

# Double, Synchronous Pituitary Adenomas Causing Acromegaly and Cushing's Disease. A Case Report and Review of Literature

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**Abstract** Double pituitary adenomas are very rare and present up to 1 % of pituitary adenomas in unselected autopsy series and up to 2 % in large surgical series. We report a case of a 47-year-old man presented slight clinical features of acromegaly with 2 years duration. Endocrine evaluation confirmed active acromegaly and revealed adrenocorticotropin hormone-dependent hypercortisolemia. Preoperative magnetic resonance imaging of the pituitary demonstrated clearly separated double microadenomas with different intensity. The patient underwent transsphenoidal surgery and both tumors were completely removed and were fixed separately. The histological and ultrastructural examination confirmed coincidence of the double, clearly separated pituitary adenomas in one gland. Postoperative function of the hypothalamo-hypophyseal axis was normalized. We conclude from this case and a literature review that double endocrinologically active pituitary adenomas leading to acromegaly and Cushing's disease may occur. Additionally, a review of the literature regarding multiple pituitary adenomas has also been performed.

**Keywords** Double pituitary adenoma · Acromegaly · Cushing's disease · Immunohistochemistry · Electron microscopy · Magnetic resonance · Transsphenoidal surgery

## Introduction

Pituitary adenomas are usually benign epithelial tumors arising from and consisting of adenohypophyseal cells. They are most often slow growing, expansive tumors, confined to the sella turcica [1]. Pituitary adenomas can be diagnosed in every age group, but they are rarely found in prepubertal age. They comprise approximately 10–15 % of all intracranial tumors and cause typical clinical syndromes attributed to overproduction or insufficient secretion of hypophyseal hormones and/or local mass effects [2]. The vast majority of pituitary adenomas are monoclonal tumors which have hormone immunoreactivity and ultrastructural features of known adenohypophysial cell types [3]. Among them are plurihormonal tumors capable of producing two or more hormones that differ in immunoreactivity and biological effects [4, 5]. Exceptionally, truly multiple pituitary adenomas are recognized [6]. Authors present a case of double, clearly separated pituitary adenoma with different histological features causing Cushing's disease and acromegaly. Both tumors were recognized on preoperative MR imaging.

## Case Report

A 47-year-old male was admitted to the Neurosurgical Department with typical clinical features of acromegaly (enlarged doughy hands and feet, frontal bossing, coarsening of facial features with increased interdental spacing and prognathism, thickened lips, etc.) with 2 years duration. On admission to hospital, clinical examination showed oily

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skin, weight gain with central fat distribution, slight purple striae on the abdomen, and spontaneous ecchymosis. Patient's body weight was 117 kg and gained over 20 kg per last year. His height was 181 cm and body mass index (BMI) was 35.7 kg/m<sup>2</sup>. Observed central obesity was not typically cushingoid without moon face and buffalo hump. Patient's main complaints were progressive headaches, lowered mood, and decreased libido. His blood pressure was slightly elevated and controlled with antihypertensive drugs (selective beta blocker, ACE inhibitor and diuretic); measured in supine position was 130/90 mmHg. His pulse rate was 64 beats per minute. Neurological examination revealed no impairment of visual acuity and visual fields and intact function of other cranial nerves. Fundoscopic examination showed no optic nerve atrophy. The patient had neither family history of pituitary adenoma nor multiple endocrine neoplasia. Endocrine investigation revealed slightly elevated basal serum level of growth hormone (GH) and somatomedin-C (insulin-like growth factor-1) with abnormal oral glucose tolerance test (OGTT) and abnormal circadian rhythm of adrenocorticotropin hormone (ACTH) and cortisol (Table 1). The high dose dexamethasone suppression test (8 mg) markedly reduced the concentration of ACTH, cortisol, and its metabolites (17-OHCS and 17-KS) although this effect was not observed with low dose (1 mg) of dexamethason. Serum levels of GH and thyroid-stimulating hormone (TSH) were increased in response to an intravenous administration of thyrotropin-releasing hormone, as shown in Table 2. The preoperative serum prolactin (PRL) level was within normal limits—15.1 ng/ml. Other pituitary hormones including TSH and gonadotrophins (follicle-stimulating hormone (FSH) and

