

## Case report

# Rare case of Cushing's disease due to double ACTH-producing adenomas, one located in the pituitary gland and one into the stalk

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### ABSTRACT

We describe a patient affected by Cushing's disease due to the presence of double pituitary adenomas, one located within the anterior pituitary and the other in the infundibulum associated with a remnant of Rathke's pouch. Cure was achieved only after the infundibulum lesion was surgically removed. **CASE REPORT:** A 38-year-old female presented with unexplained weight gain, hirsutism, amenorrhea, asthenia, recurrent cutaneous mycotic infections and alopecia. Hormonal studies indicated Cushing's disease and MRI showed an enlarged pituitary gland with a marked and homogeneous enhancement after injection of gadolinium and an enlarged infundibulum with a maximum diameter of 8 mm. As a venous sampling of the inferior petrosal sinus after 10 µg iv desmopressin stimulation revealed a central to peripheral ACTH ratio consistent with a pituitary ACTH-secreting tumor, transphenoidal explorative surgery was performed and a 4-mm pituitary adenoma immunopositive for ACTH was disclosed and removed. Since postoperative hormonal evaluation showed persistent hypercortisolism, confirmed by dynamic tests, the patient again underwent surgery by transcranial access and the infundibulum mass was removed. Histology and immunochemistry were consistent with an ACTH-secreting adenoma. A few months after the second operation, cushingoid features were significantly reverted and symptoms improved. **CONCLUSION:** Although Cushing's patients bearing multiple adenomas have already been documented, the presence of two adenomas both immunohistochemically positive for ACTH is a very rare cause of Cushing's disease and this is the first report of a case of double ACTH-producing adenomas, one located in the pituitary gland and one attached to the stalk.

**Key words:** Cushing's disease, Double ACTH-producing adenomas, Magnetic resonance imaging, Pituitary stalk

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Received: 12-11-2012, Accepted: 14-6-2013

## INTRODUCTION

Multiple pituitary adenomas are defined as simultaneous, morphologically or immunocytologically, distinct tumors<sup>1</sup> and are classified as *contiguous* and *clearly separated double tumors*. These tumors are rarely detected among surgical specimens (0.004-0.01%), the most frequent clinical manifestation in the reported patients being acromegaly.<sup>2</sup> The diagnosis of double pituitary adenomas is, in most cases, based on histopathologic examination, since preoperative evaluation and MRI are able to identify multiple adenomas in only a few cases. These adenomas can belong to the same or to different hormone groups, making different combinations possible: ACTH-PRL secreting tumors appear to be the most common, followed by GH-non functioning adenomas and GH-PRL adenomas.<sup>2</sup> Herein we describe, to the best of our knowledge, the first case in the recent literature of a middle-aged woman with Cushing's disease due to double adenomas, one located within the anterior pituitary and the other in the infundibulum.

## CASE PRESENTATION

A 38-year-old woman was referred to our Endocrinology Unit as she had shown over the last three years progressive unexplained weight gain (>25 Kg bw) and hirsutism. Secondary amenorrhea had been present for six months. A polycystic ovary syndrome had been previously diagnosed and she was enrolled in a weight reduction program, without, however, any improvement. Moreover, one year before she developed typical hypercortisolemic clinical features including weight gain, depression, alopecia, profound asthenia, recurrent cutaneous micotic infections. She denied current use of alcohol. She did not suffer from other multiple endocrine neoplasia (MEN1) or Carney complex clinical manifestations.

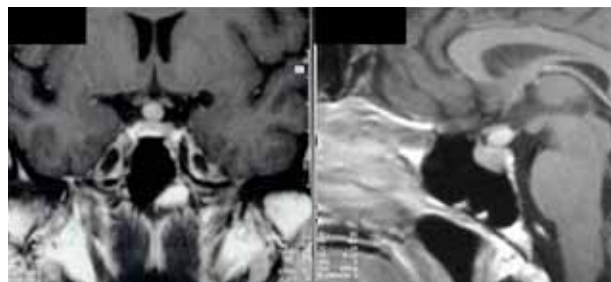
On physical examination, vital signs were normal, weight was 90 kg and height was 169 cm (BMI 31.5 kg/m<sup>2</sup>). Other clinical signs, e.g. moon face with mild plethora, truncal obesity, alopecia, thin skin with many bruises and abdominal striae, suggested the presence of Cushing's syndrome.

Her morning plasma ACTH and serum cortisol levels were 40-70 pg/ml and 497-821 nmol/L, respec-

tively. Both overnight low dose (1 mg) dexamethasone (DXM) and low dose (2 mg for 2 days) DXM test showed an inadequate suppression of her serum cortisol (390 nmol/L/dl and 355 nmol/L, respectively; normal suppression <50 nmol/L). Hypercortisolism was further confirmed by elevated urinary free cortisol (407-960 nmol/24h; normal range 35-275 nmol/24h). High dose dexamethasone suppression test (8+8 mg for 2 days) revealed suppression of both serum cortisol (from 868 to 108 nmol/L) and UFC (urinal free cortisol) levels (from 960 to 59 nmol/24h). A corticotropin releasing hormone test (CRH; 1 mcg/kg bw) revealed greatly increased levels of both cortisol and ACTH (by +76% and +92%, respectively, over baseline).

