).

Octreotide LAR was continued, and metyrapone was administered to reduce hypercortisolemia. However, the tumors gradually increased in size. The patient was hospitalized in May 2012 for cholecystitis and peritonitis and was treated at that time by intraperitoneal drainage. Subsequently, the tumor perforated into the intestine, and palliative care was begun. In the fall of 2012, the patient died; an autopsy was not performed.

In this case, genetic testing for MEN type 1 (MEN-1) and related abnormalities was not performed.

Table 3. Ectopic Secretion of ACTH and GHRH by a Neuroendocrine Tumor: 6 Patients.

Age	Gender	Origin	GHRH (pg/mL)	ACTH (pg/mL)	Cortisol (μ g/dL)	Acromegalic feature	Cushingoid feature	References
41	F	Pancreas	GRF10,000	194	22.8 ~ 61.2	-	+	12
18	M	Foregut	GHRF+	1,500	42.2	+	+	13
23	M	Lung	45,000	300	36.8	+	+	14
49	M	Thymus	699 ~ 1,500	200 ~ 250	54.3 ~ 65.2	-	+	15
37	F	Thymus	2,245.8	169.6 ~ 205.2	13.3 ~ 24.4	-	+	16
61	F	Pancreas	9,230.4	205.9	15.2	-	+	

The last case is the present case.

Discussion

Initially, the present patient appeared to have a non-functioning PNET, but from the findings of deterioration of glucose control, tongue pigmentation and moon face, the diagnosis of ectopic ACTH-producing syndrome was made. In addition, an abnormal secretion of GH was demonstrated, possibly due to ectopic GHRH secretion. Immunostaining of the pancreatic specimen obtained at first diagnosis suggested that the PNET had been producing and secreting these hormones simultaneously.

In the present case, because the clinical features of Cushing's syndrome or acromegaly were lacking at first presentation, detailed investigations were not performed at that time. Along with the progressive enlargement of the tumor (Fig. 1), clinical manifestations of Cushing's syndrome and an abnormality of GH secretion became apparent. It is conceivable that there may have been a subtle hormone excess at the initial presentation, and that the increase in tumor mass could have resulted in the development of more apparent manifestations of hormone excess.

Neuroendocrine tumors often produce and secrete multiple hormones (2). However, tumors simultaneously producing GHRH and ACTH are very rare. Only five cases have been reported, as far as we could determine based on a search of the pertinent literature (5-9), and the present case is the second reported case derived from a primary pancreatic tumor (Table 3). Cushingoid features were evident in all these cases, but features of acromegaly were present in only two cases. It is conceivable that some PNETs may simultaneously produce GHRH and ACTH on a subclinical level, as this phenomenon has not yet been thoroughly investigated.

In ectopic ACTH syndrome cases, small-cell carcinoma of the lung is most frequently observed, and pancreatic tumors account for only 10% of the cases (10). In cases of ectopic ACTH syndrome caused by PNET, many are aggressive and the prognosis is poor (11, 12). In ectopic ACTH syndrome, increased visceral fat associated with hypercortisolemia is observed in slowly progressive cases, whereas weight loss and cachexia are prominent features in rapidly progressive cases of tumors, such as small-cell carcinoma of the lung (10). In the present case, the progressive clinical course precluded some of the more common physical manifestations of hypercortisolemia; indeed, findings of decreased

visceral and subcutaneous fat (Fig. 1B) were accompanied by the progression of ectopic ACTH syndrome.

Ectopic acromegaly caused by GHRH-producing tumors is rare. To the best of our knowledge, only 74 (13) and 99 (14) cases have been reported previously. Primary tumors are most commonly found in the lung, followed by the pancreas, with frequency of 25% (13) or 33% (14). Other tumors include those of the digestive tract, pheochromocytomas, and tumors of the thymus. Most of the reported cases of ectopic acromegaly were detected and diagnosed due to clinically evident acromegalic features of varying intensity. The reported latent period to display clinical signs of active acromegaly was as long as 8.3 years (14). However, some of these tumors had modest levels of GHRH production and secretory functions. Such cases may not develop acromegaly due to modest GHRH production and secretion, or no GHRH secretion despite GHRH production (13).

In patients with ectopic acromegaly, the serum GH levels after an oral glucose challenge may show a paradoxical increase, and those levels often display a paradoxical increase to a TRH challenge (14, 15). In the present case also, the serum GH levels were not suppressed despite hyperglycemia, and a TRH challenge revealed a paradoxical GH increase. These results are clinically consistent with acromegaly, but no clinical features of acromegaly were present in this patient. This may have been due to the short duration of the disease.

Mutations in the *MEN1* gene are found in approximately 10% of functional PNET cases (2). However, this was unlikely in the present case because of the absence of any findings suggesting hyperparathyroidism, the normal pituitary MRI findings, and the lack of a family history of endocrine disorders; therefore, genetic testing for MEN-1 was not performed.

In conclusion, in cases of PNET, it appears to be important to carry out detailed investigations to reveal the entire extent of endocrinology disturbances.

The authors state that they have no Conflict of Interest (COI).

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