Reduction of a Pancreatic Tumor after Total Removal of an ACTH Secreting Pituitary Tumor: Differential Diagnosis of Cushing's Syndrome

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Abstract. Endocrinologic tests sometimes fail to distinguish adrenocorticotrophic hormone (ACTH)-secreting pituitary adenoma from ectopic ACTH-secreting tumor. The authors experienced a case of Cushing's disease associated with a pancreatic tumor. Venous sampling contributed to the final diagnosis of Cushing's disease in this complex case, while endocrinologic tests showed paradoxical results. A 54-year-old woman presented with Cushing's syndrome and pancreatic tumor. Magnetic resonance imaging (MRI) failed to reveal a pituitary tumor, but a gadolinium-enhanced tumor with cystic components was seen in the pancreatic tail. Results of conventional endocrinologic tests suggested ectopic ACTH syndrome, but venous sampling including cavernous sinus sampling indicated an ACTH-secreting pituitary adenoma. Transsphenoidal surgery revealed a pituitary microadenoma, and total removal of the tumor was achieved. Postoperative abdominal MRI revealed that the pancreatic tumor diminished gradually without treatment. Selective cavernous sinus sampling was useful for distinguishing ACTH-secreting pituitary adenoma from ectopic ACTH syndrome in this complex case. This was a rare case in which the pancreatic tumor diminished after total removal of the ACTH-secreting pituitary adenoma.

Key words: Cushing's disease, Ectopic ACTH syndrome, Pancreatic neoplasm, Petrosal sinus sampling

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CUSHING'S disease accounts for approximately two-thirds of the cases of Cushing's syndrome [1]. Most patients of ACTH dependent Cushing's syndrome have adrenocorticotrophic hormone (ACTH)-secreting pituitary microadenoma, but ectopic ACTH syndrome, which causes 9–18% of Cushing's syndrome [2], is sometimes responsible. Laboratory studies fail to accurately distinguish these two etiologies in 10–30% of cases [3–6], and the sensitivity of magnetic resonance imaging (MRI) for detection of ACTH-secreting pituitary microadenoma is reported to range from 54% to 91% [7–10]. Therefore, ectopic ACTH syndrome is

sometimes misdiagnosed.

Herein, we describe a patient with ACTH-secreting pituitary adenoma and a mass in the pancreatic tail that was detected by abdominal MRI. Laboratory studies suggested ectopic ACTH syndrome, but selective cavernous sinus sampling (CSS) indicated the presence of ACTH-secreting pituitary adenoma. The pituitary adenoma was surgically removed and subsequently the pancreatic tumor decreased in size without any treatment. We discuss the difficult differential diagnosis in this case and describe the rare phenomenon that occurred after surgery.

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Case Report

Clinical findings and laboratory studies

A 54-year-old woman presented with central obesity, moon face, and muscle weakness. Cushing's syndrome was suspected, and she was admitted to Osaka University Hospital. Relevant laboratory values included sodium 148 mmol/l, potassium 2.9 mmol/l, fasting blood glucose 210 mg/dl, HbA1c 7.9%, and urinary 17-hydroxycorticosteroid 45.8 mg/day. Overnight low- (1 mg) and high-dose (8 mg) dexamethasone suppression tests showed lack of suppression of serum ACTH and cortisol levels, and there was no ACTH or cortisol response to intravenous injection of corticotropin-releasing hormone (CRH) (100 µg). The serum CRH level was 9.1 pg/ml (normal range: 3.2–14.7 pg/ml; Radio Immuno Assay method, SRL, Tokyo, Japan). After intravenous administration of 10 µg of desmopressin, the cortisol and ACTH levels did not increase significantly. The summary of clinical data including endocrinologic tests is shown in Table 1. On the basis of these laboratory findings, ectopic ACTH syndrome was suggested.

