



CASE REPORT

Successful long-term control of Cushing's disease after partial resection of gigantic ACTH-secreting pituitary adenoma

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Abstract

Only 4–9% of patients with Cushing's disease (CD) harbor pituitary macroadenomas. Clinical and biochemical features of macrocorticotropinomas are poorly understood. Some evidence exist that these tumors presents clinical features more similar to a non-functioning adenomas, being though defined silent corticotropinomas, rather than to ACTH-secreting adenomas. In this paper, we report a case of a 60-year old woman with a history of obesity, arterial hypertension and diabetes mellitus who presented with overt central hypothyroidism. Magnetic resonance imaging disclosed giant pituitary adenoma measuring 50 mm. Endocrinological evaluation confirmed CD: ACTH 50.3 pmol/L, urinary free-cortisol of 739 nmol/24h and cortisol of 639 nmol/L after 1 mg dexamethasone suppression test. Tumor mass was reduced by 50% using purely endoscopic transsphenoidal approach. Thirty-eight months after the partial resection, the patient had well controlled CD: ACTH 20.2 pmol/L, urinary free-cortisol of 238 nmol/24h, cortisol of 105 nmol/L after 1 mg dexamethasone suppression test. To the best of our knowledge, this is the largest ACTH-secreting adenoma ever reported. Our case suggests that tumor size does not necessarily correlate with aggressiveness of CD in patients with macrocorticotropinomas and that long-term control of CD may be achieved albeit incomplete surgical removal. Further studies are needed in order to determine the best treatment option for patients with macrocorticotropinomas.

Key words: Cushing's disease, macroadenoma, central hypothyroidism, pituitary surgery, remission

1. Introduction

Pituitary adenomas are classified into functional and nonfunctional (silent) tumors on the basis of hormone secretion. Ten to 15% of tumors are ACTH-producing adenomas, which can cause Cushing's disease (CD) [1]. Only 4-9% of patients with CD harbor macrotropinomas (tumors larger than 10 mm) [2-4]. Silent corticotropinomas are defined as pituitary adenomas with positive immunoreactivity for ACTH without any signs or symptoms of Cushing's disease, whereby plasma ACTH level is usually normal [5,6]. However, a case of transformation of a silent corticotropinomas into CD has been reported [7]. Silent corticotropinomas are mostly macroadenomas that present with hypopituitarism and other compressive symptoms.

On the other hand, Central hypothyroidism (CH) is defined as hypothyroidism due to insufficient stimulation of the thyroid gland by TSH [6], often caused by hypothalamic and/or pituitary disorders, amongst which pituitary adenoma is the most frequent. Patients with CH caused by pituitary tumors frequently present with multiple other pituitary hormone deficiencies [8]. Interestingly, patients with CD have lower TSH levels and higher prevalence of CH when compared with other types of microadenomas, regardless tumor size [9].

In this paper, we report the case of a 60-year old woman presenting with central hypothyroidism and CD caused by agiant ACTH-secreting pituitary adenoma.

2. Case report

A 60-year-old woman with a history of obesity, arterial hypertension and diabetes mellitus presented to her general practitioner with increasing fatigue, hoarse voice and weight gain. Diabetes and hypertension were controlled with 5 mg of amlodipin and 1500 mg of metformin. Thyroid functionality essays suggested central hypothyroidism (TSH 0.16 mIU/L, 0.4-4.0; T4 54 nmol/L, 65-160; T3 1.21 nmol/L, 1.1-3.0). Treatment with 100 mcg of levothyroxine was administered and the patient was referred to our Clinic three weeks later. Endocrinological evaluation showed normal fT4, fT3 levels and suppressed TSH. Morning serum cortisol of 687 nmol/L (normal range 138-800), IGF-I of 111ng/ml (normal range 115-420), serum prolactin of 15 mcg/L (normal range 2-30) implied normal pituitary function. The patient did not report any vision abnormalities or

headache that would have suggested mass involving the sellar region. Levothyroxine was gradually reduced over a 9-month period to 25 mcg. Repeated tests confirmed central hypothyroidism (TSH 0.394 mIU/L, FT4 6.7 pmol/L and T4 40.8 nmol/L). Magnetic resonance imaging (MRI) revealed a 50×24×26 mm pituitary adenoma (Figure 1A). The results of repeated endocrinological evaluation were consistent with CD: ACTH 50.3 pmol/L (2.0-13.3), morning cortisol 850 nmol/L, urinary free-cortisol of 739 nmol/24h (72.5-325) and morning cortisol of cortisol 639 nmol/L after 1 mg dexamethasone suppression test. Endoscopic transsphenoidal surgery was performed. Pathological report confirmed a basophilic pituitary adenoma; focal ACTH immunostaining was disclosed (Figure 2). Morning cortisol on the first postoperative day was 89 nmol/L. Hydrocortisone replacement therapy was introduced, but three months later discontinued due to slightly increase of urinary-free cortisol levels. CH did not recover. Postoperative MRI showed residual tumor tissue within the right cavernous sinus and the sella turcica, where the suprasellar component of the tumor has fallen. Three months follow-up, serum cortisol and urinary-free cortisol levels were within normal ranges and residual tumor mass showed no signs of increase, so that repeated pituitary surgery was not performed.

