

Double Pituitary Adenoma

—Two Case Reports—

Seiji KANNUKI, Keizo MATSUMOTO, Toshiaki SANO*,
Yasumi SHINTANI**, Hiroshi BANDO**,
and Shiro SAITO**

*Department of Neurological Surgery, *First Department of Pathology,
and **First Department of Internal Medicine, School of Medicine,
the University of Tokushima, Tokushima*

Abstract

A 43-year-old male and a 39-year-old male presented with multiple pituitary adenomas with two distinct histological types. The first patient who had multiple endocrine neoplasia type 1 had developed acromegaly due to a growth hormone-releasing hormone (GHRH)-producing pancreatic tumor. Both plasma GHRH and growth hormone (GH) levels decreased to normal after resection of the pancreatic tumor. However, the plasma GH level gradually increased again and magnetic resonance imaging revealed pituitary adenoma formation. Histological examination revealed two different histological types of pituitary adenoma: GH cell adenoma and null cell adenoma. The second patient, with no such genetic condition, had a non-functioning pituitary adenoma. Histological examination revealed two different histological types of silent GH cell adenoma and silent gonadotroph adenoma. Careful histological examination is required to exclude the possibility of multiple pituitary adenomas.

Key words: pituitary adenoma, double pituitary adenoma, multiple endocrine neoplasia type 1

Introduction

Pituitary adenomas with multiple histological types have rarely been discussed. The fragmentation of specimens of adenoma tissue obtained by the transsphenoidal approach may make accurate diagnosis of multiplicity more difficult. Therefore, the actual incidence of double pituitary adenomas in surgical material is unknown. However, almost all pituitary adenomas are solitary tumors with a histologically uniform pattern^{6,8)} including plurihormonal adenoma.^{5,12,16)} Therefore, accurate histological diagnosis of pituitary adenoma is considered possible even based on small tumor fragments. Accurate histological diagnosis of plurihormonal pituitary adenomas is also possible based on tumor fragments.^{3-5,7,16,18)} Multiple pituitary adenoma is usually detected at autopsy,^{2,9,11,13,14,17)} with an incidence of 8.9% in one large series.⁹⁾ When adenoma fragments showed dissimilar histological and immunohistochemical fea-

tures, two different types of adenomas can be recognized.¹⁰⁾

Here we describe two cases of histologically double pituitary adenoma and discuss the combinations of immunohistochemical subtypes.

Case Reports

Case 1: A 43-year-old male was admitted to our hospital with increased pituitary mass and an elevated plasma growth hormone (GH) level in September 1992. His past history was notable for multiple endocrine neoplasia (MEN) type 1. He was found to have primary hyperparathyroidism when aged 31 years. Parathyroidectomy was performed three times between 31 and 34 years to control hypercalcemia caused by primary hyperparathyroidism. Thereafter, he developed acromegalic features. Abdominal computed tomography disclosed a tumor mass in the tail of the pancreas. Hormonal examination revealed elevated plasma GH-releasing hormone (GHRH) level, suggesting that the pancreatic mass was

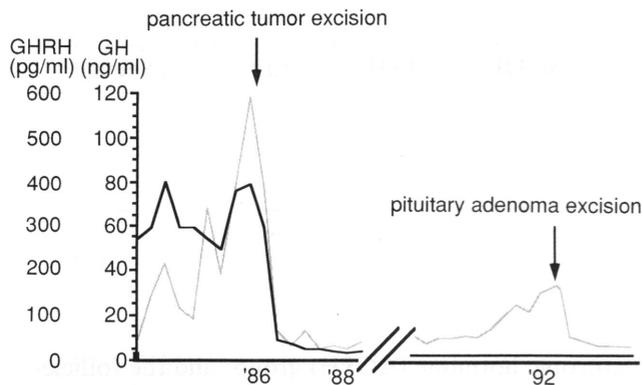


Fig. 1 Case 1. Changes in serum hormone levels showing normalization of serum GH level after pancreatic tumor excision but subsequent reincrease. *solid line: GHRH, dotted line: GH.*