luteinizing hormone (LH)) were also within normal ranges. Intravenous administration of LH-RH caused increased secretion of LH, FSH, and PRL (Table 2). Serum level of testosterone was low but within normal limits. The function of the thyroid gland was normal and intact parathyroid hormone concentration was normal. Plain skull X-ray film showed slightly enlarged pituitary fossa with thickening of its floor without destruction of the dorsum sellae. Initial MR imaging of the sellar region (coronal and sagittal T1-weighted before Gd-DTPA administration) demonstrated a slightly enlarged and asymmetrical pituitary gland (Ryc 1). Coronal T1-weighted scan after administration of the contrast medium revealed a nonhomogenic region on the right side of the pituitary gland and a hypointensive area on its left side. Coronal T2-weighted MR visualized a hyperintensive signal of the smaller microadenoma on the right side, close to the right cavernous sinus, and a nonhomogenic region on the left side. Preoperative MR imaging suggested the presence of two different tumors in the sella. Both of them are intrasellar microadenomas without cavernous sinus invasion (Fig. 1).

Both, endocrine investigation and neuroimaging of the pituitary gland strongly indicated coincidence of two different (double) pituitary tumors causing acromegaly and Cushing's disease. No additional invasive diagnostic procedures (bilateral inferior petrosal sinus or cavernous sinus sampling) were performed.

The patient underwent transsphenoidal operation. During the surgery, the sella was exposed and the H-shaped incision of the dura was made. The dura mater was opened and separated from the pituitary capsule to expose the entire anterior surface of the pituitary. Then the gland was carefully explored, regardless of MRI findings. Preoperative suggestion

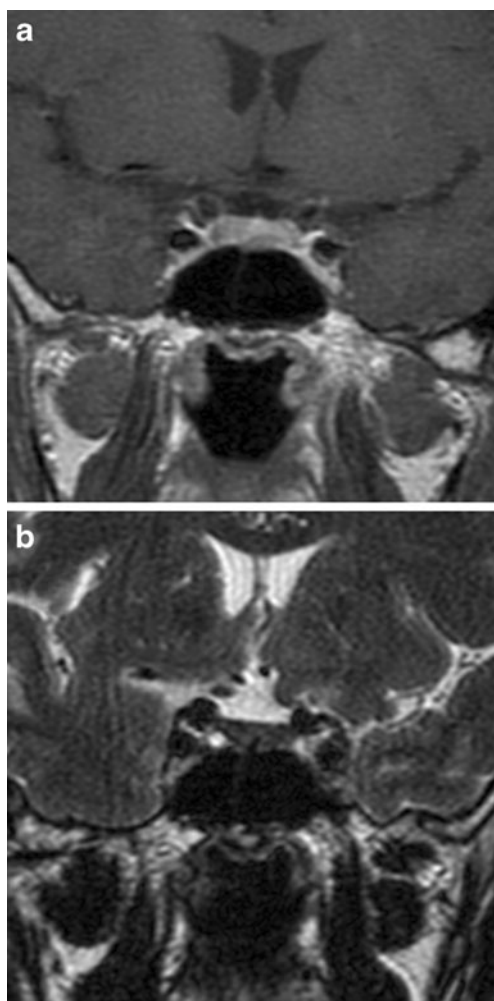
**Table 1** Preoperative hormonal test values

