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Ectopic dopamine agonist-resistant macroprolactinoma to the clivus masquerading as a chordoma – A case report

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Objective. Pituitary neuroendocrine tumors (PitNETS) are common intracranial tumors, but extrasellar or ectopic PitNETS are very rare and supposed to originate from some pituitary remnants. They are mostly found in sphenoidal sinus. But particularly, ectopic clival PitNETS are highly aggressive and can cause bone invasion and can be misdiagnosed as other lesions of the skull base such as chordomas.

Case Report. We report a challenging case of an ectopic prolactin-secreting PitNET arising in the clivus in a young female presenting with secondary amenorrhea and sellar mass effect symptoms. On magnetic resonance imaging (MRI), the tumor showed osteolytic features that firstly oriented towards chordoma. Regarding the very high levels of prolactin that constantly exceeded 200 ng/mL, prolactinoma was indeed very presumable. Dopamine agonist treatment was progressively introduced to its maximal tolerated dose, but with neither hormonal response nor size reduction. Hence, surgical resection was decided and the patient underwent an endoscopic transsphenoidal resection of the tumor that was purely ectopic to the clivus. The diagnosis of prolactinoma was confirmed by pathological examination and immunohistochemical staining was intensely and diffusely positive for prolactin and focally for follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The surgery succeeded to normalize prolactin level, but with residual tumor on the fourth month MRI control.

Conclusion. Management of these rare tumors should be individualized with multidisciplinary collaboration.

Keywords: ectopic, PitNETS, prolactinoma, clival, chordoma, dopamine-agonist

Pituitary adenomas, also called pituitary neuroendocrine tumors (PitNETS), are the second most common intracranial tumors after meningiomas. Based on their functioning status, PitNETS can be either functioning or non-functioning and prolactinomas represent more than 50% of all of them. In female patients, incidence of prolactinomas is three times higher than in males and macroprolactinomas are eight times less common than microprolactinomas (Lee 2023; Petersenn et al. 2023).

Extrasellar or ectopic PitNETS are very rare and supposed to originate from some pituitary remnants during embryological migration and can be found in the sphenoid sinus, cavernous sinus, pituitary stalk, and the clivus. Ectopic clival PitNETS are highly aggressive and can cause bone invasion and can

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be misdiagnosed as other lesions of the skull base such as chordomas (Demir et al. 2024). We report a challenging case of a macroprolactinoma disguising as a chordoma in a female patient.

Case presentation

A 41-year-old female patient with no medical history presented with six-year history of secondary amenorrhea, galactorrhea, holocranial headaches, and reduced vision. Physical examination revealed grade 1 obesity (BMI=31.8 kg/m^2), decreased axillary and pubic hair. Cardiopulmonary and neurological examinations were normal, especially there were no cranial nerves disorders nor visual field defect. Magnetic resonance imaging (MRI) of the sellar and parasellar regions demonstrated an intrasellar lesion of size 3.4×2.7×3.6 cm with hypointensity on T1-weighted images, hyperintensity on T2-weighted images, and homogenous enhancement. The mass was osteolytic and extending into the sphenoid sinus with sellar floor and posterior clival wall cortical rupture. It was extending superiorly, slightly deviating the normal pituitary gland and bilaterally to the cavernous sinuses (Figure 1).

Chordoma was initially very likely. Laboratory examinations revealed hyperprolactinemia (598.4 ng/mL; reference range: <20 ng/mL) and hypogonadotropic hypogonadism with follicle-stimulating hormone (FSH) of 3.95 IU/L (reference range: 3–9 IU/L) and luteinizing hormone (LH) of 0.10 IU/L (reference range: 2–9 IU/L) suggesting the possibility of ectopic macroprolactinoma. Level of 8:00 a.m. cortisol was in the lower limit: 97 μg/L (reference

