CASE REPORT

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Ectopic intracavernous corticotroph microadenoma: case report of an extremely rare pathology

ADRIAN FLORIAN BĂLAŞA[1)], RAREŞ CHINEZU[1)], DANIEL MIHAI TELEANU[2)], MARIA IONELA PAŞCANU[3)], LAURA CHINEZU[4)], ANGELA BORDA[4)]

[1)]*Department of Neurosurgery, University of Medicine and Pharmacy of Tîrgu Mureş, Romania*
[2)]*Department of Neurosurgery, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[3)]*Department of Endocrinology, University of Medicine and Pharmacy of Tîrgu Mureş, Romania*
[4)]*Department of Histology, University of Medicine and Pharmacy of Tîrgu Mureş, Romania*

Abstract

Ectopic pituitary adenomas (EPAs) are most likely tumors developing from the cellular remnants following the migration of Rathke's pouch. We present the case of a 54-year-old female diagnosed with Cushing's syndrome. Magnetic resonance imaging (MRI) identified an ectopic microadenoma located in the median wall of the cavernous sinus. Microscopic transsphenoidal surgery was performed and the lesion was completely removed without any postoperative surgical complications. Based on characteristic microscopic and immunohistochemical features and on recent clinicopathological prognostic classifications, the histopathological diagnosis was non-proliferative, non-invasive corticotroph pituitary neuroendocrine tumor, grade 1a. Complete remission of disease was achieved postoperatively and was maintained for one year following surgery. MRI showed complete resection, without tumor recurrence at one and two years. Occurrence of an ectopic intracavenous adrenocorticotropic hormone (ACTH)-secreting adenoma is extremely rare and poses difficulties both in the identification, surgery, histopathological grading, and adequate endocrinological treatment and follow-up.

Keywords: pituitary gland, corticotroph adenoma, ectopic adenoma, intracavernous adenoma.

Introduction

Ectopic pituitary adenomas (EPAs) are defined as tumors that are in no direct contact with the pituitary gland [1, 2]. Ectopic pituitary tissue is a common finding in autopsies and is believed that these small islands of pituitary tissue are remnants from the migration of Rathke's pouch [2]. These remnants can sometimes undergo tumor differentiation and are considered the cause of EPA [3].

Occurrence of an adrenocorticotropic hormone (ACTH)-secreting EPA localized in the cavernous sinus is an extremely rare event. This localization determines significant difficulties in both the adequate imaging identification of the microadenoma, as well as complete tumor resection [4–6].

Aim

We present the case of an intracavernous ACTH-secreting EPA and its multimodal management.

Personal consent and approval of the Ethics Committee of Emergency County Hospital, Tîrgu Mureş, Romania, were obtained prior to publication of this paper.

Case presentation

Clinical status

A 54-year-old woman (M.A.), previously known with arterial hypertension, chronic cardiac ischemic disease, insulin dependent type II diabetes and hypothyroidism following thyroidectomy for nodular disease, presents six months prior to consultation with weight gain, facial plethora, uncontrollable high blood glucose levels, and increased fatigability.

On general examination, she was found with a height of 159 cm, weight of 87 kg, body mass index (BMI) 34.4 kg/m^2, arterial pressure of 150/100 mmHg. Electrocardiogram (ECG) showed no pathological modifications with normal systolic rhythm with a heart rate of 80 beats per minute (BPM). The patient presented also with all clinical traits of Cushing's syndrome: moon face, abdominal obesity cutaneous striae, hirsutism, and buffalo hump.

Laboratory tests indicated increased midnight plasma cortisol of 10.6 µg/dL [normal value (NV) <3.5 µg/dL], absence of cortisol suppression after low-dose Dexamethasone suppression test – 13.3 µg/dL (NV<1.8 µg/dL), and an elevated level of 24-hour urinary free cortisol (UFC) – 922.4 nmol/24 h (NVs: 100–379 nmol/24 h). ACTH level was 30.73 pg/mL (NVs: 7.2–63.3 pg/mL).