	Measured value			Reference range
GH	5.42 µg/l			<5 µg/l
IGF-I	608 µg/l			180–325 µg/l
ACTH	68.8 pg/ml	66.4 pg/ml		<60 pg/ml
kortyzol	20.7 µg/dl	16.2 µg/dl		7–25 µg/dl
24-HourUFC	197 ng/24h...213 ng/24h			13.8–75.3 ng/24h
LDDST	8.86 µg/dl			
HDDST–kortyzol	20.7 µg/dl	4.2	2.48	
HDDST–17-OHCS	21.1 mg/d	11.2	5.7	
HDDST–17-KS	30.2 mg/d	15.9	10.8	
TSH	1.01 mIU/ml			0.3–3.5 mIU/ml
ft4	1.49 ng/dl			0.8–2.0 ng/dl
LH	1.12 mIU/ml			0.8–7.6 mIU/ml
FSH	5.01 mIU/ml			0.7–11.1 mIU/ml
PRL	15.1 ng/ml...MTC 60'...30.2 ng/ml			<20 ng/ml
Testosteron	278 ng/ml			262–1,593 ng/ml

**Table 2** Hormone loading test results

	0 Min	30 Min	60 Min
LHRH test			
LH (mIU/ml)	1.12	10.9	9.54
FSH (mIU/ml)	5.01	8.77	9.87
TRH test			
GH (ng/ml)	3.6	4.32	4.17
PRL (ng/ml)	11.8	24.6	22.3
TSH (mIU/ml)	1.5	7.26	6.22

about the presence of two different, clearly separated tumors was confirmed. The mass on the left side of the sella was yellowish, fibrous, and compact and that on the right side was creamy, soft, and brittle. Both tumors were separated by



**Fig. 1** MR imaging of the sellar region demonstrated a slightly enlarged and asymmetrical pituitary gland. **a** Coronal T1-weighted after Gd-DTPA administration—a nonhomogeneous region on the right side of the pituitary gland and a hypointensive area on its left side near the sellar floor. **b** Coronal T2-weighted—a hyperintensive signal of the smaller microadenoma on the right side, close to the right cavernous sinus and a nonhomogeneous region on the left side

normal pituitary tissue. Excised lesions were fixed separately for further histological examination.

### Pathomorphological Methods

Material was fixed in 10 % formalin, embedded in paraffin, and routinely stained with hematoxylin and eosin (H&E). Immunohistochemical staining was performed on paraffin-embedded specimens according to the labeled EnVision Flex Visualization System (Dako, K8000) with DAB as chromogen using antibodies against anterior pituitary hormones or subunits: prolactin (PRL, dilution 1:200), growth hormone (GH, dilution 1:500), ACTH (dilution 1:500),  $\beta$ -TSH (dilution 1:200),  $\beta$ -FSH (dilution 1:500),  $\beta$ -LH (dilution 1:200)—all antibodies from Neo Markers; the glycoprotein  $\alpha$ -subunit (dilution 1:100, Novocastra); somatostatin receptors: sstr2A and sstr5 (dilution 1:1500, BioTrend) and Ki-67 (MIB1 clone)—from Dako. MIB-1 labeling index was established.

For electron microscopy, small pieces of tissue were fixed in 2.5 % cold glutaraldehyde, washed in cacodylate buffer, postfixed in 1 % osmium tetroxide, dehydrated in a graded series of ethanol, and embedded in Epon 812. Ultrathin sections were counterstained with uranyl acetate and lead citrate and examined with a Philips CM120 BioTWIN electron microscope (Fig. 2).

