Synchronous Posterior and Anterior Pituitary Tumors: A Case Report of a Hypothetic Paracrine Relationship

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Abstract

Tumors of the posterior pituitary are a distinct group of low-grade sellar neoplasms. Furthermore, the coexistence with an anterior pituitary tumor is extremely unlikely and could not be a mere coincidence and could be a paracrine relationship. Here, we present a case of 41-year-old woman with Cushing syndrome and two pituitary masses on magnetic resonance imaging. Histologic examination shows two distinct lesions. The first consisted of a pituitary adenoma with intense adrenocorticotropic hormone immunostaining and the second lesion consisted of a proliferation of pituicytes arranged in vague fascicles or pituicytoma. After a narrative review of the literature, we found that synchronous pituitary adenoma and a thyroid transcription factor 1 (TTF-1) pituitary tumor were only reported eight times in the past. These patients included two granular cell tumors and six pituicytomas and all of them coexisted with pituitary adenomas, seven functioning and one nonfunctioning. We analyze the hypothesis of a possible paracrine relationship for this concomitance, but this exceedingly rare situation is still a matter of debate. To the best of our knowledge, our case represents the ninth case of a TTF-1 pituitary tumor coexisting with a pituitary adenoma.

Keywords
- TTF-1 pituitary tumor
- pituitary adenoma
- pituicytoma
- Cushing disease

Introduction

Tumors of the posterior pituitary are a distinct group of low-grade neoplasms arising from the sellar region, including pituicytomas (PC), granular cell tumor (GCT), spindle cell oncocytomas (SCO), and sellar ependymoma (SEP). They are thought to be non-neuroendocrine tumors and derived from glial cells, called pituicytes, of the neurohypophysis.[1,2] According to the newest World Health Organization (WHO) classification of endocrine tumors, the posterior pituitary tumors encompass a group of entities with the NK2 homeobox 1 factor or thyroid transcription factor 1 (TTF-1) as an immunomarker.[1,3]

The majority of these tumors occur in the fourth or fifth decade of life and have a slight female predominance.[4] Neuroradiological findings consist of large, solid tumors

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with suprasellar extension that are very hard to distinguish among other pituitary tumors. Clinical manifestation of the tumors is most consistent with tumor mass effect on surrounding structures.[5] High prolactin levels are considered to result from the pituitary "stalk effect"; however, there are reports of PC and GCTs that present with hypersecretion of hormones associated with endocrine disorders such as acromegaly and Cushing syndrome.[6,7]

The presence of a collision sellar lesion represents a very uncommon event. A preoperative diagnosis of a dual sellar pathology is very difficult, since most of the cases are presented clinically and radiologically as pituitary adenomas.[8] There have been only a few reports of the coexistence of a pituitary adenoma and tumors of the neurohypophysis and these cases may not be considered as mere coincidences.[9]

In this study, we present a case of 41-year-old woman suffering from Cushing syndrome with the presence of two pituitary masses on magnetic resonance imaging (MRI). We originally presumed that the tumors were adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas, but histopathological examination corrected the diagnosis to a PC coexisting with a corticotrophinoma. The relevant literature is reviewed and discussed.

Methods and Results

Ethics Regulations

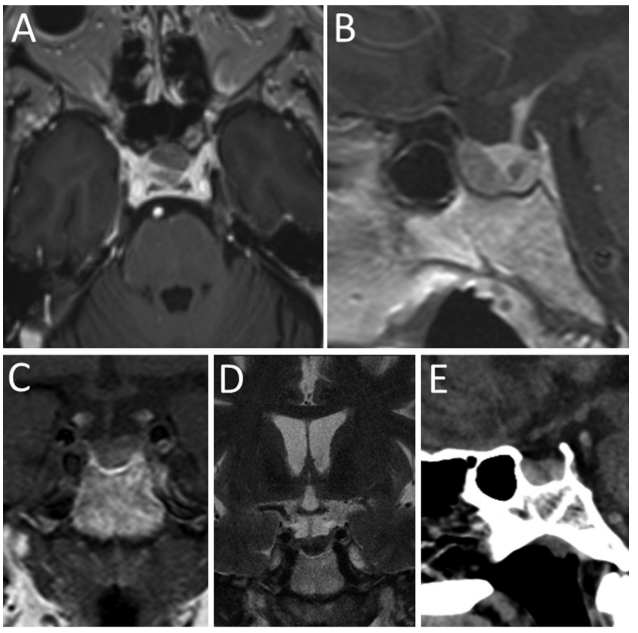
Institutional review board approval was obtained for this study. The patient consent process was waived as this is a retrospective study stripped of all identifying information. Data collection was performed under the protocols of the Human Research Protection Office of our institution.