Table 1. Summary of preoperative clinical data including endocrine tests

Basic value		
ACTH (pg/ml)	121	
Cortisol (µg/dl)	47.7	
Urinary free cortisol (ng/dl)	1603	
17-OHCS (mg/day)	45.8	
17-KS (mg/day)	18	
ACTH daily rhythm	7:00	23:00
ACTH (pg/ml)	165	78
Cortisol (µg/dl)	47.7	33.1
CRH loading test	pre	post
ACTH (pg/ml)	193	154
Cortisol (µg/dl)	46.6	43.5
1mg Dexamethasone loading test	pre	post
ACTH (pg/ml)	165	—
Cortisol (µg/dl)	55.4	63
8mg Dexamethasone loading test	pre	post
ACTH (pg/ml)	270	—
Cortisol (µg/dl)	113.9	135.9
dDAVP loading test	pre	post
ACTH (pg/ml)	273	315
Cortisol (µg/dl)	—	121.7

17-OHCS, 17-hydroxycorticosteroid; 17-KS, 17-ketosteroid; dDAVP, desmopressin; pre, preload value; post, peak value after loading.

Imaging studies

MRI of the pituitary region, including dynamic study, failed to reveal microadenoma (Fig. 1A). Abdominal MRI revealed a 3 cm × 3 cm mass lesion of low intensity in the tail of the pancreas that was partly enhanced by gadolinium (Fig. 2A). Abdominal positron emission tomography with 2-[fluorine-18] fluoro-2-deoxy-D-glucose (FDG-PET) showed an uptake area consistent with the location of the lesion (Fig. 3A). Endoscopic retrograde cholangiopancreatography revealed a solid and partly cystic mass lesion in the pancreatic tail with communication between the lesion and the main pancreatic duct. Accordingly, the pancreatic tumor was considered the most likely source of the ACTH.

Bilateral CSS of ACTH

Venous sampling was performed to determine the origin of the excessive serum ACTH. The catheter was

Fig. 1. (A) Preoperative head MRI. No apparent microadenoma was shown in the sella. (B) Postoperative head MRI. Fat tissue was replaced at the resected cavity.

Fig. 2. Abdominal MRI with contrast enhancement (A) Preoperative. A solid mass with cystic components was shown with contrast enhancement in the pancreatic tail. (B) Postoperative (7 months after operation). The mass diminished after the total removal of the ACTH-secreting pituitary adenoma.

introduced from the right femoral vein and the blood samples were taken at several sites. The left inferior petrosal sinus (IPS) was hypoplastic, and a microcatheter was introduced into the cavernous sinuses from the right IPS. The levels of ACTH at the respective sites and the levels of prolactin (PRL), which was measured at both cavernous sinuses as reference to ensure adequate venous sampling, are shown in Table 2. The levels of ACTH in the inferior vena cava (peripheral to the junction with the bilateral renal veins), right cavernous sinus, and left cavernous sinus were 51, 242, and 302 pg/ml, respectively. The central-to-peripheral ratio of the serum ACTH level was 4.74 in the right cavernous sinus and 5.92 in the left. The left-to-right gradient was 1.24 and a normalized ACTH/PRL the left-to-right gradient was 1.34.

Fig. 3. (A) Preoperative FDG-PET. There is an uptake of FDG consistent with the tumor in the pancreatic tail. (B) Postoperative FDG-PET (4 months after operation). No uptake was shown in the same region.

Table 2. Summary of selective venous sampling

	ACTH (pg/ml)	Cortisol (μg/dl)	PRL (ng/ml)
IVC (peripheral of bilateral renal vein)	51	14.2	
lt. renal vein (peripheral of lt. adrenal vein)	42	10.6	
lt. renal vein (central of lt. adrenal vein)	41	10.8	
lt. adrenal vein	42	25.8	
hepatic vein	51	11.9	
rt. cavernous sinus	242		52.5
lt. cavernous sinus	302		48.8

IVC, inferior vena cava; rt, right; lt, left.

