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Case report

Clival prolactinoma masquerading as a chordoma: a case report ^{☆,☆☆}

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ABSTRACT

Ectopic pituitary adenomas are a rare clinical entity and are frequently mistaken for other base of skull lesions on imaging. We report the clinical presentation and management of a woman presenting with an ectopic prolactinoma located in the clivus. A 66-year-old female presented with a 6-month history of headaches and light-headedness. Anatomical imaging demonstrated a clival lesion most suspicious for chordoma. Endocrinological assessment revealed modestly increased prolactin level with lower-than-expected gonadotrophins levels for her age. Surgical resection confirmed an ectopic prolactinoma.

A skull base lesion in a patient with hormonal derangement should lend to a high clinical suspicion of an EPA as they may be treated with medications before surgery. Guidelines could assist clinicians investigating skull-based lesions to identify the rare, but important diagnosis of ectopic pituitary adenomas.

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Introduction

Pituitary tumors are common intracranial neoplasms, comprising an estimated 10%–15% of diagnosed intracranial tumors [1–3]. Approximately 90% of pituitary tumors are adeno-

mas and are typically found within the sella turcica [4]. Extrasellar or ectopic pituitary adenomas (EPAs) most likely arise from remnants of the embryological migratory path of the pituitary gland [1,3,5–7]. EPAs are a rare presentation of pituitary adenomas and have mostly been described in case reports [3,5,8–12]. Because they are so uncommon, EPAs may be

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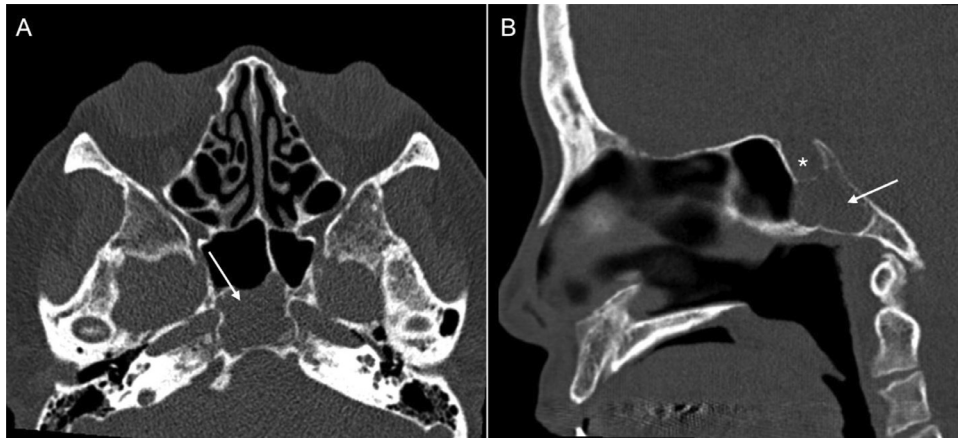


Fig. 1 – Axial (A) and sagittal (B) non-contrast CT of the skull base demonstrates a lytic lesion within the clivus (arrow). The sella (*) is not expanded but does have some focal areas of bone erosion along the floor.

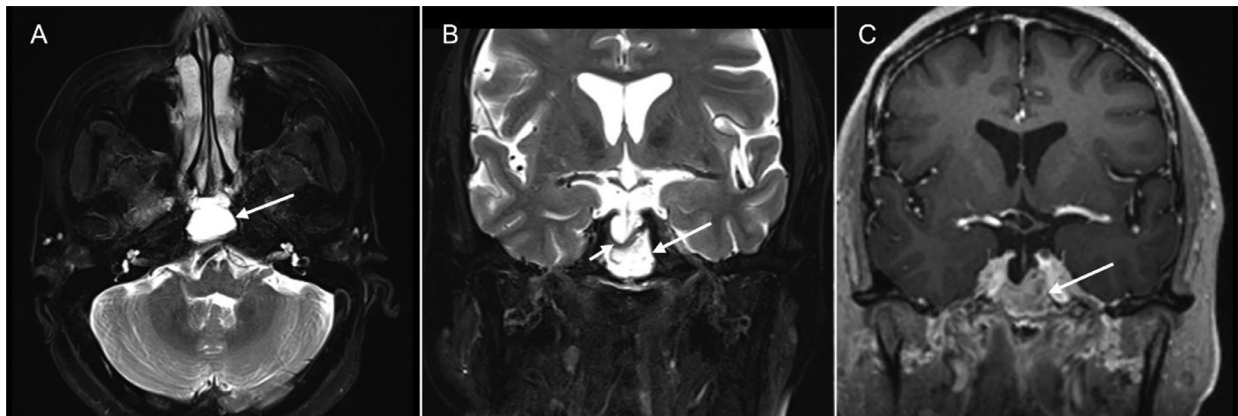


Fig. 2 – MRI of the brain and skull base. Axial T2 (A) and coronal T2 (B) sequences show a hyperintense lesion within the clivus (arrows). The normal pituitary tissue is seen above but in close proximity to the lesion (short arrow). On the coronal T1 with contrast sequence (C), the lesion shows heterogeneous internal enhancement (arrow).