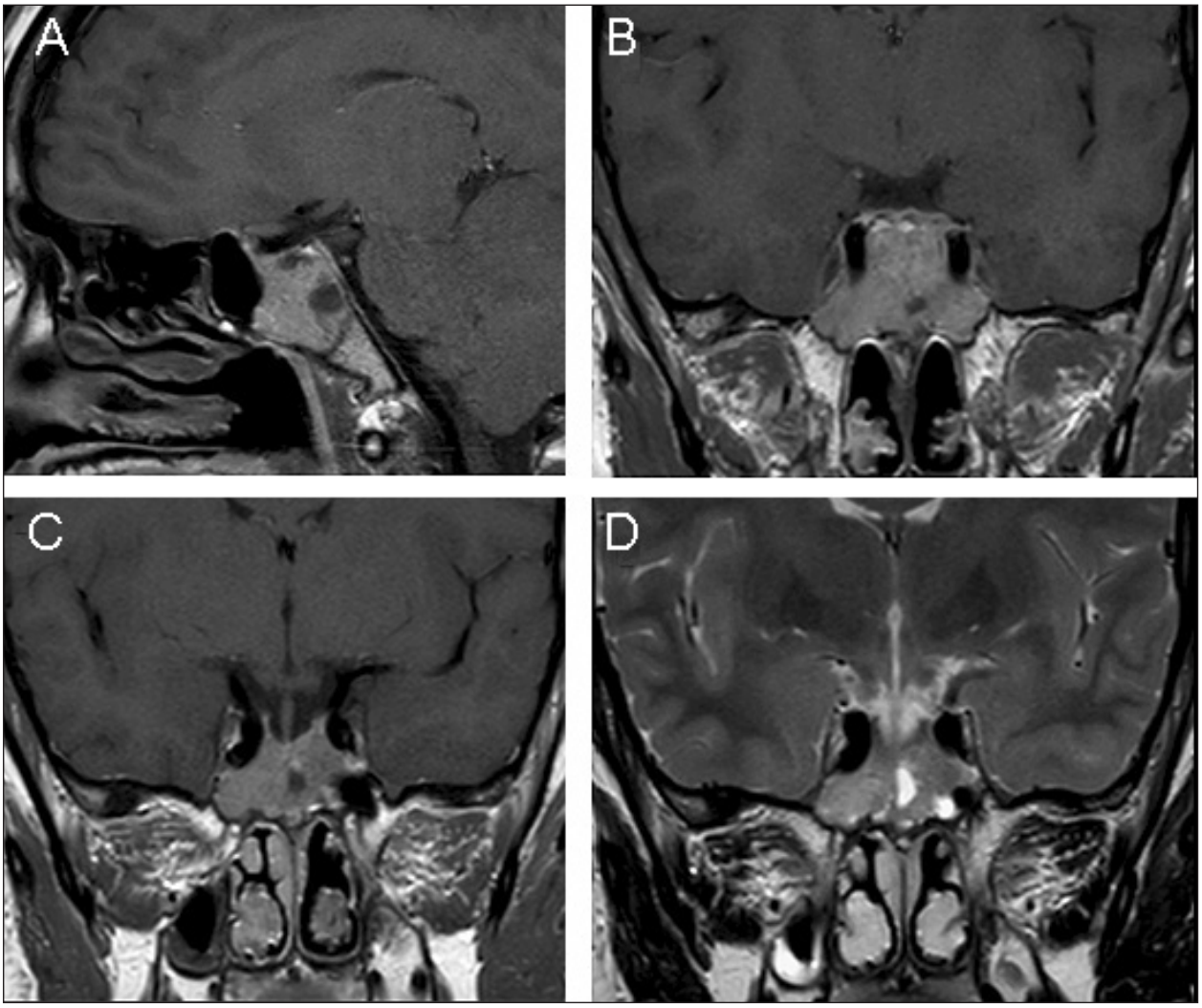

Figure 1. Magnetic resonance imaging (MRI) of the sellar and parasellar regions. **(A)** Sagittal T1-weighted; **(B)** coronal T1-weighted; **(C)** coronal contrast-enhanced T1-weighted; and **(D)** coronal T2-weighted.