Imaging

A pituitary magnetic resonance imaging (MRI) was performed showing in T1 sequences a distinct hypointense lesion of approximately 5.5×6.5×6.8 mm located at the level of the medial wall of the right cavernous sinus. The lesion was distinct from the pituitary gland and presented discrete contact with the intracavernous segment of the internal carotid artery, posterior-inferior intrasellar procidence with slight impingement of the pituitary stalk. On T2 sequences, the lesion appeared as hypointense. After administration of paramagnetic contrast agent (Magnevist®, 469 mg/mL, 0.2 mL/kg, Bayer AG, Leverkusen, Germany)

on T1 sequences, the lesion presented persistent delayed enhancement (Figure 1, A–C).

No cranial CT scan was performed preoperatively. Bilateral inferior petrous sinus sampling was not performed, as it was not available on site at the moment of diagnosis.

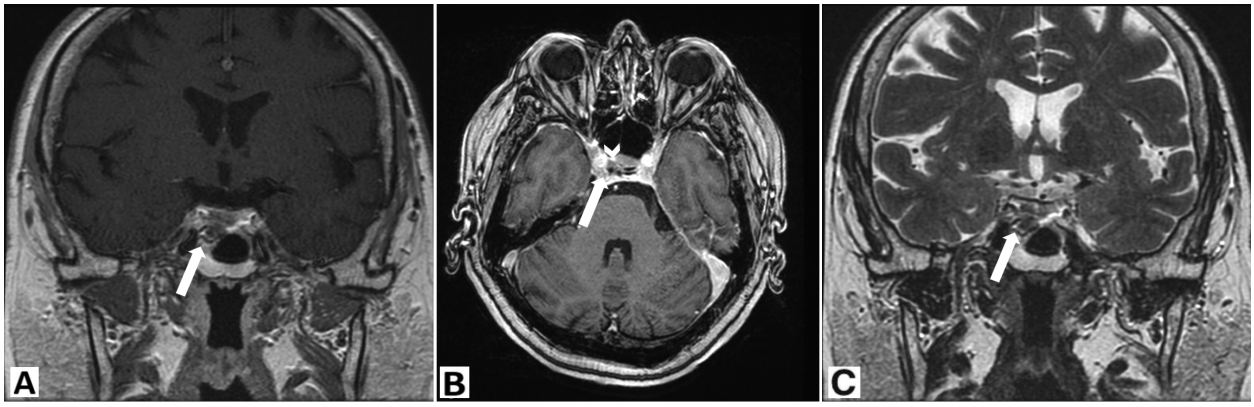

Figure 1 – ***Sellar MRI: (A) Coronal T1 + contrast image. The arrow shows the lesion situated in the right cavernous sinus adjacent to the intracavernous carotid and slight procidence at the right posterior inferior junction of the cavernous sinus with the sella; (B) Axial T1 + contrast. The arrowhead shows the delimitation between the normal sella and the intracavernous EPA; (C) Coronal T2 image showing the hypointense densities of the lesion, densities that were not characteristic to the fluid-like structure of the tumor. MRI: Magnetic resonance imaging; EPA: Ectopic pituitary adenoma.***

Surgery and postoperative outcome

Between March 17–23, 2015, the patient was admitted in the Department of Neurosurgery, Emergency County Hospital, Tîrgu Mureş (Admission file No. 9685/2015). She underwent a microscopic transsphenoidal approach with the posterior wall of the sphenoid sinus opened widely towards the right cavernous sinus.

In the sellar compartment, we noticed that the lesion was completely detached from the pituitary gland and was located at the level of the medial wall of the right cavernous sinus. The tumor was covered with an extremely thin and transparent layer of the dura mater and was bulging in the sellar space. This ectopic, intracavernous tumor had a slight compressing effect on the pituitary gland, but no continuity between the lesion and the pituitary gland was visible. The transparency of the dural layer allowed us to note that the tumor had a brown to yellowish color.

The dural layer covering the tumor was carefully incised and a fluid like tumor tissue was found. The contents of the tumor were easily aspirated, with apparently complete intraoperative resection. A partial right pituitary resection was also performed and the normal tissue together with the tumor tissue was sent also for pathological examination.

Closure of sella was performed in a watertight fashion using an autologous abdominal fat pad placed at the level of the sphenoidal sinus.

The postoperative course was uneventful, no cerebrospinal fluid fistula, diabetes insipidus or electrolyte imbalance was noted. The patient was discharged on the fifth day following the surgery.

