

## Case Report

# Multiple Endocrine Neoplasia Type 1 Producing Growth Hormone-Releasing Factor in an Endocrine Pancreatic Tumor

Kazuo SUGA<sup>1)</sup>, Naohiro YAMASHITA<sup>1)</sup>, Kenya CHIBA<sup>1)</sup>, Tetsuya ITO<sup>2)</sup>, Yoshifumi KAZIWARA<sup>2)</sup>, Naokata YOKOYAMA<sup>3)</sup>

<sup>1)</sup>Department of Surgery, Nishi-Isahaya Hospital

<sup>2)</sup>Second Department of Surgery, Nagasaki University School of Medicine

<sup>3)</sup>First Department of Internal Medicine, Nagasaki University School of Medicine

We report a very rare case of multiple endocrine neoplasia type 1 (MEN 1) where a pituitary tumor presenting with acromegaly was associated with a growth hormone-releasing factor (GRF) producing pancreatic tumor. Twenty-seven months after surgery for pituitary adenoma, a 27-year-old male visited our hospital complaining of epigastralgia and back pain. Radiological examination revealed a 7-cm tumor in the pancreatic tail. Endocrinological studies revealed an abnormal increase in the level of growth hormone (GH). After resection of the pancreatic tumor, the GH level was normalized. Immunohistochemical studies confirmed the existence of GRF in the tumor. A diagnosis of GRF-producing pancreatic tumor was established. Nine months after surgery for the pancreatic tumor, the GH level remained normal and the pituitary gland had decreased in size. We speculate that secondary hyperpituitarism was caused by GRF produced by the endocrine pancreatic tumor in this case.

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**Key Words:** multiple endocrine neoplasia type 1. endocrine pancreatic tumor. growth hormone. growth hormone-releasing factor

## Introduction

Multiple endocrine neoplasia type 1 (MEN 1) is still a rare disease, although the number of reported cases is on the increase due to advances in hormonal measurement and diagnostic imaging techniques. In 1991, Yoshimoto<sup>1)</sup> reviewed 45 familial cases (total of 15 families) and 61 sporadic cases reported in Japan.

**Address Correspondence:** Kazuo Suga, M.D.

Nishi-Isahaya Hospital, 3015 Kaizu-machi, Isahaya City 854-0063, Japan

TEL: +81-957-25-1150 FAX: +81-957-25-1551

E-mail: kazuosuga@aol.com

MEN 1 is characterized by multiple neoplastic lesions including hyperplasia, adenoma and cancer arising from two or all three of the following endocrine organs: anterior pituitary, parathyroid and pancreatic endocrine glands. A gene responsible for MEN 1 was found on the long arm of the 11th chromosome (11q13). However, many questions remain unsolved, such as why neoplastic lesions occur in the three endocrine organs, and why these lesions have various histological features ranging from hyperplasia to carcinoma. We presented a case of MEN 1 associated with a growth hormone (GH)-producing pituitary tumor and a growth hormone-releasing factor (GRF)-producing endocrine pancreatic tumor. The blood GH level was normalized and the pituitary gland decreased in size following resection of the endocrine pancreatic tumor. The interesting course during treatment in this case is presented.

## Case report

*Patient:* A 27-year-old male.

*Chief complaint:* Epigastralgia and back pain.

*Past history:* The patient, who had developed acromegaly and visual disorder, had undergone surgical resection of a pituitary tumor (Hardy's operation) at a hospital on May 1, 1991. The tumor was pathologically diagnosed as a chromophobic adenoma.

*Family history:* Examination revealed no notable abnormalities.

*Present illness:* The patient noticed epigastralgia on August 19, 1992. The epigastralgia was accompanied by severe back pain the following day, which led the patient to visit our hospital. He was then hospitalized for close examination the same day.

*Physical findings on admission:* Height 178 cm; weight 75 kg; blood pressure 120/60 mmHg; pulse 62/min and

regular; no anemia or icterus. There were no abnormal findings for the neck, chest or abdomen. Acromegaly was noted of the face and distal ends of the extremities.

**Laboratory data on admission:** The serum calcium (Ca) level was slightly elevated to 10.4 mEq/l, while the serum phosphorus (P) level was 3.4 mg/dl and within the normal limits. Endocrinological examination showed an abnormally elevated level of GH, slightly increased levels of somatostatin and high sensitive PTH, and decreased levels of prolactin and calcitonin (Table 1).

