A Case of Pituitary Adenoma Producing both Growth Hormone (GH) and Adrenocorticotropic Hormone (ACTH)

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Abstract. The authors report a very rare case of pituitary adenoma producing both GH and ACTH. A 29-year-old female was admitted with obesity, amenorrhea, acromegaly, hirsutism, excessive pigmentation, acne, and diabetes mellitus. Computed tomography revealed an intrasellar tumor 16 mm in height, with a destroyed sellar floor. The blood concentrations of GH, ACTH and cortisol were increased (GH: 92 ng/ml, ACTH: 94 pg/ml, cortisol: 18.3 µg/dl). No diurnal variation in the amount of cortisol was observed. The urinary 17-OHCS was suppressed by 8 mg but not by 2 mg of dexamethasone. A subtotal adenomectomy was then performed through the transsphenoidal approach, which led to a sufficient reduction of both blood GH and ACTH (cortisol). Histologically the tumor was an acidophilic pituitary adenoma. Immunoperoxidase staining showed diffuse GH and sporadic ACTH producing cells, but failed to show any cells producing both hormones. The electron micrograms of neoplastic cells showed the ultrastructural characteristics of respective GH and ACTH cells. Another increase in both GH and cortisol, which occurred 19 months after the operation, has been controlled by bromocriptine administration. This case may be the first reported case of a pituitary adenoma producing both GH and ACTH, not accompanied by prolactin (PRL) hypersecretion, which has been fully confirmed endocrinologically and histopathologically.

Key words: Acromegaly, Cushing's disease, Pituitary adenoma, Immunostaining.

IT IS WELL known that some cases of growth hormone (GH) producing pituitary adenoma may be present with hypersecretion of other anterior pituitary hormones such as prolactin (PRL) [1–3] or thyroid stimulating hormone (TSH) [4]. Immunohistochemically other anterior pituitary hormone producing cells can be detected among the GH producing cells. However, a case of GH secreting adenoma accompanied by excessive ACTH secretion is extremely rare. The authors report a rare case of pituitary adenoma which was found to secrete both GH and ACTH by endocrinological, immunohistochemical, and electron microscopic studies.

Case Report

A 29-year-old female was admitted in September, 1985 with the chief complaint being a change in her features. She had a history dating back 10 years of dysmenorrhea, obesity, hirsutism, excessive pigmentation, acne, and changes in her features. She was diagnosed as having diabetes...
mellitus at the age of 27, and had become amenorrheal one year before. On admission, she was overweight at 60.5 kg in weight and was 155 cm in height, but no truncal obesity was observed. Acromegalic features, excessive pigmentation, hirsutism, excessive sweating, and acral overgrowth were observed. Neurological and ophthalmological examinations were normal, as was the cardiovascular system.

**Endocrinological examination**

Basal levels of blood GH, ACTH and cortisol were increased (GH: 92 ng/ml, ACTH: 94 pg/ml, cortisol: 18.3 μg/dl) on admission, while the other anterior pituitary hormones were within the normal range (TSH: 1.0 μU/ml, PRL: 12 ng/ml, LH: 9.6 mIU/ml, FSH: 6.6 mIU/ml). Selective venous sampling, in which catheterization into the inferior petrosal sinus could not be achieved, revealed that the blood level of ACTH in the jugular vein was twice that in the cubital vein. A diabetic pattern was observed (fasting blood sugar: 180 mg/dl, 2 h: 334 mg/dl) during a 75 g oral glucose tolerance test in which the GH level did not fall. The blood GH level rose to six times the basal level following a 100 μg TRH (thyrotropin releasing hormone) injection. The diurnal change in cortisol disappeared.

Beside the increase in the basal urine 17-OHCS and 17-KS levels, the former was suppressed by 8 mg but not by 2 mg dexamethasone administration. Metyrapone 3 g p.o. administration and 37 μg of lisine-vasopressin injection doubled the blood ACTH and GH concentration, respectively. Bromocriptine reduced both hormone levels.

**Radiological examination**

Plain craniogram revealed prolongation of the superior branch of the mandible, enlargement of the supraorbital ridge, and thickening of the cranial vault. The sella turcica was enlarged with complete destruction of the sellar floor.

Enhanced coronal CT scan demonstrated a 16 mm-height intrasellar tumor which destroyed the seller floor (Fig. 2).

A I-131 cholesterol scintigram revealed no abnormal uptake in either adrenal gland.

In summary, the case was diagnosed as a GH secreting pituitary adenoma after the above mentioned studies. Although the main clinical manifestations were those of acromegaly, this tumor was believed to secrete ACTH concomitantly.

**Therapeutic course**

A large part of the tumor was removed through a transsphenoidal route. The tumor was uniformly

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Fig. 1. Preoperative endocrinological examinations.
Fig. 2. Preoperative coronal CT scan showing homogeneously enhanced tumor in the destructed sella turcica.