Pathology

All specimens obtained from surgery were fixed in 10% buffered formalin and embedded in paraffin. Sections of 4–6 μm were stained with Hematoxylin–Eosin (HE). On HE staining, three out of five fragments were tumor tissue and two non-tumor pituitary gland. The tumor had a diffuse arrangement with pseudorosettes, consisting of sheets of slightly basophilic cells. The cells had large nuclei, with visible nucleoli. Some binucleated cells were also noted. There was a degree of nuclear pleomorphism, but no visible mitoses. The tumor limits were regular (Figure 2A). Based on the characteristic histopathological features on HE, immunohistochemical (IHC) tests were performed using the anti-ACTH antibody (Dako, clone 02A3, monoclonal, 1:100 working dilution) and the anti-cytokeratin (CK) 18 antibody (Dako, clone DC 10, monoclonal, 1:50 working dilution). By IHC, all tumor cells were strongly positive for CK18 (Figure 2C) and expressed ACTH with various intensity of immunoreactivity (Figure 2B). Ki-67 was used for evaluation of the proliferative rate (Dako, clone MIB-1, monoclonal, 1:100 working dilution) and was approximated around 2.5% (Figure 2D).

Numerous Crooke's cells positive for CK18, sign of hypercortisolism were found in the anterior pituitary gland fragments (Figure 3).

The final pathological diagnosis was non-invasive and non-proliferative, ACTH-secreting pituitary adenoma, grade 1a according to Trouillas classification.

Long term follow-up

Clinical and biochemical remission was obtained immediately and was maintained for approximately one year. Postoperative laboratory tests showed a midnight plasma cortisol of 2.6 μg/dL, normal UFC, controllable blood glucose levels and a 5 kg weight loss. The rest of the pituitary function remained intact following surgery.

Follow-up pituitary MRI was performed at one year and two years, respectively, following surgery. No local tumor recurrence was noted on any of the examinations (Figure 4).

Still, laboratory examinations performed one year following surgery showed a recurrent hypercortisolemia (midnight plasma cortisol 9.2 μg/dL, cortisol after low-dose Dexamethasone suppression test 13.2 μg/dL, UFC 630.96 nmol/24 h, ACTH 44.3 pg/mL). Due to this and the negative MRI control studies, the patient received medical treatment with somatostatin agonist, Pasireotide (1.2 mg subcutaneous/day), with an improvement of UFC levels (306.9 nmol/24 h).