Illustrative Case

A young 41-year-old Caucasian woman was referred to the department of neurosurgery for the treatment of a sellar lesion. She has complained of leg weakness, headaches, and visual difficulty over a period of 3 months before surgery. She had a history of systemic arterial hypertension and diabetes mellitus and was diagnosed with Cushing disease (CD) by her endocrinologist. Her past medical history was remarkable for diverticulitis treated with colectomy 2 years before. Family history was unremarkable.

Physical examination revealed overweight, neck enlargement, and facial stigmata of Cushing syndrome. Neurological examination was normal except of blurry vision. Ophthalmological examination showed preserved visual acuity in both eyes without correction. Hormones levels were within normal ranges except of ACTH and plasmatic cortisol, with 76.2 pg/mL (7.2–63.3 pg/mL) and 28.9 µg/dL (morning range: 6.2–19.4 µg/dL), respectively. A fasting blood glucose was within normal ranges and a dexamethasone suppression test was negative. Other hormones values are expressed in the table included in ►**Fig. 1.**

MRI (►**Fig. 1A–E**) revealed a hypoenhancing, T2-weighted images (T2WI) hypointense, slightly T1-weighted images (T1WI) hyperintense lesion in the anterior aspect of the pituitary gland, eccentric to the left, measuring approximately 8 × 14 × 9 mm (anteroposterior [AP] by transverse by craniocaudal [CC]). There is a second smaller hypoenhancing, T2WI hyperintense, slightly T1WI hyperintense lesion in the posterior aspect of the midline pituitary gland, measuring approximately 6 × 11 × 5 mm (AP by transverse by CC). Normal enhancing pituitary tissue is seen surrounding these lesions. With these findings, the serum hormone levels and the clinical features the diagnosis of CD is mandatory.



Preoperative hormones	Serum levels
TSH	**1.52 mIU/mL** (NV 0.5-5mIU/mL)
T4, free	**0.93 ng/dL** (NV 0.8-1.8 ng/dL)
ACTH	**76.2 pg/mL** (NV 7.2-63.3 pg/mL)
Cortisol	**28.9 mcg/dL** (NV 6.2-19.4 mcg/dL)
FSH	**1.6 mIU/mL** (NV 1.5 to 12.4 mIU/mL)
LH	**1.5 mIU/mL** (NV 1.0 - 11.4 mIU/mL)
GH	**0.2 ng/mL** (NV < 10 ng/mL)
IGF-1	**32 ng/mL** (NV 65-200 ng/mL)
Prolactin	**6.9 ng/mL** (NV < 25 ng/mL)

	Preop	1-day postop	2-day postop
Cortisol, serum	28.9 ug/dL	2.7 ug/dL	1.4 ug/dL

Fig. 1 Preoperative images. Axial brain magnetic resonance imaging with contrast showing two different hypo-enhancing lesions in the pituitary gland (**A**). The anterior tumor (suspected as adrenocorticotropic hormone [ACTH]-secreting adenoma) measures approx. 8 × 14 × 9 mm (anteroposterior [AP] by transverse by craniocaudal [CC]) and the posterior tumor (suspected as pituicytoma) measures approx. 6 × 11 × 5 mm (AP by transverse by CC) (**B**). There is no cavernous sinus invasion (**C**) and the anterior tumor looks hypointense and hyperintense on T2-weighted and T1-weighted images, respectively (**D**). In brain computed tomography scan, there is a presellar type of sphenoid sinus and both tumors look slightly hyperdense (**E**). Lower table shows preoperative hormone serum values and cortisol serum values before and after surgery. There is a clear decrease of cortisol after the resection of the ACTH-secreting tumor. FSH, follicle stimulating hormone; LH, luteinizing hormone; GH, growth hormone; IGF-1, insulin like growth factor 1; NV, normal value; TSH, thyroid stimulating hormone.

Our pituitary tumor board believed that the two lesions were both pituitary ACTH-secreting adenomas. We performed a standard endoscopic endonasal approach for a transsphenoidal resection of these tumors. The pathological tissue was soft, not bleeding and easily dissectable. There were no distinctive features among both masses. We send the surgical specimens in the same bottle. The closure consisted of placing hemostatic matrix over the arachnoid, followed by a dehydrated membrane and acellular dermal matrix for sellar floor reconstruction.

