Supra- and Extrasellar Pituitary Microadenoma as a Cause of Cushing’s Disease

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Abstract. There has been accumulating evidence that pituitary adenomas which cause Cushing’s disease are located not only in sella turcica but also in various extrasellar and intracranial regions. We describe a case of Cushing’s disease caused by a supra- and extrasellar ACTH-producing microadenoma, which originated in the anterior pituitary and extended upward without connecting to the stalk. The pituitary microadenoma was identified and removed by transsphenoidal microsurgery. After the surgery the patient experienced complete remission. This type of pituitary microadenoma is considered to be rare, but in order to accomplish successful surgical treatment, it is necessary to consider that pituitary adenomas which cause Cushing’s disease may be located in such an unusual position.

Key words: Supra- and extrasellar pituitary microadenoma, Cushing’s disease

ACTH-producing pituitary adenomas causing Cushing’s disease are usually small and located in the sella turcica [1], but many papers have reported that pituitary adenomas may be located in various extrasellar parts of the cranial cavity [2-11]. We report the first case of Cushing’s disease caused by supra- and extrasellar microadenoma, which originated in the anterior pituitary and extended upward without connecting to the stalk.

Case Report

In December, 1995 a 24-year-old woman was referred to Kishiwada City Hospital for examination and treatment of Cushing’s syndrome.

At the age of 20, 4 years before admission, she developed a moon face, central obesity, acne, hirsutism, purple striae, pigmentation, amenorrhea, fatigue and muscular weakness. She entered another hospital where laboratory examinations demonstrated Cushing’s syndrome, and the symptoms continued despite administration of mitotane.

After admission, we performed hormone measurements to make a definitive diagnosis of Cushing’s syndrome. Basal plasma cortisol levels measured at 0800 h, 1200 h, 1600 h, 2000 h and 2300 h were 23.1, 17.7, 24.2, 25.2 and 23.4 µg/dl, respectively. Basal plasma ACTH levels also measured at 0800 h, 1200 h, 1600 h, 2000 h and 2300 h were 67, 82, 130, 73 and 100 pg/ml, respectively. Urinary cortisol level was 1270 µg a day. With a single dose overnight dexamethasone suppression test using 1 mg and 8 mg of orally administered dexamethasone, the plasma cortisol level was 18.4 µg/dl and 25.9 µg/dl, respectively. Cortisol overproduction, absence of diurnal rhythmicity of cortisol and no suppression of the
plasma cortisol level with dexamethasone suppression test confirmed the diagnosis of Cushing's syndrome. Computed tomographic scan of the chest and abdomen showed only bilateral adrenal hyperplasia resulting from the persisting hypersecretion of ACTH. The patient underwent selective venous sampling from the inferior petrosal sinus (IPS) with simultaneous sampling from the peripheral vein. While the ACTH level in the left IPS and that in the peripheral vein were 170 and 160 pg/ml respectively, the ACTH level in the right IPS and that in the peripheral vein were 360 and 130 pg/ml, respectively. The gradient of plasma ACTH levels between the right IPS and the peripheral vein was diagnostic and strongly suggested that Cushing's syndrome in this case was attributable to pituitary adenoma (Cushing's disease). In addition, magnetic resonance (MR) imaging revealed a small supra- and extrasellar mass (Figs. 1, 2). A hypointense area was also found in the left lateral wing of the anterior pituitary on a coronal T1-weighted image with gadolinium-enhancement, which might indicate adenoma causing Cushing's disease (Fig. 3). The conclusive localization of a responsible pituitary adenoma remained unknown, but we considered that a transsphenoidal operation is the best way to remove pituitary adenoma causing Cushing's disease. We therefore employed the previously reported stepwise adenomectomy by the transsphenoidal approach [12], and made plans to explore not only the intrasellar region but also the suprasellar mass.

On January 16, 1996 the first transsphenoidal operation was performed. Survey for microadenoma was started in the right lateral wing with mid- and right paramedian-vertical incisions. Because of no positive findings, next step was in the left lateral wing, but was also fruitless. A tiny excised piece in the left lateral wing was sent to pathology, and the pathological findings denied the presence of pituitary adenoma. After excision of the lower 2/3 of the adenohypophysis, we tried to find a supra- and extrasellar mass. The bilateral upper surfaces of the residued gland were separated from the intact diaphragma sellae, and the surfaces were smooth and macroscopically normal. Finally, the central upper surface of the gland was separated and checked near the stump of the stalk, but there was no suprasellar mass visible at the time.