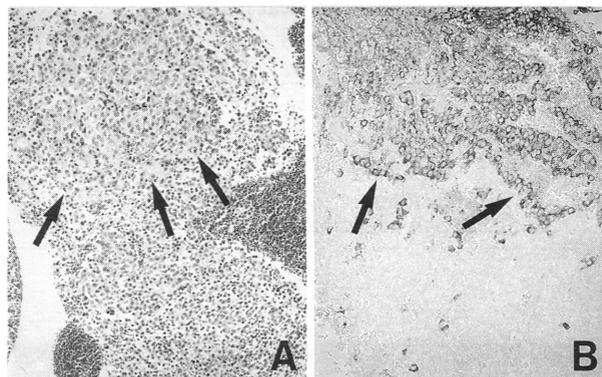


Fig. 3 Case 1. Photomicrographs of the pituitary adenoma specimen. A: The border (*arrows*) between the GH cell adenoma (upper) and the null cell adenoma (lower) is seen. The GH cell adenoma has a diffuse pattern and the null cell adenoma has a papillary pattern. The nuclei of GH cell adenoma cells are larger than that of null cell adenoma. HE stain, $\times 100$. B: Immunostaining makes the border (*arrows*) more distinct. Immunostain for GH, $\times 200$.

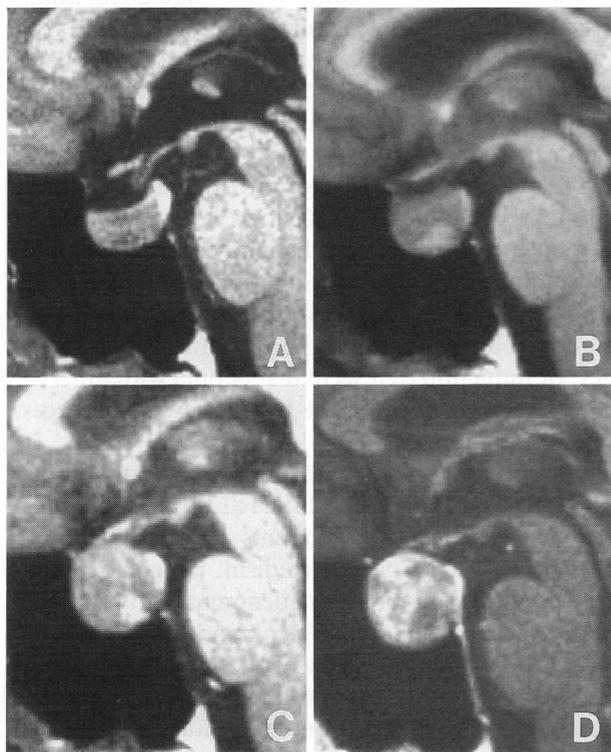


Fig. 2 Case 1. Serial MR images, 3 months (A), 1 year (B), 2 years (C), and 4 years (D) after pancreatic tumor excision, showing the pituitary gland gradually increased in size suggesting GH cell adenoma formation.

the pancreatic tumor showed GHRH but not GH. His postoperative course was uneventful, and both plasma GHRH and GH levels decreased to the normal range. However, plasma GH level increased again (Fig. 1). Magnetic resonance (MR) imaging revealed an increase in the pituitary mass over the past 4 years (Fig. 2). The pituitary adenoma was successfully resected by the trans-sphenoidal approach in November 1992. The postoperative course was uneventful. The pituitary adenoma had disappeared on the postoperative MR image, and his plasma GH level returned to the normal range.

Histological examination of the pituitary adenoma specimen showed GH cell adenoma and null cell adenoma (Fig. 3A). Immunohistochemical staining showed the GH cell adenoma was positive for GH (Fig. 3B) with a perinuclear pattern of cytokeratin distribution (densely granulated type). The null cell adenoma was only positive for α subunit (Table 1).

Case 2: A 39-year-old male was admitted to our department with complaints of headache, general fatigue, and decreased libido. Neurological examination revealed no abnormal findings including in the visual fields. MR imaging showed a pituitary mass with suprasellar extension compressing the optic chiasm. A cystic cavity was also observed in the center of the adenoma, but no indications of two different types of adenoma were seen. Preoperative hormonal loading testing using the four hypothalam-

an ectopic GHRH-secreting tumor. Laparotomy was performed for removal of the pancreatic tumor. Immunohistochemical staining of the specimen of

Table 1 Immunohistochemical findings

	GH	PRL	TSH	ACTH	FSH	LH	α Subunit
Case 1							
GH cell adenoma	+++	-	-	-	-	-	-
Null cell adenoma	-	-	-	-	-	-	+
Case 2							
GH cell adenoma	+++	-	++	-	-	-	-
Gonadotroph adenoma	-	-	-	-	++	-	-