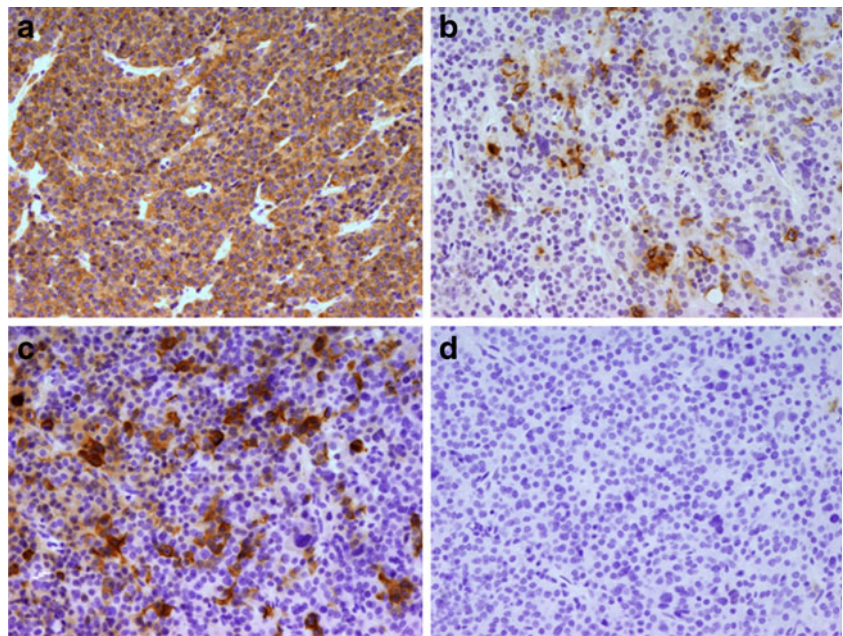
### Results

#### Histology, Immunohistochemistry, and Ultrastructure

The pathological examination revealed two separate pituitary adenomas showing different histological, immunohistochemical, and ultrastructural features.

At light microscopy, the tumor removed from the left side of the sella was insignificantly acidophilic, with a diffuse pattern. The cells were slightly pleomorphic, medium-sized, and partly angular. The round to oval nuclei showed mild nuclear atypia, single nucleoli, and moderate heterochromatin. Mitoses were very rare and <1 % of nuclei were MIB1-positive. Immunohistochemistry demonstrated strong and diffuse cytoplasmic positivity for GH, a scant positive staining for PRL and immunopositivity for  $\alpha$ -subunit in >20 % of cells. This tumor was immunonegative for ACTH, TSH, FSH, and LH. Tumor cells were strongly immunopositive at the cell membranes for somatostatin receptor sstr2A and weakly, cytoplasmic positive for sstr5. Ultrastructural examination confirmed presence of densely granulated somatotroph (GH cell) adenoma. The rough endoplasmic reticulum and the Golgi apparatus were moderately developed. Cells had relatively increased number of irregular mitochondria, scattered enlarged endosomes, and

**Fig. 2** Immunohistochemistry in the somatotroph tumor (left side of the sella). Positive staining for: GH (a), PRL (b) and  $\alpha$  subunit (c), and negative for ACTH (d). Original magnification,  $\times 200$

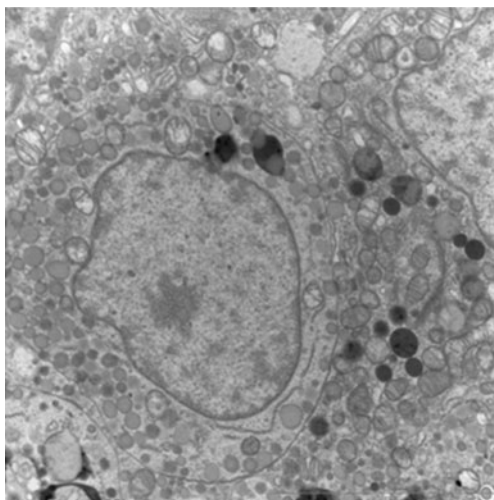


numerous spherical lysosomes. Medium-sized (250–450 nm), round to oval secretory granules with medium electron density were very numerous. Secretory granules were often noticed in cytoplasmic processes (Fig. 3).

The other tumor at the right side of the sella was basophilic adenoma with cellular pleomorphism. Histologically this tumor consisted of oval to polygonal cells with pleomorphic nuclei and often multiple nucleoli. The cells were mainly arranged in a diffused and partly palisading, or sinusoidal growth pattern. Mitotic figures were very rare and the Ki-67 nuclear labeling index (clone MIB-1) was  $<1\%$ . Immunohistochemistry demonstrated plurihormonal adenoma with intense cytoplasmic staining for ACTH. A moderate number of LH- and  $\alpha$ -subunit-positive cells ( $>30\%$ ) were

detected in a scattered distribution. The remaining adenohypophysial hormones were immunonegative.