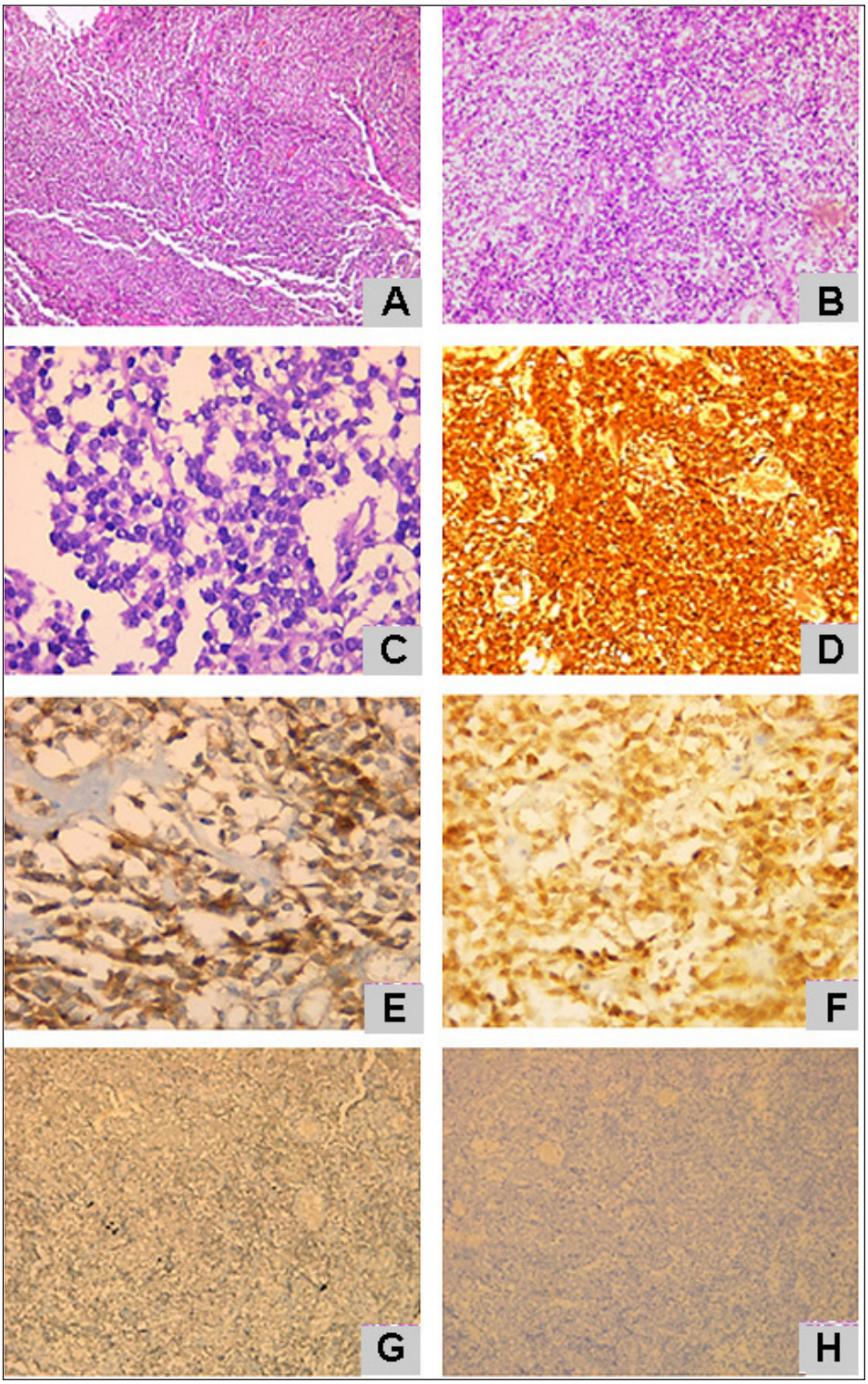

Figure 2. Pathology and immunohistochemistry staining. **(A, B)** Solid sheets of tumor cells within a fibrovascular stroma (hematoxylin and eosin staining, magnification ×40 and ×100, respectively). **(C)** Epithelioid tumor cells having a uniform nuclear morphology with stippled chromatin, inconspicuous nucleoli, and moderately abundant cytoplasm (hematoxylin and eosin staining, magnification ×400). **(D)** Diffuse expression of prolactin (immunochemistry, magnification ×100). **(E)** Focal expression of follicle-stimulating hormone (FSH) (immunochemistry, magnification ×400). **(F)** Focal expression of luteinizing hormone (LH) (immunochemistry, magnification ×400). **(G)** Negativity of adrenocorticotropic hormone (ACTH) (immunochemistry, magnification ×40). **(H)** Negativity of growth hormone (GH) (immunochemistry, magnification ×40).

range: 100–200 μg/L). The remainder of pituitary panel values was unremarkable: free thyroxine (fT4) of 11.7 ng/mL (reference range: 9–19 ng/mL) and insulin-like growth factor 1 (IGF-1) of 131 ng/mL (reference range: 97–263 ng/mL).

