Ectopic Growth Hormone-Releasing Adenoma in the Cavernous Sinus

—Case Report—

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Abstract

A 55-year-old woman presented a rare ectopic pituitary adenoma in the right cavernous sinus manifesting as acromegaly. The tumor was removed via transsphenoidal approach. Intraoperative observation showed the adenoma was located entirely within the right cavernous sinus, and separated from the normal pituitary gland by the medial wall of the cavernous sinus. There was no communication between the tumor and the pituitary. Histological examination showed a growth hormone-releasing adenoma. Including our case, only eight of 86 reported ectopic adenomas have occurred in the cavernous sinus. Such ectopic presentation may be responsible for failed transsphenoidal surgery for endocrinologically active tumors.

Key words: acromegaly, ectopic tumor, pituitary adenoma

Introduction

Ectopic pituitary adenomas have increased in incidence during the last two decades. These tumors should be considered in the differential diagnosis for parasellar mass lesions, and require the appropriate surgical approach and endocrinological treatment for functioning adenomas.^{40,50} Growth hormone (GH)-releasing adenomas with ectopic presentation have been found only in the sphenoid sinus, suprasellar, and sphenoid wing.^{10,14,22,39,42,48,51} We present a patient with acromegaly caused by a GH-secreting adenoma entirely located in the cavernous sinus (CS) without communication to the pituitary fossa.

Case Report

A 55-year-old woman had a 5-year history of dramatic changes in facial appearance, increase in the size of her hands and feet, and snoring and profuse perspiration. On admission diabetes mellitus was identified. Preoperative endocrinological analysis showed high GH level (133 ng/ml), high insulin-like growth factor-1 (IGF-1) level (731 ng/ml), and mild

increase in prolactin (PRL) level (73.0 ng/ml). Serum levels of other pituitary hormones were within the normal ranges for her age: thyroid-stimulating hormone (TSH) 1.24 μ U/ml, adrenocorticotrophic hormone (ACTH) 31 pg/ml, cortisol 14.4 μ g/dl. Her hemoglobin-A1c level had increased to 6.7%. Coronal T₁-weighted magnetic resonance (MR) imaging with gadolinium showed a mass lesion encircling the right internal carotid artery in the right CS (Fig. 1). The pituitary stalk was on the midline and the pituitary gland had normal size and shape with strong enhancement compared to the tumor. An enhanced line was observed between the gland and the tumor. Coronal T₂-weighted MR imaging also demonstrated a thin hypointense line between the gland and the tumor in the right CS (Fig. 2A). The preoperative diagnosis was adenoma in the right CS separated from the pituitary gland by a membrane, complete or redundant.

The patient underwent transsphenoidal surgery. The sphenoid sinus was covered with normal mucosa. The sella floor was opened, and the right CS and the sella entered. The soft gray tumor was entirely located in the CS. The tumor between the internal carotid artery and the medial wall of the CS was removed (Fig. 3). The lateral portion of the tumor in the CS was very fibrous and hemorrhagic,

Fig. 1 Preoperative coronal T₁-weighted magnetic resonance images with gadolinium demonstrating an enhanced diffuse tumor in the right cavernous sinus encircling the internal carotid artery. There was an enhanced line between the tumor and the well-enhanced pituitary gland (arrow). No tumor was seen in the deformed sphenoid sinus. The tumor was entirely located in the cavernous sinus.

Fig. 2 Coronal T₂-weighted magnetic resonance images demonstrating a hypointense line (arrowhead) between the tumor and the pituitary gland (A). The line (arrowhead) became obvious after surgery next to the tumor cavity in the cavernous sinus (B).

so removal was not attempted. No holes or defects were found on the medial wall of the CS. Histological examination showed eosinophilic tumor cells in the stroma, and immunohistochemical study demonstrated positive staining for GH associated with a small number of PRL-positive tumor cells. MIB-1 staining showed a low staining index of 0.57%.

The patient's postoperative course was uneventful. She did not experience nasal bleeding or dia-

Fig. 3 Intraoperative photograph and illustration showing the tumor cavity with the internal carotid artery (arrow) and the thick wall (asterisk) separating the pituitary gland behind. A gray small remnant of the tumor is seen deep in the sinus.

betes insipidus. Postoperative MR imaging showed the tumor remnant in the CS and almost normal structure of the pituitary gland and the stalk with a clear margin between the removal cavity (Fig. 2B). The high GH level (153.0 ng/ml) and IGF-1 level (748.0 µg/ml) persisted one week after surgery. Her serum PRL level decreased to 25.8 ng/ml. The basal levels of other pituitary hormones were within the normal range: TSH 0.69 µU/ml, ACTH 22 pg/ml, cortisol 8.9 µg/dl. Bromocriptine treatment did not resolve the increased secretion of GH and IGF-1. She eventually underwent gamma-knife surgery in another institute.