At last follow-up, 36 months after the surgery, endocrinological evaluation was consistent with controlled CD (ACTH 20,2 pmol/L, cortisol 497 nmol/L, urinary free-cortisol of 238 nmol/24h, cortisol after 1 mg dexamethasone suppression test 105 nmol/L) and there were no signs of tumor growth (Figure 1B).

3. Discussion

There are two points that need to be emphasized in this case study: treatment and biochemical aspects of macrotropinomas and diagnostic algorithm of central hypothyroidism.

Clinical and biochemical features of patients with macrotropinomas are poorly understood. Molecular and hysto-pathological profile of macrotropinomas is more similar to silent corticotropinomas rather than microtropinomas [10]. Some evidence exist that patients with macrotropinomas have greater ACTH/cortisol ratio. This boosted the idea that ACTH forms present in macroadenomas may include precursors that are immunoreactive but not biologically active

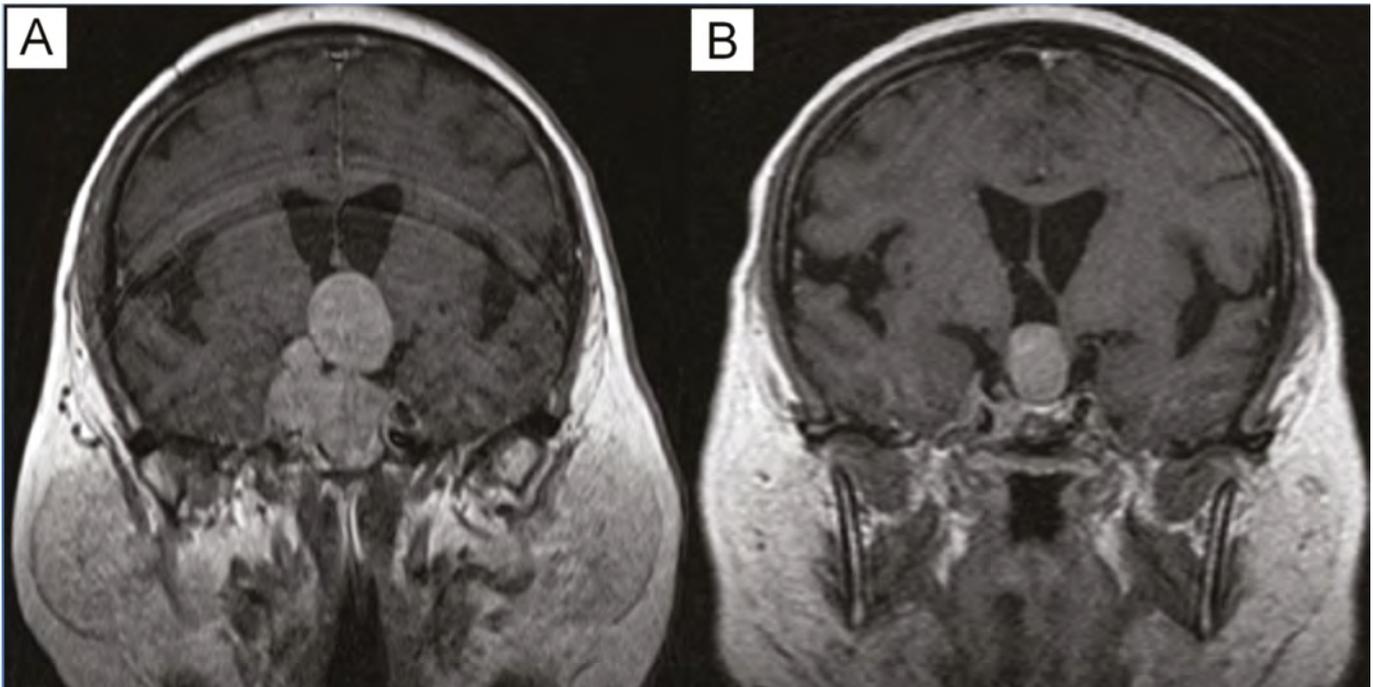


Figure 1. Coronal post contrast T1 weighted magnetic resonance images through the sella turcica showing 50×24×26 mm large „sandwich shaped’ pituitary adenoma invading the right cavernous sinus and temporal lobe (A). Suprasellar extension descended after removing the intra- and parasellar extensions of the tumor mass (B).