The patient was initially treated by 20 mg of hydrocortisone and cabergoline with a dose ranging from 1.0 mg to 4.5 mg per week, but the prolactin levels failed to normalize and remained constantly above 200 ng/mL and no size reduction was observed on MRI. Then, she was lost to follow-up for 4 years and subsequently cabergoline treatment was reintroduced for additional six months with no adequate response. Hence, surgery was decided and the patient underwent an endoscopic transsphenoidal resection of the tumor that was purely ectopic to the clivus and the dura matter was intact. The diagnosis of prolactinoma was confirmed by pathological examination (Figure 2). Immunohistochemistry staining was intensely and diffusely positive for prolactin (100%) (Figure 2D), and focally for FSH (30%) (Figure 2E) and LH (10%) (Figure 2F).

Within two weeks after surgery, the patient recovered from headaches, fatigue and galactorrhea, and was maintained on 20 mg of hydrocortisone. Prolactin level was decreased to a normal level of 17.24 ng/mL.

Four months post-surgery, prolactin levels normalized, but MRI showed a 2×2.4×2.9 cm clival mass with hypointensity on T1-weighted images,

Table 1
Clinical, biological, therapeutic, and evolution characteristics of ectopic prolactin secreting PitNETs according to Campana et al. (2022)

Case report	Ectopic PitNET site	Prolactin at diagnosis (ng/mL)	Treatment options	Treatment response
Shenker et al. (1986)	Clivus	2900	Biopsy + DA	Prolactin normalization
Lloyd et al. (1986)	Sphenoidal sinus	2900	Biopsy +DA	n.a.
Heitzmann et al. (1989)	Sphenoidal sinus	267.3	DA + Surgery + DA	Initial DA resistance, total surgical resection, prolactin normalization on DA
Hattori et al. (1994)	Sphenoidal sinus, clivus, petrosal bone tip, inner wall temporal bone	2030	Biopsy + DA	Tumor reduction
De Witte et al. (1998)	Clivus	34 000	Surgery + DA	Prolactin normalization
Ballaux et al. (1999)	Clivus	2511	DA	Prolactin normalization, and 30% tumor volume reduction
Peker et al. (2005)	Suprasellar cistern	80	DA + Surgery	DA resistance, tumor evaluation n.a.
Ajler et al. (2012)	Sphenoidal sinus	240	DA + Surgery	DA resistance, tumor evaluation n.a.
Kusano et al. (2013)	Sphenoidal sinus, cavernous sinus, left maxillary sinus, ethmoid sinus, clivus	634	Biopsy + DA	n.a
Liang et al. (2014)	Clivus, sphenoidal sinus, bilateral middle cranial fossa and medial temporal bones	>1000	Biopsy + DA	DA resistance
Karras et al. (2016)	Clivus	881	Surgery + DA	Prolactin normalization
Akinduro et al. (2018)	Sphenoidal sinus	820	Biopsy + DA	Prolactin normalization, Tumor reduction
Agely et al. (2019)	Sphenoidal sinus, clivus, cavernous sinus	n.a	Biopsy + DA	Prolactin normalization
Agely et al. (2019)	Clivus and sphenoidal sinus	393	Biopsy + DA	Prolactin normalization
Agely et al. (2019)	Sphenoidal sinus and clivus	161	DA	Prolactin normalization, Tumor reduction
Truong et al. (2021)	Clivus	188	Surgery + DA	Prolactin normalization
Campana et al. (2022)	Suprasellar cistern	13 038	DA	Prolactin normalization, 95% volume reduction

Abbreviations: DA – dopamine agonist; n.a. – not available; PitNETS – pituitary neuroendocrine tumors.

heterogenous hyperintensity on T2-weighted images, and homogenous gadolinium enhancement evoking either a residual or a recurrent tumor. Anterior pituitary gland was laminated with empty sella syndrome and cavernous sinuses were intact. Dopamine agonist (Cabergoline) was reintroduced progressively.

Discussion

We report a case of an ectopic clival dopamine agonist (DA) resistant macroprolactinoma in a female patient. Ectopic PitNETS are defined by extrasellar development with no connection to intrasellar region and their diagnosis could be challenging. They should be distinguished from invasive PitNETS associated to sellar floor defect and from empty sella (Ajler et al. 2012). In this patient, there was indeed a cortical rupture of sellar floor probably attesting the invasive nature of this PitNET.

Ectopic PitNETS are rare and their incidence is difficult to estimate with only few cases reported in the literature and occur more frequently in females with a mean age of 44.6 years at diagnosis. They are thought to originate either from pituitary remnants along the normal embryological Rathke's pouch migration path for clivus, sphenoidal sinus, and cavernous sinus PitNETS or from ectopic suprasellar peri-infundibular pituitary cells for the suprasellar tumors. Ectopic PitNETS can also occur in nasopharynx, nasal cavity, and the third ventricle (Altafulla et al. 2019; Campana et al. 2022; Demir et al. 2024).

