Full-Blown Cushing’s Disease after an Episode of Pituitary Apoplexy

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Abstract. The present study reports a rare case of full-blown Cushing’s disease several years after an episode of pituitary apoplexy. A 60 year-old woman complained of muscular weakness and generalized malaise. Ten years ago she had an episode of pituitary apoplexy. Diabetes mellitus was diagnosed at age 56, and thereafter she had been controlled her plasma glucose with diet therapy and oral hypoglycemic agents. She exhibited cushingoid feature of moon face and central obesity. Both plasma ACTH and serum cortisol levels were elevated to 170 pg/ml and 19.6 μg/dl, respectively. Dexamethasone suppression test showed that a large dose of 8 mg dexamethasone, but not a small dose of 2 mg, suppressed the pituitary-adrenocortical axis. CRH and methyrapone caused increases in plasma ACTH and serum cortisol levels. Brain T1-weighted magnetic resonance imaging depicted a low signal of pituitary tumor, which was not enhanced by gadolinium. The pituitary tumor was removed by transsphenoidal adenomectomy, and immunohistochemistry revealed an ACTH-producing adenoma. The evidence suggested the possibility that the two pituitary tumors with dormant period of several years were a recurrence of ACTH-producing tumors in the present patient.

Key words: ACTH, Pituitary adenoma, Recurrence

(Pituitary apoplexy can occur in pituitary tumors, such as GH-producing adenoma, prolactinoma and non-functioning adenoma, which can easily grow to occupy intrasellar space [1–10]. After pituitary apoplexy, pituitary function either remains to be normal [8] or falls into hypopituitarism [9–11], depending on the intensity of necrosis of normal pituitary tissue. In contrast, the pituitary adenoma in Cushing’s disease is usually a microadenoma [12, 13], and thus it is unlikely that the tumor will be damaged by circulatory distress. The recurrence of pituitary tumor from the remained pituitary tissue is theoretically possible [11, 14–16], but in our experience such a tumor is rare.

We report a rare case with Cushing’s disease, which manifested several years after an initial episode of pituitary apoplexy. In the present study, the relationship between the present pituitary tumor and the initial tumor and the related pituitary apoplexy is discussed.

Case Report

A 60 year-old woman was admitted to Jichi Medical School Omiya Medical Center complaining of muscular weakness and generalized malaise. She had menopause at age 49. She noticed reduced mental activity and short-term memory disturbance at age 50. She visited a physician, who pointed out enlargement of sella turcica in skull X-ray film, and pituitary apoplexy in magnetic resonance imaging (MRI), which probably came from a pituitary tumor (Fig. 1). The low signal at the bottom of sella turcica seemed to be
the remained pituitary tissue. At that time, pituitary hormones were determined; that is, serum prolactin level was 49 ng/ml, while the other pituitary hormones were in normal ranges. Her pituitary function thus was not deteriorated after the episode of pituitary apoplexy. Also, it was not suggested that there were symptoms or signs related to cushingoid feature or galactorrhea in her past history. She fell into manic state at age 52 and thereafter she had been followed with medication by a psychiatrist. At age 56 she was diagnosed with type 2 diabetes mellitus, and thereafter her plasma glucose was controlled with diet therapy and oral hypoglycemic agents. Her plasma glucose remained under fair control, as her hemoglobin A1c had been elevated to around 7–8% for the last 4 years. Since two years ago she complained of generalized malaise and muscular weakness. As she exhibited the feature of moon face and central obesity, function of pituitary-adrenocortical axis was determined. The point at which her cushingoid features became clinically overt can not be easily determined, but cushingoid feature seemed likely that they were emerging over a period of the last couple of years. Plasma ACTH levels were 160 pg/ml in the early morning and 130 pg/ml in the evening, and serum cortisol levels were 24.2 μg/dl in the early morning and 18.8 μg/dl in the evening. Serum GH level was 0.58 ng/ml; FSH, 24.3 mIU/ml; LH, 9.0 mIU/ml; TSH, 1.47 μU/ml; and prolactin, 5.8 ng/ml. Urinary excretions of 17-OHCS and 17-KS were 8.0 and 8.0 mg/day, respectively. Rapid and standard dexamethasone tests are summarized in Table 1. A large dose of 8 mg dexamethasone, but not a small dose of 2 mg, suppressed the pituitary-adrenocortical axis. Metyrapone caused an increase in plasma ACTH level. Also, CRH increased plasma ACTH level. There were normal responses of TSH, prolactin, FSH, LH and GH to the mixtures of TRH, LH-RH and insulin (Table 1). Skull X-ray film showed mild enlargement of sella turcica. Brain T1-weighted MRI depicted a low signal of pituitary tumor, size 10 × 15 × 13 mm, which was not enhanced by gadolinium (Fig. 2). Bone mineral density on lumbar vertebrae showed 0.336 gm/cm², a value 57.8% of that expected for her chronological age.