Neurosurgical intervention

Although the laboratory and abdominal MRI and FDG-PET findings suggested an ectopic ACTH-secreting tumor located in the pancreas, an ACTH-secreting pituitary adenoma was strongly suspected on the basis of the venous sampling. Therefore, the patient underwent transsphenoidal surgery. Upon opening of the dura of the sella on the left side, a grayish tumor was found. The tumor size seemed to be about 2 or 3 mm in diameter, which was compressed. The tumor and surrounding normal tissue were removed and the cavity was replaced by the abdominal fat. The postoperative MRI is shown in Fig. 1B. Histologic examination revealed a pituitary adenoma that was stained positively with ACTH antibody.

Postoperative course

Two weeks after surgery, daily cortisol secretion had normalized (15.1 μg/dl early in the morning and 4.9 μg/dl at midnight), and a dexamethasone (1 mg) suppression test decreased ACTH (from 26 pg/ml to 8 pg/ml) and cortisol (from 15.1 to 2.8 μg/dl) secretion. Moreover, the insulin loading test resulted in responsive increase of ACTH and cortisol (Table 3). But the response was poor, and it was considered to be compatible with postoperative status of cured Cushing's disease. Therefore, appropriate hydrocortisone replacement was administered to the patient for a while after surgery. The summary of the postoperative clinical data including endocrinologic tests is shown in Table 3.

Table 3. Summary of postoperative clinical data including endocrinologic tests

Basic value			
ACTH (pg/ml)	19		
Cortisol (μg/dl)	18.2		
Urinary free cortisol (ng/dl)	90		
17-OHCS (mg/day)	10.6		
17-KS (mg/day)	2.8		
ACTH daily rhythm	7:00	23:00	
ACTH (pg/ml)	26	<5.0	
Cortisol (μg/dl)	15.1	4.9	
1mg Dexamethasone loading test	pre	post	
ACTH (pg/ml)	26	8	
Cortisol (μg/dl)	15.1	2.8	
Insulin loading test	pre	post	
ACTH (pg/ml)	9.7	14.8	
Cortisol (μg/dl)	25	37	

Interestingly, the pancreatic tumor decreased gradually in size (Fig. 2B), and FDG-PET showed diminished uptake at 4 months after surgery (Fig. 3B).

About two years after surgery, she has been free from any clinical symptom and the pancreatic tumor has never grown again on the subsequent radiological studies.

Discussion

In this case, it was difficult to distinguish ACTH-secreting pituitary adenoma from ectopic ACTH-secreting pancreatic tumor. The results of CSS provided the final diagnosis. After total removal of the ACTH-secreting adenoma the serum ACTH level normalized, and the patient was cured.

ACTH-secreting pituitary microadenoma cannot always be identified in imaging studies such as computed tomography [7, 11] and MRI [7–10] studies. Moreover, pituitary adenoma is detected incidentally by MRI in 10% of healthy persons; false positivity can also occur [12]. Non-invasive endocrine laboratory studies, including low- and high-dose dexamethasone suppression tests [4, 5], metyrapone stimulation [3], and peripheral CRH challenge tests [6], are often used to distinguish pituitary adenoma from ectopic sources of excessive ACTH. However, each of these tests fails to distinguish the two etiologies in 10–30% of cases [3–6]. Therefore, differential diagnosis of ACTH-dependent Cushing's syndrome remains, on occasion, a considerable clinical challenge.

Our patient, who presented with symptoms consistent with Cushing's syndrome, had a solid and partly cystic tumor in the pancreas and showed lack of suppression of serum ACTH and cortisol levels in the high-dose dexamethasone test and lack of ACTH and cortisol response to the CRH test. Therefore, ectopic ACTH syndrome was suspected. However, ectopic ACTH-secreting pancreatic tumor causing Cushing's syndrome is relatively rare, accounting for about 10% of all cases of ectopic ACTH syndrome and about 2% of all pancreatic endocrine tumors [13, 14]. Moreover, most ACTH-producing islet cell tumors are malignant, and the majority of cases involve liver metastasis by the time of diagnosis [15].

Association of pancreatic tumor with pituitary microadenoma is sometimes seen in cases of multiple endocrine neoplasia type 1 (MEN 1) [16, 17]. Yoshimoto

et al. reviewed 106 cases of MEN 1 and reported that Cushing's disease was present in about 5% of patients [17]. Miyagawa *et al.* reported a case of MEN 1 consisting of Cushing's disease, primary hyperparathyroidism, and insulin-glucagonoma; the patient was treated successfully by transsphenoidal pituitary adenectomy, subtotal parathyroidectomy, and enucleation of the pancreatic tumors [16].