Sphenoidal sinus is the most common site for ecopic PitNETS (36%), but in this case, we described a rare clival tumor, only seen in 7.2% of all cases (Demir et al. 2024) that was misdiagnosed as a chordoma. In fact, clival masses includes numerous diagnosis such as chordomas, chondrosarcoma, osteoblastomas, and meningiomas, and commonly manifest by mass effect symptoms (Karthik et al. 2023).

Clinical symptoms could be classified into three categories: neurological symptoms such as headaches, visual impairment, and oculomotor dysfunction, hormonal symptoms due to either autonomous secretion of one or more hormones or to hormonal deficiency secondary to deviation or compression of the pituitary gland and finally direct mass effect symptoms such as nasal obstruction, epistaxis or cerebrospinal fluid (SCF) leak (Truong et al. 2021). The clinical presentation in this case was mainly headaches and intermittent rhinorrhea, but also to hormonal disturbances secondary to hyperprolactinemia causing amenorrhea, hypofertility and corticotropin deficiency.

On imaging study by MRI, clival PitNETS are typically heterogenous with low signal on T1-weighted images high signal on T2-weighted images and mild to moderate Gadolinium enhancement and they also can show some destructive features like bone erosion and surrounding invasion (Agely et al. 2019; Zhu et al. 2020). They may extend to the sphenoid sinus, destroy the sellar floor, and selectively invade the cavernous sinus (Demir et al. 2024), which was the case in this patient. Aggressiveness of these lesions is yet to understand and may predict recurrence. On the other hand, chordomas show variable signal intensity on MRI in both T1- and T2-weighted images with low Gadolinium enhancement and likewise the same destructive and invasive features as ectopic clival PitNETS as well as calcifications (Zhu et al. 2020).

Regarding the hormonal profile, the ectopic PitNETS are most commonly adrenocorticotropic hormone (ACTH)-secreting (25%), but with some location specificities. For ectopic clival PitNETS, they are frequently non-functional (50%), less commonly prolactin-secreting (25%) and growth hormone (GH)-secreting (21.4%), and rarely ACTH-secreting (3.6%) according to the review of (Zhu et al. 2020). Prolactinomas are not the most common types of ectopic PitNETS probably because of lacking of vascular and neurological connections with the hypothalamus and the reason of its frequency in the clivus is yet to determine (Ajler et al. 2012).

In the review of (Campana et al. 2022), seventeen cases of prolactin secreting PitNETs were reported and we detailed them in Table 1.

For this case, macroprolactinoma was evoked in the presence of amenorrhea and galactorrhea as well as constant high levels of prolactin exceeding 200 ng/mL and the final diagnosis was made histologically after surgery that was indicated following DA resistance and the probability of chordoma. In fact, DA resistance is defined by a failure to achieve normal prolactin on maximally tolerated doses of DAs and a failure to achieve 50% reduction in tumor size for at least six months of treatment (Souteiro and Karavitaki 2020). Predictors of DA resistance are believed to be male gender, large tumor size, the existence of cystic, hemorrhagic or necrotic component, invasiveness and molecularly decreased expression of D2 dopamine receptors in tumor cells (Souteiro and Karavitaki 2020; Vermeulen et

al. 2020). This patient had actually many of these predictors that were mainly the invasiveness of cavernous sinuses and the large volume. Moreover, we suppose that regarding its ectopic location with disconnection from hypothalamic neurological and vascular effects, this prolactinoma was non-responsive to DA therapy.

There are no practical guidelines for management of ectopic prolactin-PitNETS because of their low incidence and their multiple differential diagnoses and as for intrasellar prolactinomas, medical treatment by DA is the first-line option, and surgery is indicated in case of DA resistance or in the occurrence of complications such as apoplexy, severe local compression, and SCF leak (Petersenn et al. 2023).

Conclusion

Ectopic prolactinomas are extremely rare, but paradoxically the most common functional PitNET of the clivus. Diagnosis of ectopic clival PitNET was challenging in this case, regarding its rarity and location in skull base. Nevertheless, the combination of clinical, biological, and morphological features oriented towards prolactinoma. Medical treatment by DA was proposed initially, but was ineffective mainly because of the invasive characteristics of the lesion and its location. Transsphenoidal surgery (TSS) resection was successfully complete and the final diagnosis was made histologically. Multidisciplinary management of this rare entity is recommended and should be individualized.

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