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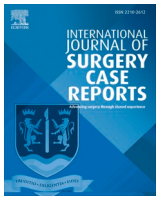

Case report

Apoplexy of a giant clival ectopic prolactinoma: A very rare case report

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ABSTRACT

Introduction and importance: Ectopic pituitary neuroendocrine tumor (EPNET) is a very rare entity, seldom with apoplexy evolution. Only three cases of intracranial ectropic pituitary neuroendocrine tumor apoplexy were reported in the literature.

Case presentation: We report the case of a 45-year-old woman with a history of amenorrhea, and headaches. Neuroimaging showed a very aggressive giant mass within the clivus with the invasion of the sphenoidal sinus and encasement of internal carotid arteries with an empty sella. Endocrinology work-up revealed an exceedingly high level of prolactin surprisingly without galactorrhea. Immunohistochemical analysis after an endonasal biopsy confirmed the diagnosis of prolactinoma. One month after Cabergoline initiation, an apoplexy of the ectopic pituitary neuroendocrine tumor occurred. Conservational management with a decrease in cabergoline dose was performed.

Discussion: This article highlights data from various cases reported in the literature in addition to our case to confirm the extreme rarity of apoplexy as a complication of EPNET.

Conclusion: Pituitary apoplexy in ectopic pituitary neuroendocrine tumor is extremely rare. Therefore, in case of unusual localization of pituitary neuroendocrine tumor, a thorough follow-up is necessary to detect complications and ensure early management.

1. Introduction

Prolactin-secreting tumors of the pituitary gland, also known as prolactinomas, are the most common secretory tumors of the pituitary gland. Prolactinomas can lead to a wide variety of symptoms, either due to mass effect or hypersecretion of prolactin. Its management requires an interprofessional team approach.

Giant prolactinoma is rare, accounting for 1 to 5 % of all prolactinomas [1]. More rarely, it can be localized outside the sella turcica, without any continuity with the intrasellar pituitary gland, and can be considered as an ectopic pituitary neuroendocrine tumor (EPNET) [2,3]. EPNET can be challenging for differential diagnosis because of their clinical diversity depending on their anatomical localization, and their hormone-secreting profile. The outcomes of EPNET are often positive after medical and/or surgical management. However, evolution to apoplexy is possible, although it is an extremely rare situation.

In this paper, we report a very rare entity of giant EPNET developed on the clivus, with empty sella turcica syndrome, which is a very rare presentation, with an exceptional evolution to apoplexy.

A written informed consent was obtained from the patient for publication and any accompanying images. This work has been reported in line with the SCARE criteria [4].

2. Observation

We report the case of a 45-year-old woman who presented to the department of Endocrinology with a secondary amenorrhea evolving for 10 years, and a history of headache during the last four years. She had a history of type 2 diabetes mellitus put on metformin for >3 years.

The physical examination was normal upon admission. Initial hormonal investigations revealed an extremely high serum prolactin level after dilution of 14,833 ng/ml (NV: 5.18–26.53, CMIA) with no detected macroprolactin. Surprisingly, the patient didn't have spontaneous or provoked galactorrhea or visual impairment. Other blood workup findings are resumed in Table 1.

The pituitary magnetic resonance imaging (MRI) found a voluminous heterogeneous mass measuring 5 × 4,2 × 2,8 cm (Height x Length x Width) i.e. 29,4 cm^3 in volume. The tumor invaded the entire clivus and

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infiltrated the sella floor and sphenoid sinus. It appeared isointense on T1 and T2-weighted images (T1WI/T2WI) and hyperintense on diffusion-weighted images (DWI). The pituitary gland was not seen with an intrasellar arachnoidocele suggesting a giant pituitary ectopic prolactinoma in the clivus. It extended to both cavernous sinus and encased adjacent internal carotid arteries (ICA) bilaterally (Fig. 1).

The case was discussed in a multidisciplinary meeting including endocrinologists, otorhinolaryngologists, neurosurgeons, radiologists, and ophthalmologists. Endonasal endoscopic exploration by transsphenoidal approach was performed. It showed a normal aspect of the middle meatus, but the mass was pulsatile and filled the sphenoidal recess. A biopsy was performed at a distance from the carotid artery, and the tissues were very hemorrhagic. The histopathological examination confirmed the diagnosis of an ectopic prolactinoma. The Ki67 index was inferior to 1 % (Fig. 2).