Ultrastructural examination revealed presence of monomorphic, sparsely granulated corticotroph pituitary adenoma. This adenoma was composed of cells that had oval or angular morphology with irregular nuclei containing large conspicuous nucleoli. The rough endoplasmic reticulum and Golgi were well developed but slightly irregular. Some cells exhibited enlarged mitochondria with disrupted cristae and scattered enlarged lysosomes. The secretory granules were pleomorphic in shape and tended to accumulate along the cell membrane. Two kinds of granules were revealed: (1) pleomorphic, high electron dense, measuring 200–450 nm in size and (2) round and small (about 150 nm in diameter), with lower electron density. No bundling of intermediate filaments was observed.



**Fig. 3** Ultrastructure of densely granulated somatotroph adenoma. Original magnification,  $\times 9,700$

#### Clinical Results

The postoperative course was uneventful. Early morning postoperative serum cortisol level, measured on the first day after surgery, was below  $1\ \mu\text{g/dl}$ . Typical replacement therapy with intravenous hydrocortisone was started and then the standard dose: 20 mg in the morning and 10 mg at 3.00 p.m. p.o. was administered and continued until the next hormonal evaluation. There were no diabetes insipidus and any water electrolyte disturbance, especially hyponatremia. Patient was discharged from neurosurgical department on the fourth postoperative day and transferred to the endocrinological outpatient clinic.

Postoperative (3 months after surgery) serum GH level was  $0.791\ \mu\text{g/l}$  and the OGTT was below  $0.4\ \mu\text{g/l}$ . The serum IGF-I level was  $120\ \mu\text{g/l}$  (within normal age- and

**Table 3** Postoperative hormonal values

	Endocrinological evaluation three months after surgery			
	30'	60'	90'	120'
GH	0.791 ng/ml			
OGTT	1.23	0.356	0.065	0.246
ACTH	12.0 pg/ml		1.03 pg/ml	
kortyzol	3.3 µg/dl		1.37 µg/dl	
Test z Synactenem	1.54 µg/dl		13,8 µg/dl	
TSH	1.71 mIU/ml			
ft4	1.42 ng/dl			
LH	4.29 mIU/ml			
FSH	4.8 mIU/ml			
PRL	8.74 ng/ml			
Testosteron	445 ng/ml			

sex-related range; Table 3). Postoperative serum (1.3 µg/dl) and urinary (12.8 µg/24 h) cortisol levels were low, as well. The patient was on hydrocortisone replacement therapy for at least 18 months. After that time, regular function of the pituitary–adrenal axis was restored and replacement therapy was withdrawn. During the overnight oral 1-mg dexamethasone suppression test, serum cortisol level was suppressed below 1.8 µg/dl. During follow-up, patient's thyroid function was normal. There were no hypogonadism. His serum levels of gonadotropins (FSH and LH) were within normal range. Postoperative PRL serum level was also normal (PRL, 8.74 ng/ml). There were no remnants of the tumors on the postoperative MR scans carried out after 6 months. Laboratory evaluation carried out 4 years after surgery