Histologic examination shows two distinct lesions. The first consists of a pituitary adenoma (►**Fig. 2A**) composed of monomorphous population of adenoma cells arranged in a sheet-like growth. ACTH immunostaining was intense. This adenoma shows no atypical cytological features and no mitoses. Ki67 labeling index is very low (< 1%) and p53 immunostaining is negative consistent with TP53 wild type. Collagen IV immunostaining (►**Fig. 2B**) confirms the loss of collagen fibers in the lesion consistent with adenoma.

The second lesion consists of a proliferation of pituicytes arranged in vague fascicles (►**Fig. 2C**). The tumor cells show the characteristic elongated bipolar morphology consistent with PC (►**Fig. 2D**). As common in PC, the tumor cells are positive for TTF1 (►**Fig. 2E**) and B cell lymphoma 2 (►**Fig. 2F**). The tumor shows no atypical features, that is, no mitoses, cytologic atypia, or necrosis.

The patient experienced an uneventful postoperative course. We assume that the anterior mass was the ACTH-secreting adenoma and the posterior mass the PC. After two postoperative days, plasma cortisol levels decreased dramatically, 2.7 µg/dL and 1.4 µg/dL in the first and second postoperative day, respectively. At 2-week follow-up, she denied visual fields problems or blurry vision and was neurologically intact. One blood pressure medication was removed and