**Table 1.** Examination results on admission and endocrinological findings

GH	49 ng/ml (<0.42)	PTH-M	0.57 ng/ml (<0.8)
Prolactin	1 ng/ml (1.5-9.7)	H-PTH	630 pg/ml (160-520)
Somatostatin	16 pg/ml (1.0-12)	ACTH	24 pg/ml (9-52)
Insulin	8 uU/ml (<17)	TSH	0.6 uU/ml (<1-8)
Gastrin	85 pg/ml (<200)	T <sub>3</sub>	1.24 ng/ml (0.85-2)
Glucagon	150 pg/ml (40-180)	T <sub>4</sub>	9.8 ug/dl (5.1-13.5)
PP	253 pg/ml (114-126)	FBS	72 mg/dl (60-110)
VIP	5 pg/ml (<10)	S-amylase	71 IU/L (45-164)
Calcitonin	19 pg/ml (36.3-75.7)	Ca	10.4 mEq/ml (8.7-10.1)
PTH-C	0.4 ng/ml (<0.5)	P	3.4 mg/dl (2.4-4.3)

( ) : within normal limits

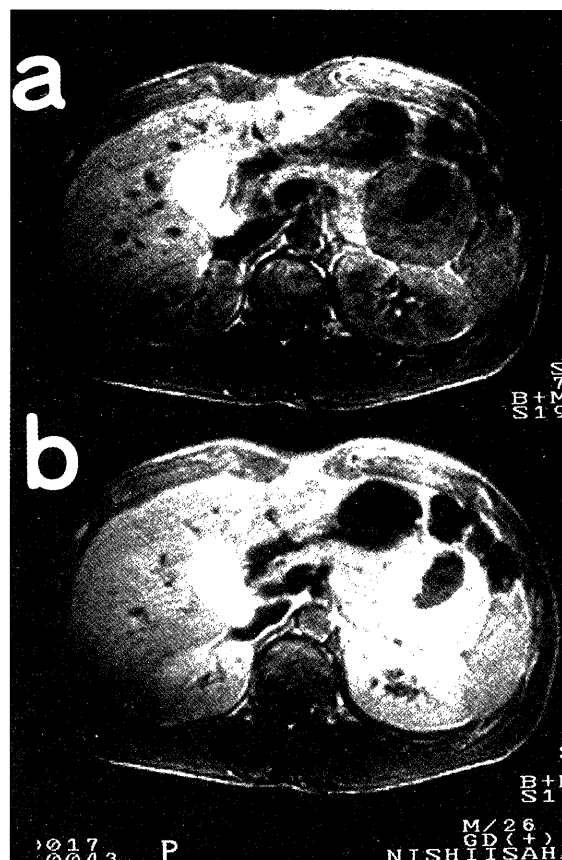
GH, growth hormone; PP, pancreatic polypeptide; VIP, vasoactive intestinal peptide; PTH-C and -M, parathyroid hormone-C and -M; H-PTH, high sensitive parathyroid hormone; ACTH, adrenocorticotropic hormone; TSH, thyroid stimulating hormone; T<sub>3</sub>, triiodothyronine; T<sub>4</sub>, thyroxine; FBS, fasting blood sugar

**Abdominal MRI findings:** A tumor, 7 cm in diameter, possessing a signal intensity lower than that of the spleen, was found in the pancreatic tail on T1-weighted images. The central part of the tumor had an even lower signal intensity suggesting necrosis. The tumor was slightly enhanced after the administration of Gd-DTPA contrast medium (Fig.1).

**Selective angiography of the splenic artery:** A lesion with a vague tumor stain was found to have a main feeder from the dorsal pancreatic artery.

**Surgical findings:** The above findings suggested the diagnosis of MEN 1 associated with GH-producing pituitary adenoma and endocrinepancreatic tumor. The patient underwent resection of the pancreatic tumor on September 16, 1992. The tumor, covered with a well-vascularized capsule, tightly adhered to the splenic port, compressing the splenic artery and vein. The tail of the pancreas was removed along with the spleen.