The patient was started on a dopamine agonist (Cabergoline) therapy at a dose of 0.5 mg twice weekly. One month after Cabergoline initiation, the patient presented to the ER with acute headaches and epistaxis. MRI showed the appearance of multiple necrotic lesions, hyperintense on T2WI and hypointense on T1WI, with increased tumor volume to 45,86 cm^3 (5,6 × 4,2 × 3,9 cm) (Height x Length x Width), suggesting an apoplexy of the EPNET. The management was conservative without further complications. Cabergoline therapy was decreased to 0.5 mg per week.

On the long-term follow-up, the headaches disappeared and menstruations became regular after 11 months. The prolactin levels decreased to 9 ng/ml (NV: 5.18–26.53, CMIA) at 10 months. On the 12-month MRI, the tumor and apoplexy remained stable.

3. Discussion

Ectopic pituitary neuroendocrine tumors account for only 0.098 % of all cases of pituitary neuroendocrine tumors [5]. They have been described in several sites, the most common location are the sphenoid sinus and suprasellar region (60 %), and cavernous sinus (13.3 %) [6–9]. Other locations were also described, such as the nasopharynx, nasal cavity, orbital region, ethmoid and maxillary sinus (11.2 % of cases), and finally in the clivus (15.6 %) [3,7,10–12]. Our patient presented with an invasive adenoma within the clivus with an empty sella.

For our review of apoplexy in EPNET. We searched in PubMED database the words “ectopic”, “pituitary neuroendocrine tumor ” and “apoplexy”. We excluded non-English written papers, abstracts without full text and other irrelevant publications. Within the limits of our research, we found 3 cases of apoplexy on ectopic adenoma [13–15] published between 1991 and 2012. The characteristics of these cases were summarized in Table 2. Our case was unique, as it is the first case to evolve into apoplexy during follow-up, to the best of our knowledge (Table 2).

Pituitary apoplexy (PA) is a very rare situation in intrasellar pituitary neuroendocrine tumor and extremely uncommon in the EPNET [13]. The pathophysiology of PA is not fully understood, but an increased metabolic demand and/or compromising of the pituitary tumor vasculature was suggested, causing acute or subacute infarction or hemorrhage or both [16]. Referring to the data of Table 2, EPNET apoplexy occurs often in women, with three females for one male only, including our case. However, in intrasellar adenoma apoplexy, a recent systematic review reported a male predominance [16]. All reported cases of EPNET apoplexy occurred in the fourth decade in women, including our patient who was 45 years-old, while the single male patient was 78 years-old.

In our case, PA occurred one month after Cabergoline initiation. Dopamin agonists are classically known to be one of important precipitating factors for apoplexy as well as reported by Turgut et al. [13], including also diabetes mellitus which was a part of the medical history of our patient. All other reported cases were discovered at diagnosis. All the previously reported cases were macroadenomas; the largest diameter was 2 cm. In fact, our case was the largest one (5.6 cm). Excepted one case that was localized in right posterior clinoid, all cases of EPNET apoplexy were within the clivus including our case. The clivus is probably a privileged localization of EPNET apoplexy (Table 2).

According to Table 2, the most predominant type of EPNET was prolactinoma (75 %), including our case. This finding is similar to the data of intrasellar PA, since among functional pituitary neuroendocrine tumor s, PA predominantly occurs in prolactinomas [16].

Headaches and visual impairment were the major symptoms found in patients with EPNET apoplexy (Table 2). Moreover, our patient presented with secondary amenorrhea. Surprisingly, the patient did not exhibit galactorrhea even with very high levels of prolactin.

Currently, there are no guidelines for the specific management for EPNET apoplexy. Therefore, their management follows that of intrasellar adenoma apoplexy. Management of PA begins with resuscitation of the electrolyte abnormalities and hemodynamic stabilization. Cortisol and thyroid hormone deficiency substitution should be prioritized without any delay. Once stabilized, further management choice between conservative or surgical treatment, its type (endoscopic or microscopic), its timing (early or delayed) is nowadays controversial. However, patients with stable neurological and ophthalmic state are candidates for conservative management [16]. In our patient, given the risk of vascular and nervous damage and the absence of visual impairment, we have chosen a conservative approach. The dose of Cabergoline was decreased at the apoplectic event. The symptoms improved, but the MRI findings remained unchanged.

4. Conclusion

Ectopic macroprolactinoma in the clivus is a rare entity that requires multidisciplinary and collegial management. However, the evolution into apoplexy in such tumor is exceptional. In our case, Cabergoline use may have precipitated the occurrence of apoplexy in our patient. Therefore, a close monitoring is mandatory for an early diagnosis and management of this rare situation. Finally, the lack of recommendations

Table 1
Hormonal assessment.