Because we suspected an association of two different tumors in our case, we performed selective CSS even though endocrine laboratory studies suggested that an ectopic ACTH-secreting tumor in the pancreas was the likely cause of the excessive serum ACTH. CSS findings indicated the presence of an ACTH-secreting tumor, and thus CSS was very useful for distinguishing ACTH-secreting pituitary adenoma from ectopic ACTH syndrome in our case.

A number of studies have evaluated the role of venous sampling by microcatheter in the diagnosis of ACTH-dependent Cushing's syndrome [18–22]. Oldfield *et al.* reported that a central-to-peripheral ACTH ratio of greater than 2.0 has a sensitivity of 95% and specificity of 100% and after CRH administration the ratio of greater than 3.0 has a sensitivity and a specificity of 100% in inferior petrosal sinus sampling (IPSS) [18]. However, additional experience has revealed some false-negative results. Using the same cut-off value, a false-negative rate of 1–10% in patients with proven Cushing's disease has been reported [23–26]. False-negative results with IPSS have been attributed to wide variation of venous drainage [24]. Recently, Findling *et al.* suggested that the measurement of PRL (as an index of fidelity of pituitary venous effluent during IPSS) and the establishment of a normalized ACTH/PRL petrosal sinus to peripheral ratio will identify patients with Cushing's disease who fail to have a peak ACTH inferior petrosal sinus to peripheral ratio greater than 3.0 after CRH [27].

On the other hand, Teramoto *et al.* described the usefulness of CSS compared to IPSS and suggested that the tentative cutoff ratio is 5 for the diagnosis of pituitary lesions [19]. In our case, we obtained a ratio of greater than 5 in left cavernous sinus and fortunately the origin of excessive ACTH was in the pituitary gland. However, Teramoto *et al.* also reported that basal C/P ratios in the cavernous sinus exceeded 10 in most cases of Cushing's disease [19]. Taking these facts into consideration, for a more reliable diagnosis we should perform CSS after CRH administration or

measure the level of PRL from peripheral vein and cavernous sinus, and calculate a normalized ACTH/PRL petrosal sinus to peripheral ratio.

As for lateralization of the tumor in the pituitary gland, Oldfield *et al.* also reported that a greater than 1.4-fold difference in ACTH concentrations between the two inferior petrosal sinuses accurately localized the microadenoma in 68% of cases during basal sampling [18]. The accuracy of determining lateralization by means of bilateral inferior petrosal sinus sampling is reported to be approximately 75% [28], and that by means of bilateral CSS ranges widely from 40% to 94% [19, 29, 30]. In this case, the basal left-to-right gradient showed 1.24, but the normalized ACTH/PRL left-to-right gradient showed 1.34, which was near 1.4. Therefore, we opened the dura surrounding the sella on the left side. The pituitary adenoma was located on the left side of the pituitary gland and was totally removed. Therefore, it can be said that selective CSS is necessary

for differential diagnosis of ACTH-dependent Cushing's syndrome, especially in cases of difficult differential diagnosis. Flitsch *et al.* also recommend CSS for diagnostic purposes in complex cases [31]. However, Suzuki *et al.* reported a rare case with an ACTH-producing ectopic pituitary adenoma in the sphenoid sinus [32]. Therefore, we should consider the possibility of such a case even if CSS indicated the pituitary origin as the more likely source of excessive ACTH.

It was interesting that the pancreatic tumor decreased in size. Unfortunately, histologic confirmation has not been obtained, but we speculate that the pancreatic tumor was hormone dependent because it diminished postoperatively with changes in the hormonal environment such as decreases in the serum ACTH and cortisol levels. In the literature, there was no report that a pancreatic tumor diminished after total removal of an ACTH producing pituitary adenoma. Ours is the first report of such a rare and interesting case.

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