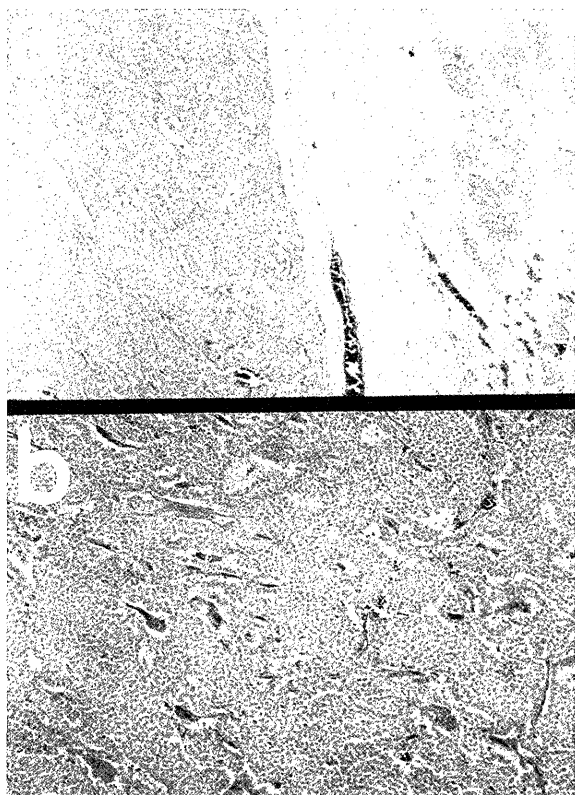
**Pathological findings:** The encapsulated tumor, 7.5 x 7.0 x 6.5 cm in size, had a yellow-brown solid cut surface with central necrosis (Fig.2). Microscopically, the tumor had a capsule clearly distinguishable from normal pancreatic tissue (Fig.3 a). The tumor cells showed a



**Figure 1.** Abdominal MRI: a. A tumor with a 7-cm diameter was found in the pancreatic tail on a T1-weighted image. The central part of the tumor had a lower signal intensity suggesting necrosis. b. The tumor was slightly enhanced after the administration of Gd-DTPA.

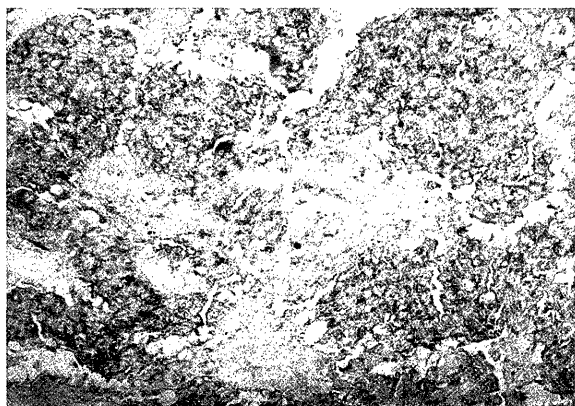


**Figure 2.** Macroscopic findings (cut surface): The encapsulated solid tumor measuring 7.5 x 7.0 x 6.5 cm exhibited central necrosis.

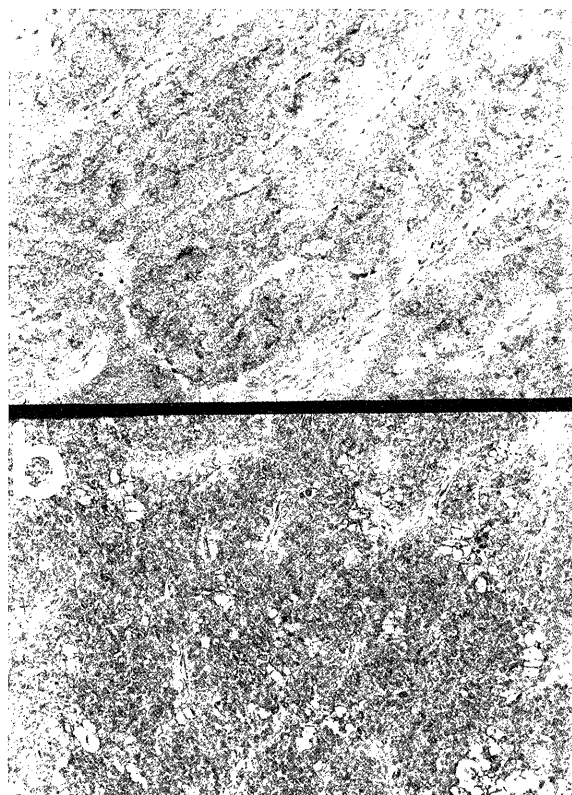


**Figure 3.** Histopathological findings: a. The tumor had a capsule clearly distinguishable from normal pancreatic tissue (HE stain, x 40). b. Tumor cells showed a funicular or zonate arrangement and a medullary appearance in some parts (HE stain, x 100).