	At admission	At 1 month of follow-up	At 3 month of follow-up	At 6 month of follow-up	At one year of follow-up	Normal range
Prolactin (ng/ml)	14,833		496	148	9	(5.18–26.53)
ESTRADIOL (pg/ml)	20				98	(35–169)
FSH (mui/ml)	6.4				3.34	(3.3–10)
LH (mui/ml)	2.2				3.13	(2–12)
CGA (mui/ml)	0.27				–	(0.04–0.6)
TSH (mui/l)	1.79				–	(0.27–4.2)
FT4 (pmol/l)	16.9	13	13		16.03	(10.6–19.4)
Midnight cortisol (ng/ml)	17				–	(<18)
Cortisol 8 AM (ng/ml)	182	121			174	–
IGF-1 (ng/ml)	153.6				–	(64–236)

CGA: Chorionic gonadotropin Alpha Subunit, FSH: Follicle stimulating hormone, LH: luteinizing stimulating hormone, TSH: thyroid stimulating hormone, FT4: Free thyroxine hormone, IGF-1:Insulin-like growth factor 1.

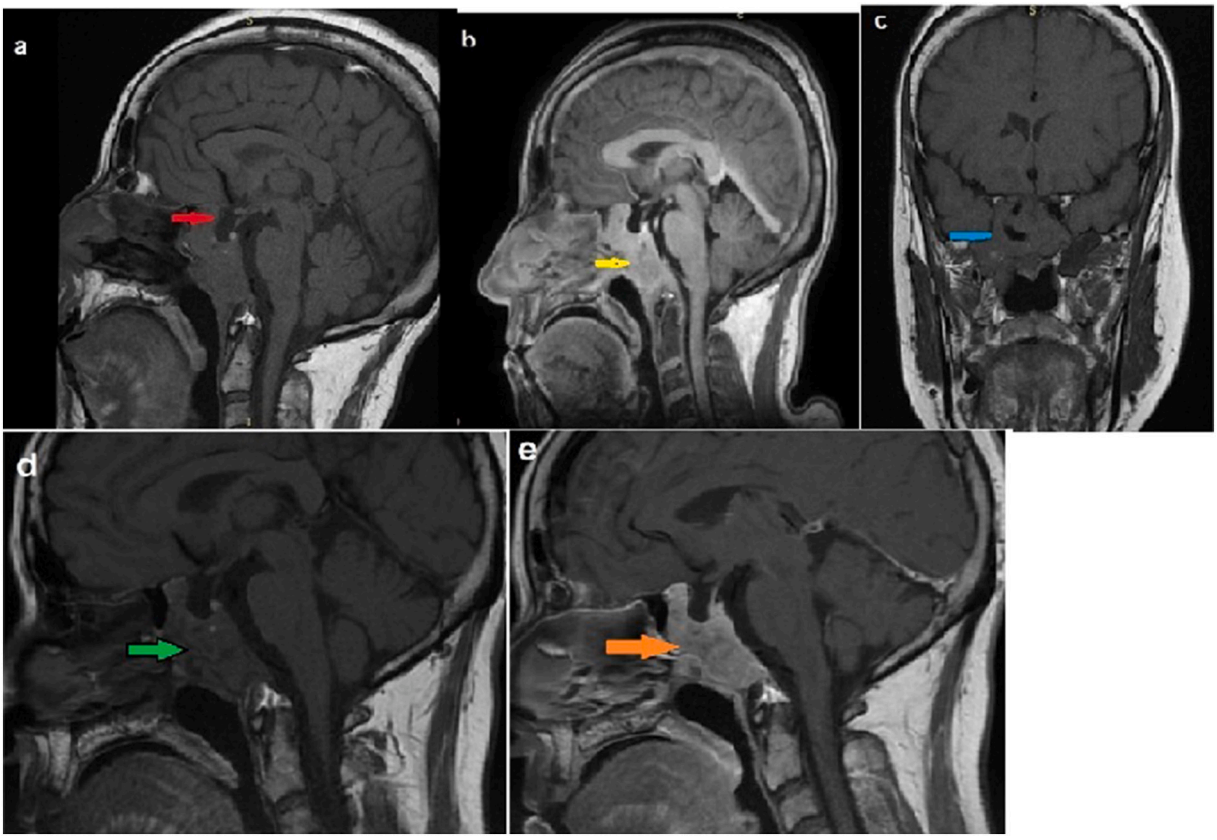

Fig. 1. a: Sagittal MRI T1WI showing the mass within the clivus, isointense, and arachnoidocele (white arrow)
b: Sagittal T1 weighted contrast-enhanced image showing the mass within the clivus (yellow arrow), with homogenous enhancement
c: Coronal MRI T1W1 showing the clival mass encased adjacent carotid artery (blue arrow)
d: Sagittal MRI T1WI showing the isointense mass within the clivus with multiples hypointense necrotic lesions (green arrow) 1 month after Cabergoline initiation
e: Sagittal MRI T1-weighted contrast-enhanced image showing the heterogeneous enhancement of the tumor with multiple necrotic lesions suggesting EPNET apoplexy (orange arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

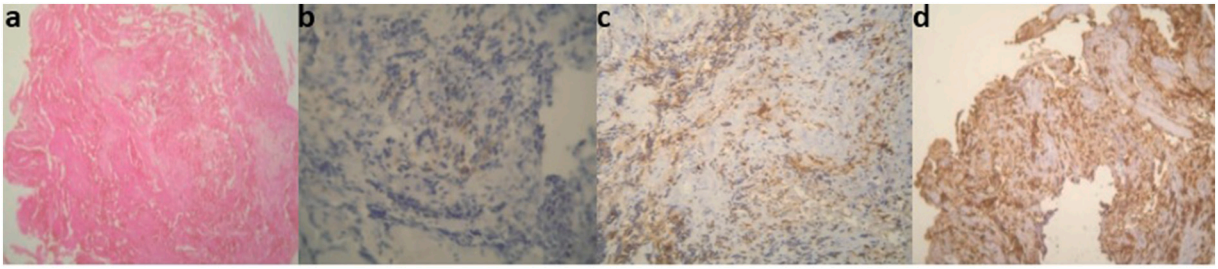

Fig. 2. (a) Histologic section showing epithelial neoplasm with monomorphic cells composition (x10)
(b) Label of neoplasm cells by prolactin (x20)
(c) The proliferation index is <1 % on Ki-67 staining (x40)
(d) Immunohistochemical staining positive for Chromogranin (x10).

for the management of EPNET make the analysis of reported cases important to guide treatment and long term follow-up.

Our conclusions remain limited by the small number of EPNET apoplexy. Multicentric studies are necessary to confirm our findings.

Abbreviations

EPNET	Ectopic pituitary neuroendocrine tumor