Fig. 3. Clinical course: Both blood GH and cortisol levels considerably reduced after the operation. The re-increase in both hormones, which occurred 19 months later, was controlled by bromocriptine administration. SM-C; somatomedine-C.
Fig. 4. a, HE stain revealing pituitary adenoma with sinusoid pattern. b, Immunoperoxidase staining revealing diffuse but faint GH producing cells. c, Immunoperoxidase staining revealing sporadic and distinct ACTH producing cells.
Fig. 5. a, Electron microgram showing that one of the majority of neoplastic cells, densely granulated GH cells, contains numerous secretory granules in the 300–600 nm diameter range. bar=1 μm. b, Immunostaining electron microgram with protein A gold confirmed the presence of GH in the secretory granules. bar=1 μm.
soft and milky white. After the operation, the blood concentrations of GH and ACTH (cortisol) were considerably reduced. Her diabetes mellitus could be controlled more easily and fasting blood sugar was normalized. She lost about 7 kg in one month after the operation.

About 19 months after the operation, however, she regained 19 kg and weighed 72 kg. Both blood GH and cortisol increased again without apparent tumor recurrence on a CT scan.

Subsequently bromocriptine administration (10 mg/day) was begun, and with its maintenance the blood levels of GH and cortisol have been normalized, with slight increases in cortisol and ACTH for several months without any particular reason.

Histopathology
Histological examination revealed an acidophilic pituitary adenoma of sinusoidal type (Fig. 4a). Immunoperoxidase staining with primary antisera (purchased from DAKO Chemical Products) revealed diffuse but faint GH positive cells (Fig. 4b), with sparse but distinct ACTH positive cells (Fig. 4c) among them. In the other anterior pituitary hormone (LH, PRL) positive cells were only rarely detected.

Figure 5a is an electron microgram of one of the majority type of tumor cells. It had a round or oval nucleus containing fine chromatin. The cytoplasm contained numerous secretory granules in the range of 300–600 nm diameter. Mitochondria and rough ER were well developed. These cells, which composed one third of the tumor cells, were classified into densely granulated growth hormone cells [5].

Somehow, microscopically the GH producing cells are not so distinct as ACTH secreting cells. However, electron microscopic gold immunostaining confirmed the presence of GH as the gold particles were seen in the secretary granules (Fig. 5b).

Figure 6 shows a classical ACTH cell in the tumor. The periphery of the cytoplasm contained secretory granules smaller than those of the GH cells. The so called type 1 microfilaments [6] were mainly around the nucleus.
Discussion

Endocrinologically and histologically, this case was diagnosed as a both GH and ACTH secreting pituitary adenoma. Multi-hormone secreting adenomas which produce more than one hormone have often been reported. It is particularly well known that some GH secreting adenomas hypersecrete prolactin, too [2, 3, 7]. The other combinations, such as GH and TSH [4], GH and α-subunit [8] ACTH and PRL [9], PRL and TSH [4], FSH and PRL [10] have been only occasionally reported. To our knowledge, there have been three reported cases of both GH and ACTH producing adenoma [11–13]. But all these cases were accompanied by prolactin hypersecretion. So this may be the first report of an adenoma hypersecreting only GH and ACTH.

In this case, were GH and ACTH produced by the single neoplastic cell type? The immunostaining revealed obviously different populations of each hormone producing cell. In addition, the immunostaining of the mirror section failed to show neoplastic cells definitely producing both hormones. It is therefore more probable that the two hormones were produced by different cell types.

One of the two characteristics of this case was that the GH responses to the dexamethasone suppression test, lysine-vasopressin test, metyrapone test and bromocriptine test were similar as those of ACTH (cortisol). So the two types of neoplastic cells may have the same membranous receptor, though we cannot assert it because of the lack of an in vitro study.

The reduction in the amount of ACTH in the bromocriptine test and normalization of cortisol levels by bromocriptine therapy suggested that the pathogenesis of this tumor might be due to a disturbance of the hypothalamic dopaminergic suppressive system, as Lamberts speculated [1].

The co-authors found that, immunohistochemically, at least one or more anterior pituitary hormones other than GH were observable in 41 out of 48 GH secreting adenoma tissues [14]. The most frequently detectable hormone was PRL (82.5%). LH, FSH, and TSH positive cells were seen in about half of the cases, while ACTH positive cells were seen in 25.0% of the cases. GH secreting adenoma may therefore be essentially designated as a plurihormone producing adenoma.

However, in almost all cases, no GH producing adenoma is present with the hypersecretion of other anterior pituitary hormones. Generally, this discrepancy may be attributed to the synthesis of biologically inactive hormone [15], minute amounts of hormone being produced, or the mis-secreting of secretory granules [16]. In addition, the extreme rarity of the GH and ACTH combination might be attributed to the suppressive effect of hypercorticism on GH secretion [17]. Furthermore, in this case, the pathognomonic symptoms of Cushing's disease, such as central obesity with thin extremities, were not seen in spite of a high blood cortisol level. This fact must be attributed to the mutually antagonistic effects of these hormones on protein and fat metabolism [18, 19]. The clinical diagnosis of both GH and ACTH producing adenoma might therefore be concealed by these antagonistic effects. More meticulous endocrinological and immunohistochemical examinations of the GH secreting adenoma cases may disclose the real incidence of this combination.

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