funicular or zonate arrangement and a medullary appearance in some parts (Fig.3 b). Immunohistochemical examination showed that the tumor cells were positive for neuron specific enolase (NSE) (Fig.4 a). Chromogranin A was also detected in the cytoplasm (Fig.4 b). With an immunological staining method (an enzyme antibody technique using GRF (1-44) NH<sub>2</sub>), GRF-positive cells were found, although GH staining was negative (Fig.5).



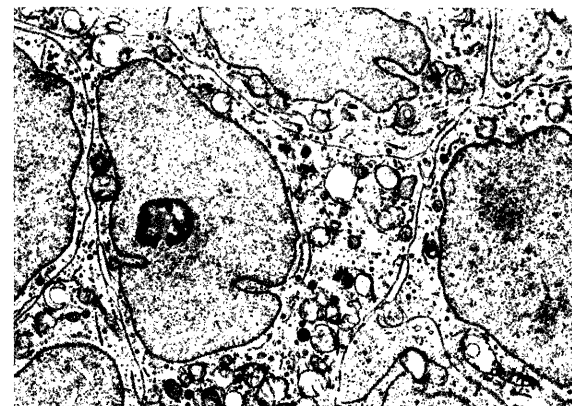
**Figure 5.** Immunological staining: GRF-positive cells were found (x 200).



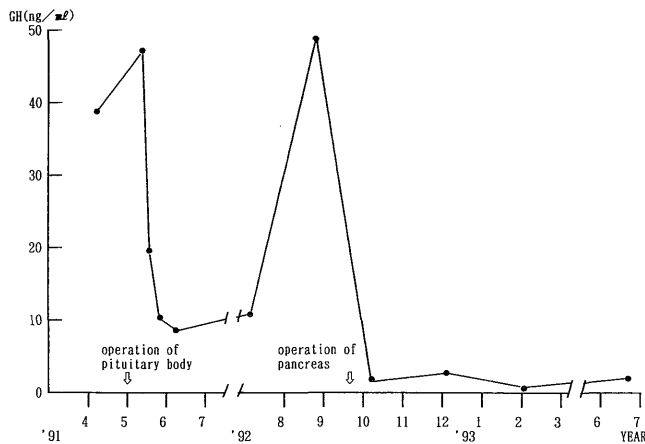
**Figure 4.** Immunohistochemical findings: a. The cytoplasm of the tumor cells was positive for NSE (x 100). b. It was also positive for chromogranin A (x 100).

The tumor cells were negative for Grimelius staining. Upon electron microscopy, a large number of immature secretory granules with diameter less than 150 nm were found in the cell body (Fig.6).

*Changes in GH during the patient's clinical course:* The GH level was temporarily elevated after resection of the pituitary adenoma. The value decreased and remained at approximately 10 ng/ml thereafter. Before surgery for the pancreatic tumor, the GH level in-



**Figure 6.** Electron microscopic findings: A large number of immature secretory granules with a diameter less than 150 nm were found in the cell body.



**Figure 7.** Changes in GH during the patient's clinical course.

creased, to 49 ng/ml, again. After the surgery, it quickly returned to a value within the normal limits (Fig.7).

*Postoperative course:* Nine months after surgery, MRI revealed that the pituitary gland had decreased in size.

## Discussion

As for the endocrine pancreatic tumors in MEN 1, several histological types have been reported; gastrinomas presenting with Zollinger-Ellison syndrome and insulinomas causing hypoglycemia are frequently found, while vasoactive intestinal peptide (VIP)-producing tumors, which cause watery diarrhea, hypokalemia, achlorhydria (WDHA) syndrome, and glucagon-producing tumors causing glucagonoma syndrome are rather rare. Immunohistological studies have also confirmed the existence of asymptomatic tumors which produce pancreatic polypeptide. Pancreatic tumors produce various hormones.