A positive response to ACTH (from 43 to 112 pg/ml, +160%) and cortisol levels (from 507 to 757 nmol/L, +49%) was found also after desmopressin stimulation (DDAVP; 10 mcg i.v.).

Magnetic resonance imaging (MRI) of the hypothalamic-pituitary region revealed an enlarged pituitary gland with a marked and homogeneous enhancement after gadolinium i.v. Indeed, the infundibulum was enlarged with a maximum diameter of 8 mm and impinged on the optic chiasm (Figure 1). Visual field evaluation revealed a minimal peripheral loss. As MRI did not identify a typical intrapituitary tumor, the patient underwent bilateral inferior petrosal sinus sampling during desmopressin stimulation. The central to peripheral ratio of ACTH was 6.17 on the



**Figure 1.** On the left, coronal T1-weighted, contrast-enhanced MR imaging showing a rounded mass located at the level of the pituitary stalk, over the pituitary gland, that appears intact; on the right, sagittal T1-weighted, contrast-enhanced MR imaging confirming the presence of a round mass located at the level of the pituitary stalk, over the pituitary gland, which in this plane seems enlarged in volume.

left side after desmopressin, suggesting a possible corticotropinoma on that side. No pituitary hormones deficiencies were present.

The patient underwent transsphenoidal surgery to search for an intrapituitary microadenoma. After careful exploration of the pituitary gland, a grey soft tumor was identified and completely removed. The surgical specimen consisted of 4 mm of tissue and microscopically showed fragments of pituitary adenoma. The adenoma cells were immunoreactive for ACTH (Figure 2A) and immunonegative for LH, FSH, GH, PRL and chromogranin A.

Despite these findings, postoperative hormonal evaluation showed persistent hypercortisolism.

Thereafter, based on the preoperative MRI findings, we strongly suspected that the lesion observed in the enlarged infundibulum might be a further source of ACTH secretion. Thus, one month later the patient underwent a second operation in order to remove the infundibulum lesion by transcranial access. Histological examination revealed remnants of Rathke's pouch associated with a pituitary microadenoma. Immunohistochemical staining again

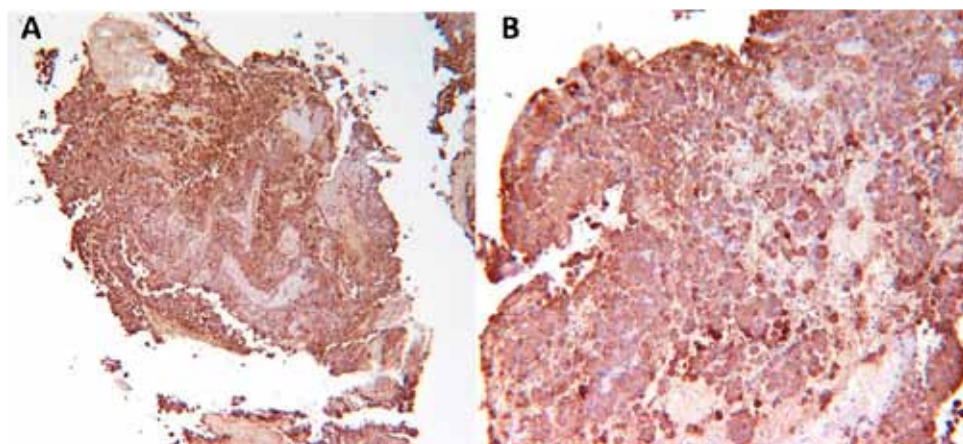
demonstrated a positive reaction for ACTH (Figure 2B) and negative ones for LH, FSH, PRL, GH and chromogranin A.

Soon after the operation, ACTH and cortisol levels decreased to 4-7 pg/ml and 11-57 nmol/L, respectively, (Table 1). In the subsequent days, weakness, fatigue, hypotension and skin pallor, indicative of a hypoadrenal condition, progressively ensued. As signs of central hypopituitarism (LH <0.1 mIU/ml, FSH <0.1 mIU/ml, TSH 0.01  $\mu$ UI/ml) appeared, hormonal replacement therapy was initiated, including cortisone acetate, l-thyroxine, desmopressin and estrogenic therapy.

## DISCUSSION

We herein describe a patient with Cushing's disease due to the presence of two ACTH-secreting adenomas, one located within the anterior pituitary and the other in the infundibulum.

Very recently, an incidence of 2.6% of double pituitary adenomas in an unselected surgical series of 117 patients undergoing surgery for pituitary adenoma was reported.<sup>3</sup> Previously, Kontogeorgos et al<sup>4</sup>



**Figure 2.** A: Intrapituitary microadenoma: adenomatous cells with positive immunohistochemistry for ACTH (4 $\times$ ); B: Adenoma attached to the stalk: adenomatous cells with positive immunostaining for ACTH (10 $\times$ ).