CMIA	chemiluminescence imunoassay
T1WI	T1-Weighted imaging
T1WI	T2-Weighted imaging
MRI	Magnetic Resonance Imaging
CT	Computed Tomographic
ICA	Internal Carotid Artery
PA	Pituitary apoplexy

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Consent

Written informed consent was obtained from the patient for

Table 2
Literature review of cases of ectopic pituitary adenoma with apoplexy.

Reference	Age (years)/ Gender	Predisposing risk factors to apoplexy	Symptoms	Imaging		Hormonal secretion	Time to apoplexy	Management	Follow up (duration)
				Location	Adenoma size				
O'Connor et al.,1991 [28]	42/F	–	Headache, Unilateral blurring of vision	Right posterior Clinoid	Macro-adenoma (2 cm)	Prolactin	At diagnosis	Complete tumor excision by fronto-temporal craniotomy	No recurrence of symptoms, normal visual field and biochemistry (5 years)
De Witte et al., 1998 [27]	47/F	–	Headache	Clivus	NA	Prolactin	At diagnosis	Endonasal transsphenoidal partial resection + bromocriptine	No recurrence of symptoms, Normalization of lab values (4 months)
Mudd et al., 2012 [31]	78/M	Prostatectomy (Prostate cancer), without drugs intake	Acute onset blurred vision	Clivus	Macro-adenoma (1.5 cm)	Non-functional	At diagnosis, during surgery	Transnasal endoscopic resection of the clival mass	No recurrence of symptoms Normal hormones levels. No recurrence of the mass (2,5 years)
Our case	45/F	Diabetes mellitus Cabergoline therapy	Headache, Amenorrhea	Clivus	Giant macroadenoma (5.6 cm)	Prolactin	1 month after Cabergoline treatment	Cabergoline	Regression of symptoms, and normal hormones levels (1 year)

F: female, M: male, NA: not available.

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Ethical approval

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Data availability

The patient's data used to support the findings of this study can be retrieved from the archives of the Department of Endocrinology-Diabetology and Nutrition, at the Mohammed VI University Hospital of Oujda, Morocco.

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