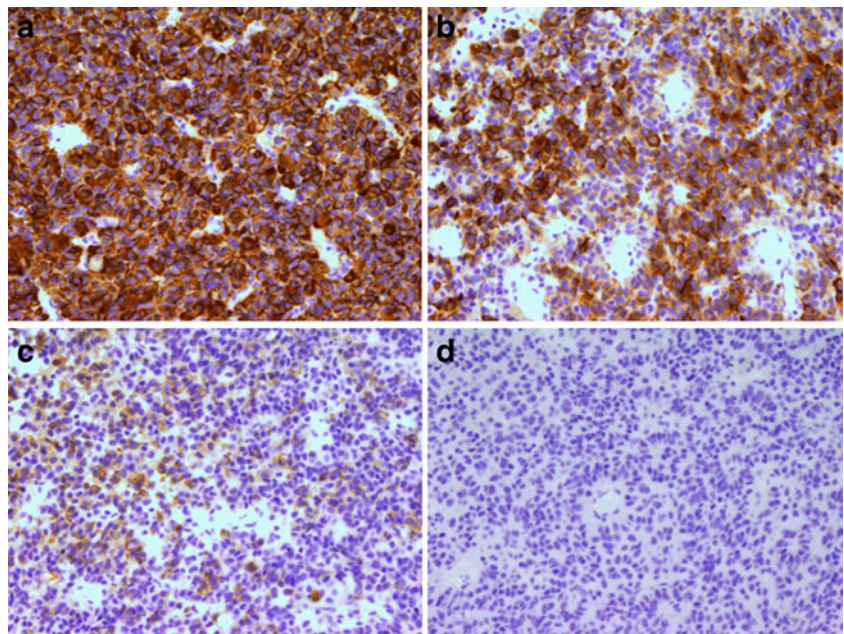
confirmed normal pituitary function. There were no hypocorticism, hypothyroidism, and hypogonadism. During the follow-up period (6 years), the patient's pituitary function has been normal and we have not observed pituitary adenomas regrowth on the MR imaging (Fig. 4).

## Discussion

Multiple pituitary adenomas are defined as two or more simultaneous adenomas with distinct light microscopic and immunohistochemical features in a single gland [6]. They are classified as clearly separated tumors visible at preoperative imaging or during surgical exploration and contiguous adenomas which might be recognized only by pathologist [7]. From the clinical point of view, it should be stressed that multiple pituitary lesions are very rare. These tumors usually are microadenomas and most of them are clinically silent. Their incidence was evaluated at 0.9–1 % in unselected autopsy series [1, 8]. Kontogeorgos et al. identified 20 (4.26 %) cases of multiple adenomas in 470 pituitary autopsies [8]. Buurman and Seager found multiple adenomas in 17 (5.4 %) out of 316 studied autopsies [9]. Surgical case reports presented their rate at 0.2–1.8 % [10–12]. Kontogeorgos et al. in a study of 3,000 surgically removed pituitary tumors reported 11 cases (0.36 %) synchronous detected of more than one pituitary adenoma in one gland [6].

Most of the presented multiple adenomas were found in acromegalic patients. Kontogeorgos et al. have noted seven GH-secreting pituitary tumors out of 12 cases of double pituitary adenomas [6, 8]. Another six cases have been described by Sano et al. [11]. The majority of double

**Fig. 4** Immunohistochemistry in the corticotroph tumor (right side of the sella). Positive staining for: ACTH (a), LH (b), and  $\alpha$  subunit (c), and negative for GH (d). Original magnification,  $\times 200$



adenomas were composed of somatotropinoma and prolactin-secreting or nonfunctioning adenomas [10, 13, 14].

However, one should remember that multiple adenomas might occur at increased frequency in patients with Cushing's disease, as well. A study by Ratliff and Oldfield found double pituitary adenomas in 13 of 660 operated patients, 11 of which were detected in patients with Cushing's disease [12]. Meij et al. reported three cases of double pituitary lesions in patients with Cushing's disease [15]. Two out of three patients harboring double pituitary tumors reported by McKelvie presented ACTH-dependant hypercortisolemia [16]. Rotondo and coworkers presented very interesting and rare case of double, separate adenomas with different histological and immunohistochemical features, one of which demonstrating immunopositivity for ACTH and the second for LH and alpha subunit [17]. There is only one known case of double clearly separated pituitary adenomas both secreting ACTH [7]. The most common incidental lesions coexisting with ACTH-secreting adenoma were prolactinomas [12].

Multiple pituitary adenomas ordinarily occur simultaneously. Thodou et al. presented a metachronous double adenomas which have been occurred in the same patient [18].