**Table 1.** Serum cortisol and plasma ACTH levels before and after surgery

		Before surgery	After 1 <sup>st</sup> surgical operation	After 2 <sup>nd</sup> surgical operation	Normal range
Cortisol (nmol/l)	Basal	503	420	<28	140-700
	After DXM 1mg	390	-	<28	<50
ACTH (pg/ml)		43	71	7.7	10-90

showed that 8.9% of adenomas found at autopsy were multiple and, overall, 0.9% of autopsies detected the presence of multiple pituitary adenomas. It has also been emphasized that these tumors may occasionally co-exist with other brain tumors<sup>1,5-9</sup> and that they may be distinguished as *contiguous* and *clearly separated double tumors*.

In autopsy specimens of double adenomas, prolactin was the most common immunoreactive secreted hormone,<sup>4,10</sup> while most of the double adenomas in surgical series were a combination of GH-secreting and clinically non-functioning adenomas:<sup>1,7,11-13</sup> in fact, acromegaly has been shown to be the most frequent clinical feature in surgical series of double pituitary adenomas.<sup>1,5,7</sup> Patients with somatotropinoma plus gonadotroph adenoma and cases of prolactinoma associated with GH-secreting adenoma have also been described.<sup>1,7,14</sup> It is of note that multiple (as many as three) intrapituitary non-functioning adenomas have also been described.<sup>15</sup>

By contrast, immunostaining for adrenocorticotrophic hormone in surgically resected double adenomas have rarely been described and these corticotroph adenomas were either “silent” or clinically active. In any case, isolated cases of Cushing’s disease patients with double<sup>4,6,7,16</sup> and also triple<sup>17</sup> adenomas have been documented.

As far as double adenomas are concerned, ACTH-secreting pituitary adenomas have been described together with silent prolactinomas in two cases,<sup>16,17</sup> with active PRL-secreting adenomas in four cases,<sup>1,2,6,16</sup> with a somatotropinoma associated with acromegaly in one patient<sup>6</sup> and with a silent FSH-secreting adenoma in another one.<sup>18</sup> Only one case of double pituitary adenomas ACTH-secreting has been reported recently in the literature<sup>19</sup>.

Owing to the rare occurrence of double pituitary adenomas, their pathogenesis is not known, but several possible mechanisms may be considered. One is a multicentric origin in the same pituitary, i.e. real double adenoma. The cause of multicentric adenomas might include incidental occurrence, promotion of the second adenoma growth through autocrine/paracrine pathways and a common origin. For example, studies on transgenic mice reported that several pituitary-driven growth factors can induce pituitary hyperplasia.<sup>20</sup>

Some authors suggested that one adenoma can induce the formation of another, mainly in cases of GH-secreting adenomas which release factors that may promote the proliferation of a secondary adenoma.<sup>1,7</sup> Anyway, the role of pituitary and extrapituitary factors in inducing clonal expansion of genetically altered cells would be considered in the occurrence of multiple adenomas. In our patient, the existence of multicentric adenomas would be more plausible because the co-existing adenomas were completely separated from each other. In this context, the origin of the adenoma located within the stalk may be explained as a consequence of corticotroph basophilic invasion from the residual intermediate lobe into the posterior lobe. Starting from young adulthood, some corticotrophs in the zona intermedia proliferate into the posterior pituitary lobe and become more prominent with aging. A basophilic invasion has also been implicated as the possible origin of the extremely rare pituitary ACTH secreting adenomas arising from within the posterior lobe.<sup>21,22</sup>

A poor surgical outcome has been reported in patients with double adenoma in whom the noncausative lesion was removed during the first operation. In the present case, hormonal data soon after surgery indicated the persistence of hypercortisolism and led the neurosurgeon to remove the lesion suspected at preoperative MR imaging of an enlarged infundibulum. The early occurrence of hypoadrenalism in the postoperative days indicated that a second corticotropinoma was resected: in fact, both tumors stained for ACTH on immunohistochemistry.

It is noteworthy in this regard that ACTH-secreting adenomas originating in, or extending into, the pituitary stalk have been previously observed.<sup>23</sup> These observations, together with the present case of double ACTH-producing adenomas, one in the anterior pituitary and the other attached to the pituitary stalk, once again emphasize that double ACTH-secreting adenomas may occur and that they need careful surgical management to recognize multiple lesions and to achieve a clinical resolution of Cushing’s disease. On the other hand, the normalization of hormone hypersecretion cannot be achieved when the co-existing hypersecreting tumor is missed during surgery. In our case, the preoperative MR imaging of an enlarged infundibulum enabled us to discover,

after the surgical failure, a second ACTH-secreting adenoma associated with a remnant of Rathke's pouch. To our knowledge, this is the first case of double ACTH-producing adenomas, one located in the anterior pituitary and the other attached to the pituitary stalk, reported in the literature.

## DISCLOSURE

The authors have no financial conflict of interest.

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