In the present case, immunohistochemical examination confirmed the presence of GRF and the absence of GH in the pancreatic tumor. The GH level returned to a normal value after surgery. Therefore, it was considered that GRF was produced in the pancreatic tumor, although plasma hormonal concentrations were not measured. In 1982, peptides with GRF activity were extracted from pancreatic tumors in patients with acromegaly to determine the chemical structure<sup>2,3</sup>). The substance possessing GRF activity was found to consist of three peptides, GRF (1-44) NH<sub>2</sub>, GRF (1-40) OH and GRF (1-37) OH, with the same structure at the N terminus. These peptides are now known as pancreatic GRF (pGRF) because they originate from the pancreas. Studies at many institutions have confirmed

that pGRF has the same structure as hypothalamus GRF. GRF-producing tumors have been attracting the attention of investigators as an important disease model for the mechanism of acromegaly and pituitary pathology in MEN 1. There are 34 reported cases of GRF-producing tumors presenting with acromegaly. In most of these 34 cases, the pituitary pathology was hyperplasia. There are only three cases, including the present case, where an adenoma was confirmed. It is noteworthy that all three cases were pGRF-producing MEN 1. It is still controversial whether excessive secretion of GRF due to GRF-producing tumors can be a trigger of hyperplasia in pituitary GH cells. Recent genetic investigations suggest that pituitary adenomas cannot be generated by GRF stimuli, but they may be caused by somatic mutation<sup>4</sup>). MEN 1 is supposedly caused by mutation at the responsible gene at site 11q13<sup>5</sup>).

Saito et al.<sup>6,7</sup>) reported a case of MEN 1 presenting with acromegaly. In their case, the pituitary decreased in size and acromegaly improved after resection of a GRF-producing pancreatic tumor, although surgery for a pituitary tumor was later required due to recurrence of symptoms and regrowth of the pituitary. Pituitary adenomas are either GH cell adenomas or non-functioning adenomas. Acromegaly associated with pancreatic tumor is mostly attributable to GH cell hyperplasia caused by pGRF. Therefore, it is considered that pituitary adenomas arise due to the lack of a cancer-suppressive gene at sites 11q12-13. In our case, the GH level, which decreased after surgery for the pituitary tumor, was maintained at a slightly elevated value. Therefore, it was suggested that the endocrine tumor was already located in the pancreas, and that the adenoma and hyperplasia coexisted in the pituitary gland at the time of pituitary surgery. After surgery for the pancreatic tumor, the GH level normalized and the pituitary gland decreased in size. These findings suggest that the pituitary GH cell hyperplasia returned to normal after the removal of pGRF stimuli released from the pancreatic tumor. Aida et al.<sup>8</sup>) reported a case of MEN 1 presenting with acromegaly where the GH level decreased rapidly after surgery for GRF-producing pancreatic carcinoid tumor subsequent to resection of a pituitary adenoma. In their case, the pituitary function was probably elevated by the same mechanism as has been speculated in our case. Although adenomas are rarely associated with hyperplasia, such condition may occur undersecondary hyperpituitarism due to pGRF.

As for the generation of pituitary adenoma, the following observations are interesting to note: In one reported case<sup>9</sup>) of gangliocytoma in the hypothalamus GRF production was accompanied by a GH cell tumor

in the pituitary; GRF-producing pancreatic tumors should be classified as endocrine neoplasms according to a report<sup>10)</sup> that pGRF is predominantly found in and around islets originating from the ventral primordium in the dorsal inferior part of the pancreatic head, and is sometimes found in the pancreatic tail; The pancreatic endocrine gland has genetic potentials characteristic of the pituitary gland because thyrotropin-releasing hormone (TRH), a peptide originally produced in the hypothalamus to stimulate the anterior pituitary gland, and corticotropin-releasing hormone (CRH) were found to exist in the pancreatic endocrine gland<sup>11)</sup>; Ectopic GRF-producing tumors are not accompanied by pituitary tumors. These observations may suggest that GRF produced in endocrine neoplasms has a close relationship to the generation of pituitary adenomas and the proliferation and development of already generated adenoma cells. Further studies are necessary to evaluate this hypothesis.

Further investigations, including gene analysis of the tumor tissue, should be performed in our case to establish the participation of pGRF in the generation of pituitary adenoma.

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