A Case of Pituitary Somatotroph Adenoma with Concomitant Secretion of Growth Hormone, Prolactin, and Adrenocorticotropic Hormone – An Adenoma Derived from Primordial Stem Cell, Studied by Immunohistochemistry, in situ Hybridization, and Cell Culture

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Summary

Somatotroph adenomas often secrete prolactin (PRL) besides growth hormone (GH) and are sometimes immunostained for other anterior pituitary hormones or their subunits, such as thyroid-stimulating hormone (TSH) β-subunit and glycoprotein hormone α-subunit (αSU). However, somatotroph adenomas showing hypersecretion of adrenocorticotropic hormone (ACTH) are extremely rare. There have been, to our knowledge, only five published reports on somatotroph adenomas accompanied by excessive ACTH secretion. Here we report a case of intracavernously invading somatotroph macro-adenoma with high serum GH, PRL, and ACTH levels. We examined the case using immunohistochemistry (IHC), in situ hybridization (ISH), and cell culture, and confirmed GH, PRL, and ACTH, as well as αSU, production, and the expression of Pit-1 protein by the adenoma, which is known as a transcriptional factor for GH, PRL, and TSH, not for ACTH. Therefore, the presence of unknown transcriptional factor other than Pit-1, common to GH, PRL, and ACTH, may be speculated to be expressed in this adenoma. In our previous study, we had found plurihormonal mRNA expression, especially for ACTH, the β-subunit of follicle-stimulating hormone and luteinizing hormone in some somatotroph adenomas, using non-radio-isotopic ISH, and suggested that these adenomas might be derived from plurihormonal primordial stem cells. Our present case is significant from the viewpoint of histogenesis of pituitary adenomas, because it further supports the cell origin of somatotroph adenomas from plurihormonal primordial stem cells, and moreover it suggests the presence of unknown transcriptional factor other than Pit-1, common to GH, PRL, and ACTH.

Keywords: Adrenocorticotropic hormone; hypersecretion; plurihormonal primordial stem cell; somatotroph adenoma.

Introduction

The anterior pituitary originates from Rathke’s pouch and the primordial anterior pituitary stem cells proliferate during the embryonic stage [14]. These primordial stem cells give rise to the acidophilic and basophilic cells that serve as precursors for various hormone-expressing cells [14]. The acidophils are the progenitors of both somatotrophs and lactotrophs, whereas the basophils give rise to cells that produce adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) [6]. Somatotroph adenomas have been considered to be derived from the acidophilic cell line, namely, somatotrophic, acidophilic stem and mammamastrotropic cells [12, 14]. Somatotroph adenomas often secrete prolactin (PRL) besides growth hormone (GH) and are sometimes immunostained for other anterior pituitary hormones or their subunits, such as TSH β-subunit and glycoprotein hormone α-subunit (αSU). However, somatotroph adenomas showing hypersecretion of ACTH are extremely rare. There have been, to our knowledge, only five published reports of somatotroph adenomas accompanied by excessive ACTH secretion [2, 5, 8, 21, 24]. We also experienced a case of somatotroph adenoma with high serum GH, PRL, and ACTH levels. In this paper, we describe the fea-
tures of this case revealed using immunohistochemistry, in situ hybridization (ISH), and cell culture, together with a histogenetic consideration of somatotroph adenomas whose hormonal gene expression is analysed using non-radioisotopic in situ hybridization.

**Case History and Histological Examination**

**Clinical History and Course**

A 27-year-old man was admitted to the University of Tokyo Hospital on April 13, 1994, with a four-year history of changes in his features, hyperhidrosis and enlarged feet. Physiological examination revealed an acromegalic face and enlarged hands and feet.

**Endocrinological examination:** Basal levels of serum GH and somatomedin-C (SMC) on admission were elevated, being 35.0 (normal range: < 1.46), 1,184.6 (100-315) ng/ml, respectively. Levels of PRL, ACTH, and cortisol (CS) were also elevated, being 1,082 (<30) ng/ml, 181 (<50) pg/ml, and 20.4 (7-16) μg/dl, respectively. An oral glucose tolerance test showed no suppression of GH values. A growth hormone releasing factor (GRF) stimulation test showed a slight response of GH secretion. Neither a thyrotropin releasing hormone (TRH) stimulation test nor a luteinizing releasing hormone (LHRH) stimulation test showed a paradoxical response of GH secretion. Oral intake of 2.5 mg bromocriptine reduced the serum GH and PRL levels, from 20.2 and 962 to 6.37 and 210 ng/ml, respectively, 6 hours after loading. Serum ACTH levels were elevated throughout the day, being 128, 88, 54, 63 pg/ml at 9, 13, 17, 21 o’clock, respectively. Urinary 17-ketosteroid (17-KS) was within the normal range and 17-hydroxycorticosteroid (17-OHCS) was remarkably elevated, at 15.3 mg/day (3.6-9.0). The levels of other anterior pituitary hormones were within the normal ranges and their reactions to stimulation tests were normal.

**Radiological examination:** A plain craniogram revealed an enlarged sella turcica, erosive changes in the sella floor, and thickening of the cranial vault. The heel pad was thickened, being 28 mm, and cauliflower-like changes were noticeable in the fingers. Computer-assisted tomography (CT) showed a relatively high density mass arising from the sella turcica, which was homogeneously enhanced with contrast material. T1-weighted magnetic resonance imaging (MRI) revealed an iso-intensity mass, which also showed iso-intensity on the T2-weighted image and was heterogeneously enhanced with gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA), with lateral invasion into the right cavernous sinus and encasement of the right internal carotid artery (Fig. 1 a).

On the basis of the clinical findings, the patient was diagnosed as having acromegaly with a somatotroph pituitary adenoma, which was considered to secrete PRL and ACTH concomitantly.

**Surgical treatment and postoperative course:** Transcranial surgery via the right pterional route was carried out on May 10. The anteromedial triangle (Dolenc’s triangle) of the cavernous sinus was opened between the lateral aspects of the optic nerve within the optic canal and the medial aspects of the oculomotor nerve within the sheath of dura entering the superior orbital fissure. The tumour around the internal carotid artery was removed subcapsularly. The lateral triangle of the cavernous sinus was also opened between the second and the third division of the right trigeminal nerve, and the laterally extending portion of the tumour was extensively removed. The postoperative MRI demonstrated that the major part of the tumour had been extirpated (Fig. 1 b). The elevated serum GH, PRL, and ACTH levels evaluated during surgery at 50% tumour removal were decreased to 23.8, 915 ng/ml and 44 pg/ml, respectively. Postoperative endocrinological studies, carried out 20 days