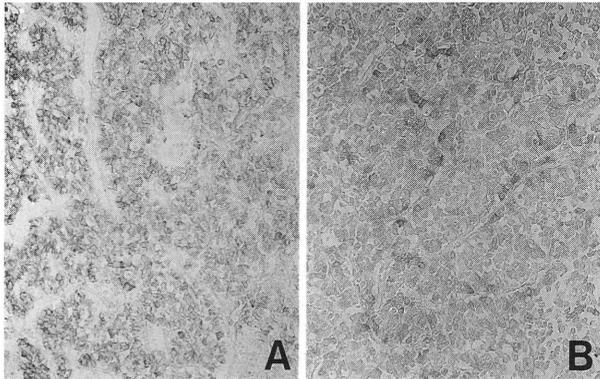


Fig. 4 Case 2. Photomicrographs of the pituitary adenoma specimen showing positive GH immunostaining of part of the GH cell adenoma (A: $\times 200$), and FSH immunostaining of part of the gonadotroph adenoma (B: $\times 200$).

ic releasing hormones (GHRH, thyrotropin-releasing hormone, corticotropin-releasing factor, and luteinizing hormone [LH]-releasing hormone) disclosed almost normal anterior pituitary function except for mildly decreased gonadotropic hormones. This clinically non-functioning pituitary adenoma was resected through the trans-sphenoidal approach. No signs of different adenoma types were distinguished during the operation. The postoperative course was uneventful, and postoperative MR imaging disclosed total removal of the pituitary adenoma.

Histological examination revealed two different types of pituitary adenomas in different tissue fragments: GH cell adenoma which had an alveolar pattern, and gonadotroph adenoma with a papillary pattern (Fig. 4). The border of the two adenomas was not identified.

Discussion

Almost all pituitary adenomas can be divided into three groups: the GH-prolactin (PRL)-thyroid-stimulating hormone (TSH) group, the adrenocor-

ticotropic hormone (ACTH) group, and the follicle-stimulating hormone (FSH)-LH group.¹⁵⁾ Each group contains functioning and non-functioning adenomas. Therefore, double pituitary adenoma combinations can be divided into three patterns: GH-PRL-TSH + FSH-LH groups, GH-PRL-TSH + ACTH groups, and ACTH + FSH-LH groups. These combinations include all 16 reported cases of double adenomas including ours^{10,19)} and 20 immunohistochemically proven autopsy cases.⁹⁾ The GH-PRL-TSH + FSH-LH groups were most frequent, accounting for seven of 16 surgical cases and nine of 20 autopsy cases. Both our cases had this common pattern.

The possible pathogenesis of double or multiple pituitary adenomas is as follows¹⁰⁾: concurrence of two independent tumors, distinctly separate with no causal link; partial transformation of one adenoma type to another with different histochemical, immunocytological, and/or ultrastructural characteristics; or induction of a second adenoma with different biological and histological features by some excessive stimulation.

MEN type 1 is an autosomal dominant disease caused by a chromosome 11 (11q13) tumor suppressor gene deficiency.^{1,20)} Patients with MEN type 1 present with hyperparathyroidism, pancreatic endocrine tumors, and pituitary adenomas. Pituitary adenomas occur in about 60% of patients with MEN type 1.²⁰⁾ In addition, most of these pituitary adenomas are macroadenomas producing GH or PRL. The possible mechanism of double pituitary adenoma in our Case 1 may have been GH cell hyperplasia and secondary GH adenoma formation associated with a pre-existing non-functioning adenoma based on the preceding GHRH overstimulation. Multiple pituitary adenomas have not been reported associated with MEN type 1, although multiple pancreatic tumors associated with MEN type 1 occur sometimes.²⁰⁾ More extensive histological examination of patients with MEN type 1 may identify more cases of multiple pituitary adenomas.

Our Case 2 had no genetic background such as

MEN type 1. However, the same combination of GH-PRL-TSH and FSH-LH groups was seen. Therefore, the possibility of cooccurring independent tumors with no causal link was suspected.

Our present cases show that careful histological diagnosis of fragmented adenoma tissues is required to exclude the possibility of double pituitary adenomas within the same pituitary gland.

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Address reprint requests to: S. Kannuki, M.D., Department of Neurological Surgery, School of Medicine, the University of Tokushima, 3-18-15 Kuramotocho, Tokushima 770, Japan.