misdiagnosed as other skull lesions such as chordomas, chondrosarcoma, meningioma or astrocytomas [3,8].

Case report

A 66-year-old female presented with a six-month history of headaches and light-headedness. Her background was notable for invasive localized ductal breast cancer treated with breast conserving surgery, adjuvant hormonal therapy and adjuvant radiation therapy approximately ten years prior. Computerized tomography (CT) demonstrated a lesion within the clivus which was quadrangular in shape with internal foci of calcification (Fig 1). On magnetic resonance imaging (MRI) the tumor was isointense on T1 and hyperintense on T2 with avid enhancement, and no sellar extension was present (Fig 2). On MRI the pituitary gland appeared normal with a midline infundibulum. The lesion was photopenic on bone scan. The lesion was highly suspicious for chordoma, with differentials including plasmacytoma, myeloma, or an aggressive pituitary lesion.

Serum biochemistry included hyperprolactinemia (variable severity, between 4.6-8x the upper limit of normal [ULN]) with no significant macroprolactin detected (Table 1). Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) were lower than expected for her post-menopausal state while other pituitary hormones were intact (Table 1).

The lesion was debulked via an endoscopic transnasal approach. Histologically, the tumor was comprised of cells with round nuclei with some variation in nuclear size. Mitotic activity was not identified in the specimen. On immunohistochemistry (IHC), the lesional cells showed positive staining for chromogranin, scattered positive staining for cytokeratins CK8/18 and AE1/AE3, patchy positive staining for prolactin, and negative staining for FSH, LH, growth hormone (GH), adrenocorticotropic hormone (ACTH) & thyroid-stimulating hormone (TSH). These findings identified the lesion to be a prolactinoma.

Her post-operative MRI demonstrated no evidence of residual disease (Fig 3). Two months post-surgery, low dose cabergoline (0.25mg once weekly) was commenced in light of the histology and her serum prolactin remaining elevated at 2x

Table 1 – Hormone panel.

HORMONE	Presentation	Prior to operation	1 week Post-op	2 Months post op ^a	4 Months post-op ^b	10 months post-op ^c	11 months post-op	Reference ranges
Prolactin	2300 - 3990	2470	1210	1190	42	1110	<30	<500 mU/L
	Not detected	-	-	-	-	-	-	-
Macroprolactin								
LH	13	-	32	8	-	-	-	11-59 U/L*
FSH	32	-	9.9	23	-	-	-	17-115 U/L*
Estradiol	<37	-	-	<50	-	-	-	<100 pmol/L*
IGF-1	21	-	-	-	-	-	-	4.2-3.1 nmol/L
GH	0.07	-	-	-	-	-	-	0.05-8.00 ug/L(mass)
TSH	1.3	0.7	-	0.9	0.9	-	1.9	0.3-4.5 mU/L
T4	13	12	-	15	15	-	14	7.0-17 pmol/L
Cortisol	280	126	358	181	90	406	-	140-640 nmol/L
ACTH	<10	-	15	10	<10	11	-	10-50 ng/L

LH, luteinizing hormone. FSH, follicle-stimulating hormone. IGF-1, insulin-like growth factor 1. GH, growth hormone. TSH, thyroid stimulating hormone. T4, thyroxine. ACTH, adrenocorticotropic hormone.

a. Cabergoline 0.25mg once weekly commenced.

b. Cabergoline withdrawn.

c. Cabergoline 0.25mg once weekly recommenced.

* Indicates reference range for post-menopausal women.