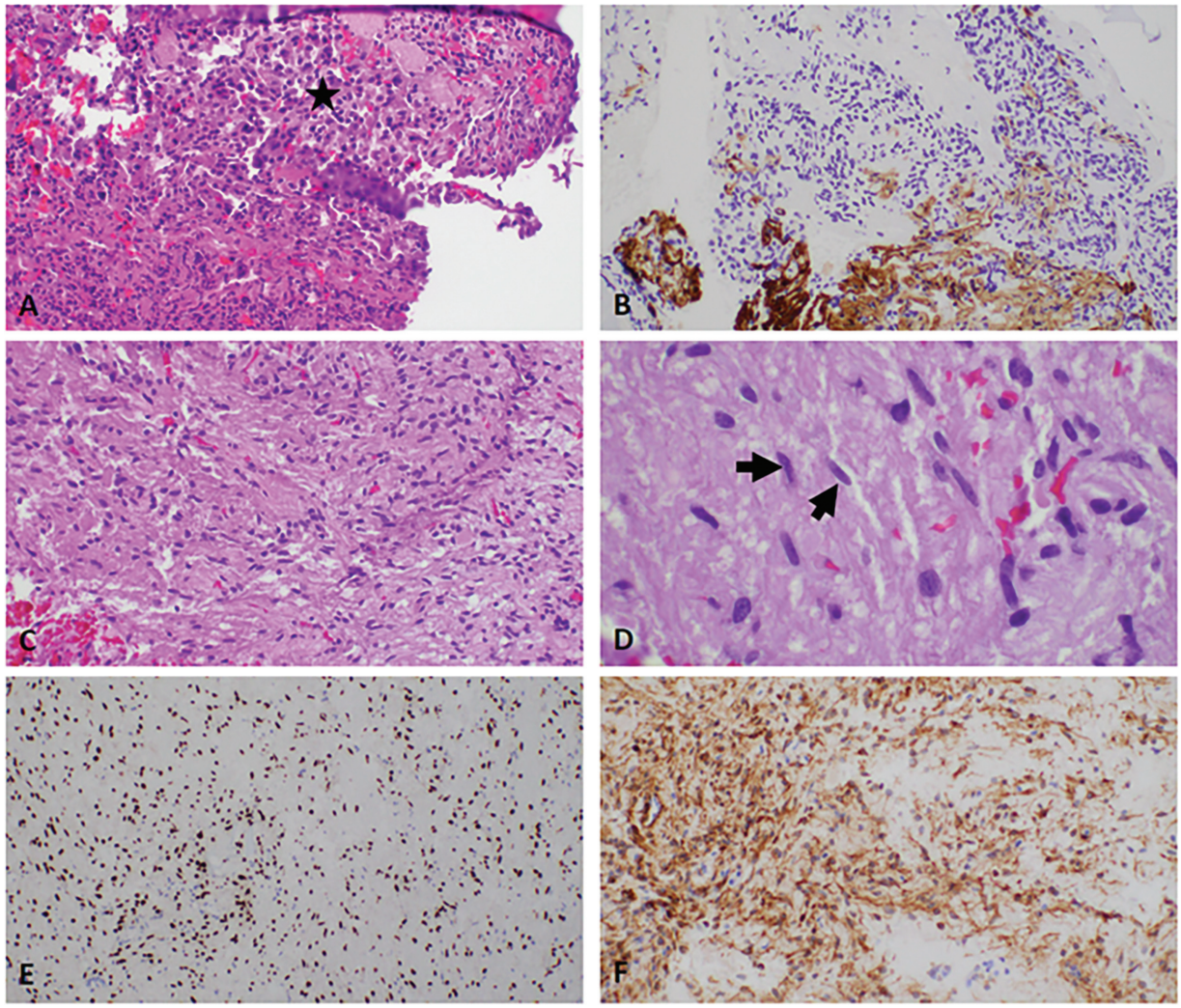


Fig. 2 Photomicrographs of surgical specimen. (**A**) Low magnification shows adenoma cells (*star*) composed of sheet-like tumor cells (original magnification ×100). (**B**) Collagen IV immunostaining shows complete loss of collagen fibers within the adenoma (Immunohistochemistry—original magnification ×100). (**C**) The pituicytoma is composed of solid growth of tumor cells arranged in vague fascicles (original magnification ×200). (**D**) The tumor cells display an elongated bipolar appearance (*arrows*). Note the absence of cytological atypical features (original magnification ×600). (**E**) The tumor cells are diffusely positive for thyroid transcription factor 1 (immunohistochemistry—original magnification ×100). (**F**) The tumor cells are diffusely positive for B cell lymphoma 2 (immunohistochemistry—original magnification ×100).

she had an optimal blood pressure control with only one medication.

Discussion

This exceedingly rare case represents the ninth case reported in the literature of a histological confirmed pituitary adenoma combined with a posterior pituitary tumor. Moreover, this is the second case with two clear pathological images in the MRI, one lesion in the anterior pituitary and another lesion in the posterior pituitary (►**Table 1**).

In the posterior pituitary gland, there are five types of specialized glial cells with sustentacular function. These five cells are a unique linage derived from the ependyma[2] and TTF-1 serves as a strong nuclear immunomarker for the diagnosis of the tumors originated from these cells (PC, GCT of the neurohypophysis, and SCO).[3,10] Regarding SEP, its existence in humans is still contradictory, not fully accepted and some authors consider this tumor a variant of PC.[11] These tumors are rare and very infrequent compared with pituitary adenomas; their real incidence is unknown. More than 70% of TTF-1 pituitary tumors have been reported in the past 8 years, which is most likely related to the increased use of radiographic imaging and the growth rate of scientific publication.[4] Patients with these tumors are typically diagnosed between the fifth and sixth decade of life and GCT is the most frequent.[12,13] Interestingly, TTF-1 tumors frequency increase with aging (up to 15% in postmortem series[14–16]) and are very rare in the pediatric population.[4] Compression of the optic pathway and headaches are the most frequent symptoms, but signs of pituitary insufficiency because of the mass effect have been reported.[4]

The neuroimaging features of posterior pituitary tumors are nonspecific, and their diagnosis relies on pathological findings.[17] Some authors have proposed that these masses are centered in the suprasellar region, have avid enhancement after contrast on T1WI, and never have a cyst component or calcification and do not infiltrate the cavernous sinuses.[6] Nevertheless, these features do not correlate with the possibility of a coexisting adenoma. Moreover, according to our review the enhancement was different in five reported cases and one author reported a patient with cavernous sinus invasion.[18] Particularly in our case, the patient had two macroadenomas with no enhancement and the only difference among them was that the posterior tumor appeared hyperintense on T2WI sequences. There is only one other reported case with a preoperative MRI showing two separate tumors in the sella turcica.[19] Surgery is the gold standard of treatment for TTF-1 pituitary tumor and gross total resection is the cure,[20] but recurrence has been described despite of being a WHO grade I neoplasm.[21] When gross total resection is not feasible and releasing the mass effect with providing histopathological specimen is a valid surgical goal.