Clinical course

In May 2002 the pituitary tumor was resected by transnasal and transsphenoidal adenomectomy. Microscopically, the tumor cells were polygonal. They had almost round nuclei and slightly basophilic cytoplasm. Adenoma cells were polygonal. They had almost round nuclei and slightly basophilic cytoplasm. Adenoma cells were polygonal. They had almost round nuclei and slightly basophilic cytoplasms. Adenoma cells were polygonal. They had almost round nuclei and slightly basophilic cytoplasms. Ada...
cortisol was decreased to 1.3 μg/dl after 1 mg dexamethasone administration. Though the dose of oral hypoglycemic agents was markedly reduced, plasma glucose control was also improved as hemoglobin A1c was reduced to 5.5%.

**Discussion**

We demonstrated a case of full-blown Cushing’s disease which had the typical clinical features of central obesity, moon face, buffalo hump, reduced bone mineral density, hypertension and diabetes mellitus. Laboratory findings strongly supported ACTH-dependent adrenal hyperfunction, and T₁-weighted MRI showed a pituitary tumor that was 10 × 15 × 13 mm in size. ACTH-producing pituitary adenoma was further evident in immunohistochemistry using anti-ACTH antibody.

In the present study we found a rare case that had two occurrence of pituitary tumors in her history. Since Cushing’s disease occurred approximately several years after the episode of pituitary apoplexy, we focused on the relationship between these two occurrence of tumors. There were two possibilities: that is, either they represented the recurrence of Cushing’s disease, or they were independent of one another. The recurrence hypothesis could be the more acceptable, because the development of two independent tumors from the anterior pituitary in the same patient is quite rare even if it takes the time difference of approximately several years [11, 14, 17, 18]. In this case after the episode of pituitary apoplexy the residual ACTH-producing adenoma might have grown slowly to form the second tumor. It is known that if pituitary tumor becomes apoplexy its tumor size generally has to reach
to a certain size [1, 5]. Pituitary tumors such as prolactinoma, GH-producing adenoma or non-functioning adenomas seem likely to develop to macroadenomas, and thus these tumors could fall into pituitary apoplexy [1]. In most clinical settings ACTH-producing tumors are microadenoma when their clinical manifes-
tations become evident, and macroadenomas producing ACTH are rare [13, 15, 19–21]. The pituitary tumor was approximately 10 × 15 × 13 mm in size in the present study, that was not so small as the typical ACTH-producing tumor. This finding suggested that the former pituitary tumor, that it caused the apoplexy, could have grown to the extent, and that it is highly likely that the tumor was an ACTH-producing adenoma [22–25].

In contrast, we account several reasons why the present case was not consistent with the recurrence of Cushing’s disease. First, there are a few reports concerning pituitary apoplexy closely in relation to Cushing’s disease in the literature [22–25]. As mentioned above, ACTH-producing adenoma could be based on microadenoma in the pituitary [12]. Second, when the patient’s past history is carefully taken into account, there are no symptoms and signs in the occasion of the former episode similar to those of the present one. Third, when the pituitary apoplexy occurred, the patient consulted a physician. At that time, only serum prolactin level was elevated to 49 ng/ml, without any other changes in pituitary hormones. This might suggest that the former tumor was prolactinoma, because the hypothalamic lesion was excluded to elevate serum prolactin levels, and she had not taken any psychiatric drug at that time. However, there was no indication of galactorrhea during the episode of pituitary apoplexy.

Type 2 diabetes mellitus was initially found 4 years ago. Diet therapy and treatment with oral hypoglycemic agents were instituted, but her plasma glucose was only fairly controlled as hemoglobin A1c elevated to around 7–8%. After the adenomectomy for Cushing’s disease, her control of plasma glucose extremely improved. The dose of oral hypoglycemic agents could be markedly reduced, and hemoglobin A1c remained as low as 5.5%.

In conclusion, we demonstrated a rare case of full-blown Cushing’s disease occurring several years after an episode of pituitary apoplexy. The dormant period between the two disorders spanned at least several years. We discussed the relationship between the pituitary apoplexy and Cushing’s disease, and would suggest the possibility of the recurrence hypothesis in the present patient.

References