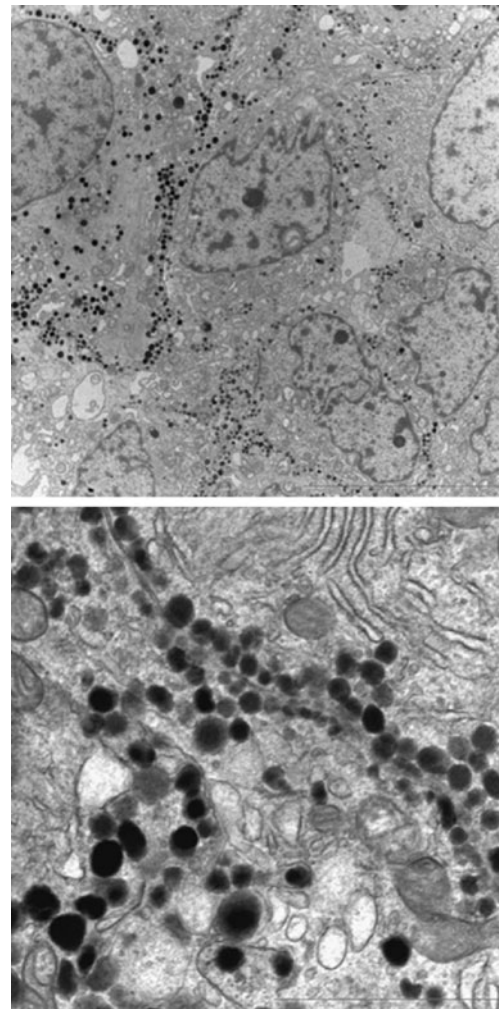
The pathogenesis of multiple pituitary adenomas remains unknown [10, 17]. In normal pituitary gland, pluripotent progenitor cell differentiates into three different lineages that produce POMC (ACTH), FSH-LH, and GH-PRL-TSH [19]. Several genetic abnormalities (e.g., mutation of Gs protein) might be involved in their transformation (oncogenesis) to the hyperplastic or adenomatous cells [20]. Autocrine/paracrine interactions may participate in the mechanisms underlying the development of the adenoma [10]. Altered hypothalamic function may play a role in pituitary tumorigenesis, as well [1, 2, 21]. Multiple adenomas may also be the result of the incidental occurrence of two or more monoclonal pituitary tumors [10]. Further molecular studies are indispensable to explain the pathogenesis of multiple pituitary adenomas and mechanisms of their multidirectional phenotypic differentiation.

There is not much information about detection of the multiple pituitary adenomas on preoperative MR images [12]. It is well known that the precise preoperative MR localization of a pituitary microadenoma is associated with greater efficacy of operative treatment and lack of such localization might be associate with surgical failure, especially in Cushing's disease and multiple pituitary tumors [22]. The identification of pituitary microadenomas is difficult because the diameter of some tumors is usually below MRI resolution [8, 12, 15]. Modern MR imaging offers greater sensitivity in the detection of pituitary tumors.

Dynamic MR imaging is considered to improve detection of minute pituitary adenoma, but Tabarin et al. reported no

significant differences between diagnostic accuracy of standard and dynamic MRI techniques [23]. Patronas et al. presented superior sensitivity and diagnostic accuracy of the spoiled gradient recalled acquisition in the steady state MRI technique compared with the spin echo (SE) MRI technique in the detection of the corticotroph microadenomas (80 vs.49 %) [24]. Ikeda et al. have recently confirmed a usefulness of the MET-PET/3.0-T MR imaging in the detection of ACTH-secreting pituitary adenomas and its higher sensitivity than other neuroradiological imaging techniques such as MR imaging, dynamic MR imaging, and CT scanning [25]. Stobo et al. have proved the applicability of 3.0 T MRI for detection of hormonally active pituitary microadenomas not visible in 1.5 T MR imaging lately [26].