The association of CD or acromegaly with these uncommon tumors is statistically extremely unlikely, so likely the patient's genetic landscape or an environmental exposure may be involved. No literature describes a pituitary adenoma being induced by other tumors, although pituitary adenomas

Table 1 Reported cases of synchronous TTF-1 pituitary tumors with anterior pituitary tumors

Author	Age	Sex	Posterior pituitary tumor	Serum hormone increased	Anterior pituitary finding	MRI features	Size (mm)	Double tumor on MRI	Immunohistochemistry	Comments
Tomita et al 1981[23]	66 y	M	GCT	GH, PRL	Adenoma	NA	NA	NA	NA	Autopsy
Cohen-Gadol et al 2003[23]	52 y	F	GCT	ACTH	Adenoma	NA	NA	NA	NA	–
Schmalisch et al 2012[19]	48 y	M	PC	ACTH	Adenoma	No enhancement	NA	Yes	TTF-1, GFAP, S100	–
Cambiaso et al 2015[9]	7 y	F	PC	ACTH	Adenoma	Homogeneous E.	NA	No	S100, GFAP, CgA	–
Neidert et al 2016[24]	67 y	F	PC	Normal	Adenoma (null type)	Heterogeneous E.	25 × 20 × 15	No	TTF-1, S-100, GFAP, Bcl-2	–
Lefevre et al 2018[25]	56 y	F	PC	ACTH	Adenoma	Normal (CSC+)	NA	No	TTF-1, S-100	–
Chang et al 2018[7]	57 y	F	PC	ACTH	Adenoma	NA	5 × 2 × 3	No	TTF-1, S-100, Vim, Syn, Bcl-2	–
Marco Del Pont et al 2020[18]	29 y	F	PC	GH	Adenoma	Homogeneous E.	15 × 17 × 12	No	TTF-1, S-100	–
Presented case	41 y	F	PC	ACTH	Adenoma	No enhancement	8 × 14 × 9/6 × 11 × 5	Yes	TTF-1, GFAP, Syn, Bcl-2	–

Abbreviations: ACTH, adrenocorticotropic hormone; Bcl-2, B cell lymphoma 2; CSC, cavernous sinus catheterization; GCT, granular cell tumor; GFAP, glial fibrillary acidic protein; GH, growth hormone; MRI, magnetic resonance imaging; NA, not available; PC, pituicytoma; PRL, prolactin; TTF-1, thyroid transcription factor 1.

can occur in conjunction with other sellar tumors, such as Rathke cleft cysts, craniopharyngioma, colloid cysts, arachnoid cysts, epidermoid cysts, as well as with other pituitary adenomas; this leads to the term "collision sellar lesion."[8]

In our comprehensive review, we found eight cases of TTF-1 pituitary tumors associated with increased serum hormones.[7,9,18,19,22–25] Hypercortisolism with increased ACTH serum values was reported in five patients and acromegaly with increased GH serum values appeared in two cases. Interestingly and according to our review, the histological finding of the pituitary adenoma or the cause of the serum hormone levels could not be determined in some of the reported cases of TTF-1 tumors.[6,7] There are few proposed hypotheses for this situation, but they require more expert consensus and are still matter of debate. One hypothesis is the possibility that TTF-1 pituitary tumors could produce some substances (cytokines, hypophysiotropic hormone-related factors) that might stimulate the adenohypophysis, as a paracrine relationship between the posterior pituitary cells and the anterior pituitary cells.[6] Another possibility is the accidental suctioning of the posterior pituitary tumor during a regular pituitary adenoma surgery. The incidence of TTF-1 pituitary tumors increases with aging, so increasing the amount of tissue for pathology examination in pituitary surgeries could increase the incidental finding of asymptomatic TTF-1 tumors.

Conclusion

We presented the ninth reported case of a TTF-1 pituitary tumor coexisting with a pituitary adenoma. Also, this is the sixth ACTH-secreting adenoma and the second one with two clearly separate pituitary tumors on MRI images. To date, the rate of the concomitance of these different subtypes is still matter of debate. We think that improving the amount of the tissue specimen available for pathology evaluation could increase the incidence of this very rare tumors.

Authors' Contributions

Ricardo J. Komotar had the idea for the article and perform the surgery with Michael E. Ivan. The literature search and data analysis were performed by Franco Rubino and Daniel Eichberg. The first draft of the manuscript was written by Franco Rubino and critically revised by Michael E. Ivan and Ali G. Saad. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical Approval

Institutional review board approval was obtained for this study. The patient consent process was waived as this is a retrospective study stripped of all identifying information. Data collection was performed under the protocols of the Human Research Protection Office of our institution.

Funding

None.

Conflict of Interest

None declared.

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