NOTE

Corticotroph Cell Adenoma without Typical Manifestations of Cushing’s Disease Presenting with Cavernous Sinus Syndrome following Pituitary Apoplexy

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Abstract. This report presents a unique case of corticotroph cell adenoma in a 30-year-old man without acromegaly or features typical of Cushing's disease, who developed cavernous sinus syndrome following pituitary apoplexy. Magnetic resonance imaging revealed a large intrasellar/suprasellar mass with pituitary hemorrhage and extension of a hematoma to the anterior base of the skull. Urgent transnasal pituitary surgery revealed an acidophilic pituitary adenoma, with immunoreactivity for ACTH and GH and expression of proopiomelanocortin (POMC) and GH messenger ribonucleic acid (mRNA) demonstrated by in situ hybridization. To our knowledge, a silent corticotroph cell adenoma with GH production has never been reported. This type of adenoma may potentially enlarge and develop tumoral hemorrhage because it is free of endocrinological symptoms.

Key words: Cavernous sinus syndrome, Cushing’s disease

A silent adenoma is considered evidence of immunoreactive hormone production in tumor cells of a pituitary adenoma not associated with endocrine symptomatology [1]. Pituitary apoplexy is no longer considered an uncommon event, and is reported to occur in 1.5% to 27.7% of patients with pituitary adenomas [2-5]. However, pituitary apoplexy rarely develops in patients with Cushing's disease [2, 6, 7]. The clinical presentation of pituitary apoplexy ranges from no signs or symptoms to a neurosurgical emergency. Cavernous sinus syndrome, in which a pituitary adenoma extends laterally into the cavernous intracranial sinus, is an uncommon complication of pituitary apoplexy [8]. In addition, a pituitary adenoma producing both ACTH and GH is highly unusual [9-11]. We report a unique case of a 30-year-old man with corticotroph cell adenoma, without acromegaly or other features typical of Cushing's disease, who presented with cavernous sinus syndrome following pituitary apoplexy. Production of both ACTH and GH was confirmed in this case using immunohistochemistry and in situ hybridization.

Case Report

A 30-year-old man was admitted to our department with headache of sudden onset and visual dis-
turbance. Physical examination was performed; his height was 180 cm and body weight was 82 kg. He had no physical appearance of Cushing’s disease or acromegaly.

Neurological examination revealed blindness in the left eye and defect of the lateral visual field (temporal hemianopsia) in the right eye. A few hours later, he showed signs of left-sided cavernous sinus syndrome: exophthalmos, chemosis, and oculomotor nerve palsy (Fig. 1a).

Endocrinological examination showed a markedly elevated plasma ACTH level (3730 pg/ml, normal 9–52 pg/ml) and an elevated serum cortisol level (180 μg/dl, normal 4–18.3 μg/dl). Basal levels of other hormones were within normal limits: GH, 3.1 ng/ml (normal <5 ng/ml); insulin-like growth factor (IGF)-I, 250 ng/ml (normal 85–369 ng/ml); PRL, 2.4 ng/ml (normal 1.5–9.7 ng/ml); TSH, 2.8 μU/ml (normal 0.34–3.5 μU/ml); LH, 2.0 mIU/ml (normal 1.8–5.2 mIU/ml); FSH, 4.2 mIU/ml (normal 2.9–8.2 mIU/ml). Stimulation tests for anterior pituitary hormones were not performed because of the urgency of the situation.

Computer tomography (CT) revealed a large high-density mass in the intrasellar/suprasellar lesion (Fig. 2). Magnetic resonance imaging (MRI) demonstrated an intrasellar/suprasellar mass of constant intensity, with a hematoma extending to the anterior base of the skull (Fig. 3).

This patient underwent urgent transnasal-transsphenoidal surgery. After the fibrous tumor capsule was dissected, the soft yellow adenoma tissue and the hematoma which extended to the anterior base of the skull were removed using a micropressure suction-irrigation system with a micromirror [12]. After surgery, the patient’s left-sided cavernous sinus syn-

![Fig. 1. Photographs of patient showing cavernous sinus syndrome which developed a few hours after admission (a) and documenting complete disappearance of this condition at discharge (b).](image1)

![Fig. 2. Enhanced CT scan taken at admission, showing a dumbbell-shaped high-density mass, indicating pituitary hemorrhage.](image2)

![Fig. 3. Sagittal enhanced T1-weighted MRI at admission, showing an intrasellar-suprasellar mass with acute pituitary hemorrhage and a hematoma extending to the anterior base of the skull.](image3)
SILENT CORTICOTROPH ADENOMA WITH PITUITARY APOPLEXY

Discussion

This patient's case is unique with regard to the evolution of hemorrhage originating from the pituitary adenoma. Pituitary apoplexy, which can be isolated or associated with subarachnoid hemorrhage or intracerebral hemorrhage, is most commonly found with pituitary adenomas [5, 6]. Extension of the pituitary hemorrhage to a hematoma at the anterior base of the skull, such as in this case, though, is highly unusual.

The patient also developed cavernous sinus syndrome. Eyelid edema and proptosis, due to venous stasis within the orbit secondary to obliteration of the cavernous sinus, are rarely encountered [8]. Orbital ophthalmoplegia is well known to be caused by a sudden increase in tumor mass associated with pituitary hemorrhage [13] and is reported to be a consequence of tumor invasion of the cavernous sinus [14]. In the present case, these signs were presumed to be caused by rapid compression of the venous channel to the cavernous sinus secondary to pituitary apoplexy because ophthalmoplegia was not present, tumor invasion into the cavernous sinus was not observed in surgery, and these signs immediately resolved after surgery.

In this case, markedly elevated preoperative serum ACTH and cortisol levels seemed to be a transient phenomenon of acute illness because the patient did not display features typical of ACTH hypersecretion. Hormonal changes occur during acute episodes of pituitary apoplexy, as has been previously reported [15-17]. If this is the case, the elevated serum ACTH level may be the result of excess hormone released into the bloodstream from the pituitary adenoma upon its destruction. Also, stress-induced ACTH secretion may have participated in the elevation of ACTH level. It remains unknown why serum GH level was not elevated in this patient although the adenoma produced GH. As a possible reason, we speculate that the tumor may have been a bimor-
phous mixed pituitary adenoma composed of two separate cell types: one the major cell population that synthesized ACTH and the other a minority one of cell GH, although this is not confirmed.

Elevated serum ACTH in the present case does not seem to be attributable to biologically inactive “Big ACTH” [18] because preoperative serum cortisol level was also markedly elevated. The reason why this case with potentially high activity of ACTH did not demonstrate such clinical endocrine signs is not known. We suggest that one possibility of the cause of the “silence” may be a minor secretion of ACTH, such as seen in most silent corticotroph cell adenomas that demonstrate normal levels of serum ACTH and cortisol [18].

From primarily immunohistochemical analysis of pituitary adenomas, the most frequently found hormone combinations are: GH and PRL; GH, PRL, and the α-subunit of the glycoprotein hormones; and 3-TSH or FSH, LH, and the α-subunit [19]. This hormone combination of ACTH and GH, produced by a single adenoma with hormone-secreting symptoms, has also been previously reported [9-11]. However, to our knowledge, a silent corticotroph adenoma with GH production, such as in our case, has never been reported. Expression of both ACTH and GH was confirmed by in situ hybridization [20]. These findings may mean that ACTH and GH were not only stored but also produced by the adenoma cells. Based on the fact that pituitary adenomas are monoclonal in origin [21], our case is significant with regard to the histogenesis of pituitary adenomas. Further studies are necessary to clarify these points.

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181–186.