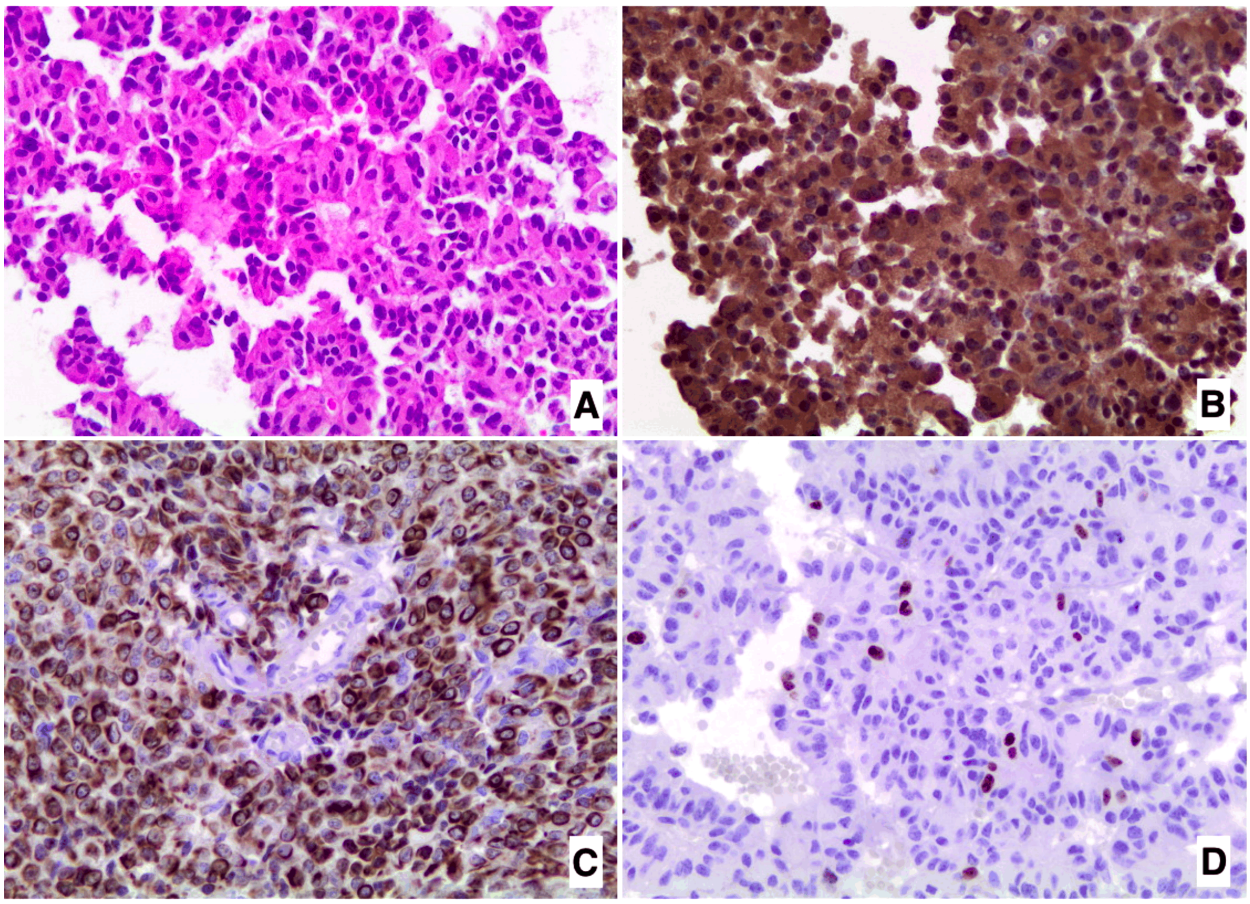

Figure 2 – ***Histopathological characteristics of the corticotroph tumor: (A) Pseudorosette arrangement of the slightly basophilic cells (HE staining, ×100); (B) Strong immunoreactivity for adrenocorticotropic hormone (ACTH) (Anti-ACTH antibody immunostaining, ×200); (C) Strong positivity for cytokeratin (CK) 18 (Anti-CK18 antibody immunostaining, ×200); (D) Ki-67 proliferation index lower than 3% (Anti-Ki-67 antibody immunostaining, ×200).***

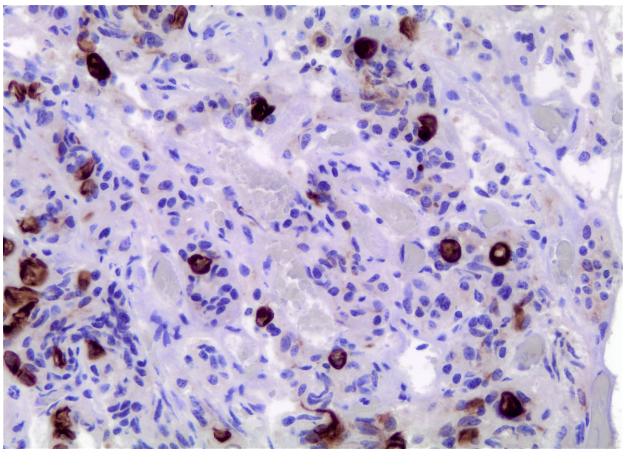

Figure 3 – ***The presence of Crooke's cells in non-tumor pituitary gland (Anti-CK18 antibody immunostaining, ×200).***

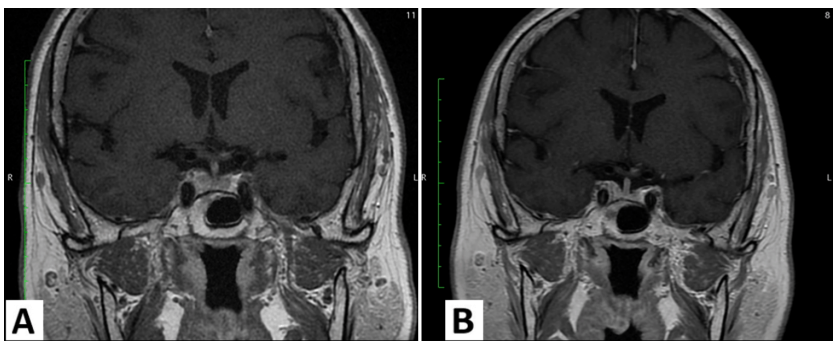

Figure 4 – ***Follow-up MRI at one year (A) and two years (B) following surgery, showing complete imagistic resection and no tumor progression. MRI: Magnetic resonance imaging.***

Discussion

Parasellar EPAs have been previously described [2, 7–12], but ACTH ectopic microadenomas in the region of the cavernous sinus are still exceedingly rare [8, 12]. A recent literature review reports only 12 cases [6].