Immediately after the first operation, the patient

![Fig. 1. Coronal T1-weighted MR image with Gd-enhancement before the first operation. A small supra- and extrasellar mass (arrow) is identified, with a relatively hypointense signal compared to the anterior pituitary and stalk.](image1)

![Fig. 2. Coronal T2-weighted MR image before the first operation. The supra- and extrasellar mass (arrow) had a hypointense signal.](image2)
did not desire reoperation. Metyrapone was used to decrease the plasma cortisol level, but hypercortisolism improved slightly. Bilateral adrenal hyperplasia and pigmentation due to increased ACTH became more distinct. MR imaging continued to demonstrate the supra-and extrasellar mass, and axial T1-weighted MR images clearly demonstrated that the suprasellar mass existed in the anterior and left side of the stalk without connecting to the stalk (Fig. 4). The mass was located slightly but significantly downward compared with the preoperative MR images (Fig. 5). It was considered that Cushing's disease was attributable to this suprasellar mass. We thought that it was feasible to remove the mass by the retranssphenoidal approach.

On March 13, 1997 we performed the second transsphenoidal operation. The bony window of the sella floor was covered with thick connective tissue and a small square incision was made on it. The lower half of the intrasellar space was occupied by yellow-coloured granulomatous tissue, which was excised to make an operating. Then the left upper surface of the residual pituitary gland was detached from the diaphragma sellae starting from the cut edge of the dural capsule. Upon extension of the detachment, a global mass of a milky white colour came into view and extended upward through the enlarged orifice in the diaphragma sellae. In the supra- and extrasellar space the mass

![Fig. 4. Axial T1-weighted MR image with Gd-enhancement after the first operation. It is clearly demonstrated that the mass (arrow) existed in the anterior and left side of the stalk without connecting to the stalk.](image)

![Fig. 3. Coronal T1-weighted MR image with Gd-enhancement before the first operation. This is a 4.5 mm-posterior slice of that shown in Fig. 1. A hypointense area (arrow) is visible in the left lateral wing of the anterior pituitary.](image)

![Fig. 5. Coronal T2-weighted MR image after the first operation. The mass (arrow) was located slightly but significantly downward compared with the preoperative MR images. Note the distance between the mass and the optic chiasma.](image)
was visualized in the anterior and left side of the stalk without connecting to the stalk as observed on the preoperative MR images. With a short cut on the medial edge of the orifice, dissection of the mass was conducted from the pituitary surface, suprasellar arachnoid membrane and medially, and the pituitary stalk was extended. This mass was encapsulated with a thin membrane and was therefore successfully excised en bloc. Its diameter was about 3 mm. Major damage to the stalk was apparently avoided. During this procedure, CSF leakage was induced. Finally, fibrine glue was injected into the suprasellar subdural and intrasellar space. Previously used nasal bone was again applied as a bridge of the sellar floor and was sealed with biobond glue.

The histological examination confirmed basophilic pituitary adenoma, and immuno-histochemical staining for ACTH was positive.

On the 2nd postoperative day transient diabetes insipidus occurred and persisted for a week. On the 10th postoperative day the plasma ACTH level was less than 5 pg/ml, and the plasma cortisol level was less than 1 μg/dl. These data indicated that the total removal of the pituitary adenoma causing Cushing's disease had been achieved. The patient required glucocorticoid replacement. With regard to other pituitary hormones, the decrease in TSH was transient. The plasma GH and PRL levels decreased significantly and continued to be low. The plasma LH and FSH levels which were suppressed before the second operation increased significantly. The oral glucose tolerance test, which had showed diabetes mellitus before the second operation, demonstrated normal glucose tolerance.

On the 21st postoperative day leakage of cerebrospinal fluid was observed and a third operation was performed immediately. The sellar floor was reconstructed with abdominal subcutaneous fat and fascia, and transient diabetes insipidus occurred during the postoperative course.