[1,11]. Indeed, there is a considerable resemblance with both cortisol and ACTH levels in microadenomas and macroadenomas, so that macroadenomas from microadenomas cannot be differentiated upon these data [2]. Furthermore, tumor size does not necessarily correlate with aggressiveness of CD as demonstrated in our case. Hence, treatment of macrocorticotropinomas may differ from microcorticotropinomas. Studies on surgical treatment of macrocorticotropinomas are scarce and show conflicting results. Some studies have concluded that patients with macroadenomas have lower surgical remission rates [2, 12]. However, the most recent study published by Wagenmakers MA et al., reported greater surgical remission rates in noninvasive macrocorticotropinomas than in microcorticotropinomas (94% vs. 60%) [13]. This could be explained by the different remission criteria used, which included only biochemical parameters. Our case demonstrated that even partial surgical resection of macrocorticotropinoma may offer long-term control of CD in terms of glucocorticoid excess and tumor mass volume.. This phenomenon

has been observed also in patients with acromegaly, in whom subtotal resection improves the effectiveness of somatostatin analogues adjuvant therapy [14]. Strict biochemical criteria for remission of CD in our patient were not met (morning cortisol <50 nmol/L after 1-mg dexamethasone suppression test), but our patient had normal morning cortisol and urinary-free cortisol levels two years after the surgery. Therefore, higher ACTH level along with normal plasma cortisol values in our patient, fits the theory of a biologically inactive ACTH secreted by macrocorticotropinomas.

Thereafter, we would like to emphasize the role of the hypophyseal magnetic resonance imaging upon suspicion of central hypothyroidism. Subnormal levels of free and total T4 and normal or low serum TSH may point out the diagnosis of CH [8] that is mostly caused by compressive effect of pituitary adenomas a/or other sellar masses along with other endocrine deficiencies. At this time, assessment of gonadotropic, corticotropic and somatotropic functions is recommended as first step in the diagnostic evaluation of central hypothyroidism

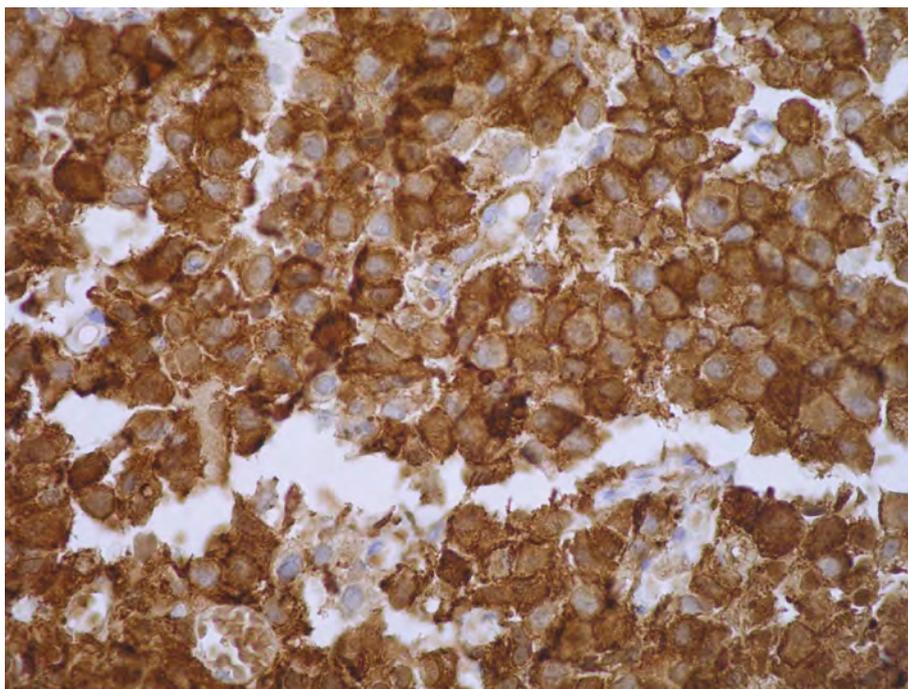


Figure 2. Immunostaining for ACTH showing pronounced diffuse expression of ACTH-receptor within the tumor tissue ($\times 400$).

with MRI examination reserved for those cases presenting other signs of pituitary deficiency [8]. However, our case discloses that patients with pituitary adenoma might have isolated CH; therefore MRI of the sellar region should be enrolled in the diagnostic work-up of clinical suspicion of CH.

Finally, it has to be remembered that patients with CD, harboring microadenomas, tend to have lower TSH levels and higher prevalence of CH when compared to other sellar lesions, regardless tumor size [9] due to the direct inhibitory effect of chronic ACTH hypersecretion on normal TSH secretion, as revealed in our patient.

In conclusion, our case highlights that tumor size does not necessarily correlate with aggressiveness of CD in patients with macrocorticotropinomas and that long-term control of CD may be achieved albeit incomplete surgical removal. Besides, patients with macrocorticotropinomas may present with isolated CH and therefore hypophyseal MRI should be considered in diagnostic algorithm upon the suspicion of CH. Nevertheless, further studies are needed in order to

determine the best treatment option for patients with macrocorticotropinomas.

Author contributions

VČ and DS performed the surgery and were engaged in patients follow-up, and gave the final approval. IK gave an idea for the case study, reviewed the previously published literature, participated in drafting the article and gave the final approval. LMC participated in drafting the article, critically reviewed the article and gave the final approval. DČ and JM participated in study design, acquisition of data, drafting the article, and gave the final approval. HIP performed radiological evaluation and gave the final approval. LP performed pathohistological analyses and gave the final approval. MV was engaged in endocrinological evaluations and follow-up and gave the final approval.

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