All cases previously presented in the literature [6], including ours, are females and from these data, it is possible to speculate that this ectopic location is likely to appear in females.

Proper imaging identification of an EPA is also extremely difficult, to date, MRI could properly diagnose the intracavernous location of an EPA only in two other cases [6, 13].

Some authors have stated that in pituitary tumors, hyperintense signal in T2 sequences is an indicator of a more fluid tumor [9]; this was not true in our case, as we encountered a fluid like tumor without hyperintensity in T2 sequence.

The presence of an EPA at the level of the cavernous sinus represents a significant surgical challenge, as the exploration of the cavernous sinus is one of the most difficult aspects in neurosurgery [6].

When using a microscopic transsphenoidal approach, there is added difficulty from the fact that lateral surgical extension towards the cavernous sinus is limited by the nasal speculum. This can sometimes significantly decrease the chances of achieving a complete resection [6].

In our case, we benefited of unexpected intraoperative aid, first from the fluid-like consistency of the tumor, and second from the localization of the lesion in the medial wall of the right cavernous sinus. These two factors significantly eased the tumor resection.

Histopathological diagnosis of corticotroph tumor based on the characteristics features on HE and IHC was not found to be difficult. The presence of Crooke's cells within the non-tumor anterior pituitary gland characterized by homogenous pink hyaline ring around the nucleus was also a diagnostic key feature. This seems to be closely related to the presence of Cushing's syndrome, but are depending on degree of hypercortisolism and individual variability [14].

At the latest terminology consensus conference [15] held in Annecy, France, a new terminology was proposed for pituitary adenomas, replacing the nomenclature to pituitary neuroendocrine tumor (PitNET).

The prognostic pathological classification of pituitary neuroendocrine tumors allows to identify earlier invasive and proliferative tumors that are suspected of malignancy and should require multimodal treatment. Based on this classification proposed by Trouillas *et al.* [16], the tumor was grade 1a, meaning a non-invasive – non-proliferative tumor. This grade is an important indicator of a low risk of local recurrence, but unfortunately it does not correlate with a prolonged remission rate. Earlier studies have shown that even the slightest tumor remnants along the dura mater or inside the cavernous sinus can still lead to delayed recurrence of Cushing's disease (CD) [17].

Recurrence of CD after transsphenoidal surgery for microadenomas is described as a loss of clinical remission at least one year following surgery [18]. The described rate of recurrence following transsphenoidal surgery described in the literature is approximately 13% [19]. An increased rate of recurrence was noted in cases presenting peak serum cortisol levels ≥9.4 μg/mL [20].

In our case, we believe that the immediate post-operative normalization of ACTH and cortisol were important, and they show a correctly performed surgery, but, nevertheless, these are not sufficient to predict long-term remission.

Conclusions

Occurrence of an intracavenous ACTH-secreting EPA is extremely rare. We present the 13th case described in the literature and the third one with MRI identification. Following the latest recommendations, the histopathological diagnosis was of ectopic corticotroph pituitary neuro-endocrine tumor non-invasive – non-proliferative (grade 1a). Transsphenoidal surgical management of these lesions is difficult and, despite apparently complete surgical resection, recurrence of the disease is still possible being directly linked to preoperative cortisol levels or microscopic tumor remnants along the dura mater of the cavernous sinus.

Conflict of interests

The authors declare that they have no conflict of interests.

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Corresponding author
Rareş Chinezu, MD, Consultant Neurosurgeon, Department of Neurosurgery, University of Medicine and Pharmacy of Tîrgu Mureş, 38 Gheorghe Marinescu Street, 540139 Tîrgu Mureş, Romania; Phone +40745–922 665, e-mail: rchinezu@yahoo.com

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