The clinical signs of Cushing's syndrome disappeared. On the basis of the clinical symptoms, endocrinological evaluations and pathohistology, we concluded that the pituitary adenoma causing Cushing's disease had been removed, and the patient experienced complete remission.

**Discussion**

Cushing's disease is usually caused by an intrasellar ACTH-producing pituitary microadenoma, and the localization of the pituitary microadenoma is not confined to a specific area in the pituitary gland [13]. In addition, there is accumulating evidence that pituitary adenoma causing Cushing's disease is found in various extrasellar and intracranial regions [2-11]. Pituitary adenomas have been found within the sphenoid sinus [2-6], within the pituitary stalk [7, 8], in the supradiaphragmatic region [9], in the superior orbital fissure [10] and in the cavernous sinus [11]. Thus pituitary microadenomas causing Cushing's disease may be located not only in the sella turcica but also in extrasellar regions. To our knowledge the patient reported in this paper is the first case in which Cushing's disease was caused by suprasellar and extrasellar microadenoma, that originated in the anterior pituitary and extended upward without connecting to the stalk. Mason et al. reported 5 patients with ACTH-secreting pituitary microadenomas arising in the sella turcica and extending upward into the stalk [8]. Our case is similar to their cases as the pituitary microadenomas arose in the sella turcica and extended toward the suprasellar area, but our case is different because the pituitary microadenoma apparently originated in the so called anterior pituitary "pars distalis" and extended upward without connecting to the stalk. The microadenoma in our case was thought to extend upward through a narrow orifice in the diaphragma sellae with a little space between it and the stalk, and to grow over the diaphragma sellae. This resulted in a condition in which the whole mass was located in the supra- and extrasellar regions without connecting to the stalk.

In several institutions the initial remission rate after transsphenoidal microsurgery in cases preoperatively diagnosed with Cushing's disease is between 79 and 86% [1, 14, 15]. The rate of negative pituitary exploration was between 5 and 7% [1, 14], and the rate of postoperatively established extracranial ectopic ACTH-producing tumor was about 2% [1, 14]. In some patients with Cushing's disease and negative pituitary exploration, it is possible that the pituitary...
adenomas are localized adjacent to but outside the pituitary gland, that is to say in the pituitary stalk [7, 8], in the cavernous sinus [11] or in the supra- and extrasellar region as in our case. Although these cases are considered to be very rare, in order to cure Cushing’s disease we should be aware that pituitary adenomas may be present in unusual positions.

So far complete remission in almost all patients with Cushing’s disease has been accomplished by total removal of the pituitary adenoma. Transsphenoidal microsurgery has become widely accepted as an ideal method and a treatment primarily selected to achieve successful removal of pituitary microadenomas with preservation of normal pituitary function [1, 13–16]. In our case we failed to find the pituitary microadenoma in the first transsphenoidal operation. The negative exploration in the intrasellar region in the first operation raised the possibility of the presence of an extrasellar ACTH-producing tumor. We therefore decided to perform the second operation to remove the suprasellar mass despite the failure of the first operation, and the suprasellar mass seemed to be accessible either by the transsphenoidal or transcranial route. For complete remission of Cushing’s disease, it is very important to avoid the regrowth of adenoma cells left behind in the borderzone between the microadenoma and the normal pituitary gland, and complete peritumoral edge resection is sometimes imperative [12]. In our case, the borderzone was thought to be more easily accessible by the transsphenoidal route than the transcranial route. Accordingly, we again employed the transsphenoidal route in the second operation. Another reason why we again employed the transsphenoidal route is the MR imaging indicating that the suprasellar microadenoma was located significantly downward after the first operation as a result of excision of the normal anterior pituitary (Fig. 5).

In summary, we report the first case of Cushing’s disease caused by supra- and extrasellar microadenoma, which originated in the anterior pituitary and extended upward without connecting to the stalk. The pituitary microadenoma was completely removed by the transsphenoidal approach. To carry out successful surgical treatment of Cushing’s disease, it is necessary to take into consideration that pituitary adenoma causing Cushing’s disease may exist in such an unusual position.

References