We detected both tumors on preoperative scanning using high-resolution 1.5 T MRI, T2-weighted, pre- and postcontrast T1-weighted SE technique. In those cases, in



**Fig. 5** Electron microscopy image of plurihormonal/corticotroph adenoma. **a** Low power view of polygonal cells with irregular nuclei and well developed organelles. Original magnification,  $\times 4,700$ . **b** Higher magnification: variability in the size and electron density of granules. Original magnification,  $\times 24,500$

which pituitary lesion is not precisely localized, intraoperative ultrasonography seems to be useful for demonstration the presence of minute adenomas or simultaneous double or multiple pituitary tumors and therefore might improve the efficacy of transsphenoidal surgery. Watson et al. reported the usefulness of this technique for the visualization of the pituitary microadenomas that are not evident on preoperative MR scans in patients with Cushing's disease [27]. Arita and coworkers found this technique capable for demonstration entire pituitary gland and its tumor, pituitary stalk, optic chiasm, and cavernous sinus invasion in patients with small adenomas [28].

In our material of more than 2,600 cases of surgically treated pituitary tumors, we recognized six "double simultaneously coexisting pituitary adenomas". Herein, we present clinical data on a case of unusual double microadenomas which were recognized and precisely localized on preoperative MR imaging and were confirmed during surgery and on histological examination.

In our case, both tumors were clinically active. The signs and symptoms of acromegaly and Cushing's disease occurred simultaneously but somatic features of acromegaly were recognized earlier. ACTH-dependant hypercortisolemia was confirmed preoperatively by scrupulous laboratory investigation. The diagnosis was based on biochemical evidence and preoperative endocrinological testing according to current guidelines [29, 30]. Initial MR imaging showed two distinct pituitary microadenomas. Both endocrine investigation and neuroimaging of the pituitary gland strongly indicated coincidence of two different (double) pituitary tumors causing acromegaly and Cushing's disease and therefore no additional invasive diagnostic procedures (bilateral inferior petrosal sinus or cavernous sinus sampling) were performed. Our suspicion was confirmed during surgery and pathological examination.

Plurihormonality is rarely seen in corticotroph and gonadotroph adenomas [31]. Ikeda et al. suggested that gonadotroph adenomas occasionally produce ACTH in amounts capable of inducing Cushing's disease [32]. We demonstrated in the tumor removed from the right side of the sella the ultrastructurally confirmed sparsely granulated corticotroph adenoma with immunohistochemical evidence of LH and alpha subunit. Monomorphic cells contained two types of granules: polymorphic with high electron density, resembled those of normal corticotrophs and round, smaller, with lower electron density granules (Fig. 5).

The first published case of two synchronous pituitary adenomas causing Cushing's disease and acromegaly was presented by Blevins et al. [33]. However, coexistence of Cushing's disease and acromegaly has been reported in several another patients harboring pituitary adenomas with concomitant secretion of GH and ACTH [34–36]. Furthermore, it should be stressed that co-occurrence of acromegaly and hypercortisolemia might be a consequence of coexistence of the GH-secreting pituitary adenoma and adrenal tumor/nodular adrenal hyperplasia or ACTH-secreting bronchial carcinoid [37–39]. Those extremely rare

coincidences are very important from the surgical point of view and responsible for treatment failure [11, 12, 14, 40, 41]. They could be an unusual cause of failure of medical therapy for PRL-secreting pituitary adenoma, as well [42].

## Conclusions

1. Scrupulous preoperative endocrinological examination has to be performed in every case of pituitary adenoma, especially functioning tumors.
2. Precised evaluation of preoperative MR imaging is mandatory in every case of pituitary lesion.
3. Extensive surgical exploration of the sella has to be thorough in order to avoid surgical failures.
4. Histopathological examination of the removed tissue according WHO recommendation should be mandatory. The immunohistochemical methods and/or ultrastructural analysis are required to confirm an exact diagnosis of the multiple pituitary adenomas.
5. Scrupulous follow-up is recommended for all patients after successful surgical removal of hormonally active pituitary tumors. It plays an important role in confirmation the diagnosis and further observation to distinguish "cured patients" from those with "apparent remission"

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