Table 1 Reported cases of ectopic pituitary adenoma

Location	Hormone								Total
	GH	ACTH	PRL	ACTH/TSH	GH/PRL	FSH	LH	Inactive	
Suprasellar	1 (48)	12 (13,24,26,40,41,60,61)	7 (13,25,28,38,46,62,67)	1 (35)	0	0	0	9 (1,11,17,33,52,55,63)	30
Sphenoid sinus	6 (10,14,22,39,42,51)	7 (7,9,15,27,50,56,59)	9 (19,20,36,37,43,53,65)	1 (36)	1 (68)	0	0	6 (6,23,29,30,58,66)	30
Cavernous sinus	1 (present case)	6 (18,50,54,69)	0	0	0	0	0	0	8
Clivus	0	0	6 (2-4,12,45,57)	0	0	0	0	1 (70)	7
Nasopharynx	0	1 (34)	0	0	0	1 (31)	0	2 (8,51)	4
Superior orbital fissure	0	2 (5,49)	0	0	0	0	0	0	2
Sphenoid wing	0	0	0	0	0	0	0	1 (51)	1
Petrous temporal bone	0	0	0	0	0	0	0	1 (51)	1
Third ventricle	0	0	0	0	0	0	1 (32)	0	1
Sellar floor	0	1 (50)	0	0	0	0	0	0	1
Temporal lobe	0	1 (47)	0	0	0	0	0	0	1
Total	8	30	22	2	1	1	1	20	86

Numbers in parentheses show the case references. ACTH: adrenocorticotrophic hormone, FSH: follicle-stimulating hormone, GH: growth hormone, LH: luteinizing hormone, ND: not described, PRL: prolactin, TSH: thyroid-stimulating hormone.

Discussion

The criteria for ectopic adenomas include evidence of anatomically normal pituitary gland based on biopsy or MR imaging and endocrinological evidence of normal pituitary function after surgery.⁶²⁾ Our patient had a GH-secreting adenoma in the CS completely separated from the normal pituitary stalk and gland, as observed by pre- and postoperative MR imaging and confirmed during surgery. The thick wall separated the tumor and the pituitary gland without perforation or defects. Postoperative endocrinological study showed normal pituitary function except for increased GH and IGF-1 levels.

Ectopic pituitary adenomas vary in hormonal activities and anatomic distribution. Table 1 shows that ACTH-secreting adenomas were the most frequently reported (37.2%), followed by prolactinomas (25.6%) and endocrine-inactive tumors (23.3%). GH-secreting adenomas account for only 10.5% of reported ectopic adenomas. In contrast, the most common type among 2,230 pituitary adenomas was prolactinoma (39%), followed by endocrine-inactive adenoma (27.4%), GH-releasing adenoma (16.4%), ACTH-releasing adenoma (16.3%), and TSH-releasing adenoma (less than 1%).⁴⁴⁾ Although the recent recognition of luteinizing hormone- and follicle-stimulating hormone-releasing adenomas among silent adenomas has changed the proportions of hormone-secreting adenomas, ACTH-releasing adenomas are not the most common. Since Cushing's disease involves chronic life-threatening problems, meticulous diagnostic examinations are mandatory for the accurate diagnosis of the tumor. These clinical efforts may contribute to the high incidence of proved ACTH-secreting adenomas in ectopic locations. Migration or aberrant presentation of ACTH cells or precursor cells during development is another possible key to explain this high incidence of ectopic ACTH adenomas.

Table 1 also shows that the suprasellar cistern and sphenoid sinus were the most frequent locations for ectopic adenomas (34.9% each), followed by the clivus (8.1%) and the CS (9.3%). The most frequent anatomical locations are on the midline. Other anatomical locations away from the midline were only sporadically reported. The rare solitary presentation of ectopic adenomas in the parasellar midline structure suggest that the origin is aberrant pituitary tissue, not disseminated tumor cells.

Infrasellar and suprasellar aberrant adenohypophyseal cells develop at different embryonal stages.²¹⁾ The adenohypophysis develops from Rathke's pouch, and loses its connection to the pharynx by rupture of its stalk during the 12- to

20-mm stage. In the infrasellar region, ectopia of the adenohypophysis due to partial persistence of the pouch persists throughout life in all individuals.⁶⁴⁾ The remnant can be identified as a pharyngeal pituitary in the walls of the nasal cavity, craniopharyngeal canal, or sphenoid sinus. In contrast, suprasellar aberrant adenohypophysis may originate later when the pars tuberalis develops from the pars anterior of the pituitary at the 41- to 55-mm stage. Suprasellar peri-infundibular ectopic pituitary tissue is common in both fetus and adult brains.²¹⁾ Therefore, pituitary cells may easily be displaced in the leptomeninges of the suprasellar region during development. This hypothesis provides a plausible explanation for the suprasellar aberrant pituitary tissue both on and out of the midline.

Only eight ectopic adenomas were located only in the CS, and six were ACTH-secreting adenomas.^{18,50,54,69)} The present case suggests that the CS may contain ectopic adenomas more frequently than expected. Careful interpretation of thin-slice coronal MR images is required for presurgical detection of ectopic adenomas in the CS. Although adenomas are rarely located in the CS, ectopic presentation should be noted as one of the reasons for the failure of transphenoidal surgery for patients with endocrinologically active adenomas. We should avoid unnecessary dissection into the pituitary gland when trying to identify microadenomas.

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