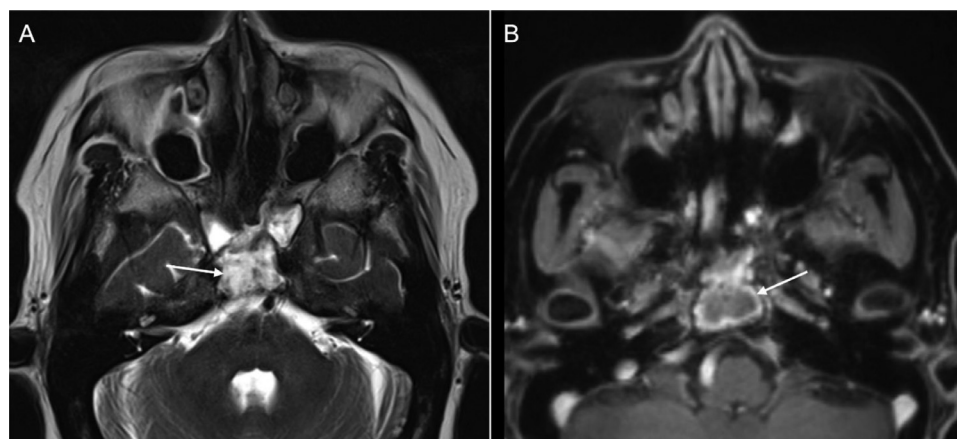


Fig. 3 – Post-operative MRI of the skull base. Axial T2 (A) and axial T1 with contrast (B) sequences demonstrate resection of the lesion, with non-enhancing, T2 hyperintense post-surgical change within the clivus (arrows).

ULN. Prolactin normalized within six weeks and cabergoline was withdrawn. Mild hyperprolactinemia (2x ULN) recurred after 10 months of surveillance, with preservation of other hypothalamic-pituitary axes. Cabergoline was reintroduced (0.25mg once weekly) which swiftly normalized prolactin and is currently well tolerated. Re-staging MRI at 12 months demonstrated no evidence of tumor recurrence.

Discussion

EPAs are an exceedingly rare presentation of pituitary tumors. EPAs have been found in a variety of locations, both intra- and extracranial. They are most commonly found in the sphenoid sinus, followed by the clivus; other locations include suprasellar, nasopharynx and the cavernous sinus [1,3]. Clival

tumors are rare, and account for approximately 1% of intracranial neoplasms. The most common differential for a clival lesion is chordoma (40%), followed by meningioma, chondrosarcoma, astrocytoma, craniopharyngioma, and rarely pituitary adenoma [3,11].

Pathogenesis and presentation

The pituitary gland arises from Rathke's pouch cells, which originate from the surface ectoderm of the pharyngeal roof. Rathke's pouch then migrates upwards to the floor of the diencephalon, and the stalk between the pouch and pharynx degenerates. The most prevalent and accepted theory is that during this migration, remnant cells of Rathke's pouch localize outside of the adenohypophysis and become progenitor cells of EPAs [1,3,5–7]. An alternative theory proposes that suprasellar EPAs arise from cells of the pituitary cells of the subdi-

apophyseal portion of the pars tuberalis [13,14]. A third theory suggests that is that abnormal fusion of the post-sphenoid cartilage during embryogenesis results in the formation of a craniopharyngeal duct which extends from the sella turcica to the nasopharynx allowing aberrant migration of pituitary cells [13–15].

Shuman et.al [1] reported that of 85 cases of EPAs described in the literature, there was no significant sex differences in presentation (43 female, 42 male) and the average age of diagnosis was 46 years. Clinical presentation of EPA can be divided into three broad categories: hormonal excess or deficiency, neurological symptoms and direct mass effect. Symptoms and signs relating to hormonal secretion are common at presentation (50%) [1]. Cushing's syndrome due to ACTH-secreting EPAs is the most reported hormonal presentation (25%), while other common presentations include acromegaly due to GH-secreting tumors (12%) and hypogonadism and galactorrhea related to prolactinomas (frequency not reported) [1]. EPA location may correlate with type of hormone secretion: sphenoidal lesions have been reported to most likely secrete ACTH; nasopharyngeal tumors TSH; and clival tumors prolactin [1]. Neurological symptoms at presentation (41%) include headache, visual impairment, oculomotor deficits, paralysis and hearing loss [1]. Mass effect symptoms are uncommon at presentation (13%) but include: airway obstruction, epistaxis and a visible mass. Three cases (4%) presented without symptoms i.e. tumors were detected incidentally [1]. It is likely that modern improvements in imaging techniques coupled with greater accessibility will lead to an increase in case detection of asymptomatic individuals.

IHC of resected EPAs has most commonly demonstrated positivity for ACTH (46%), followed by prolactin (26%), GH (22%) and TSH (16%). In contrast to sellar adenomas, ACTH-secreting and TSH-secreting tumors are over-represented in published reports of EPAs which suggests that EPAs may be under-diagnosed. Prolactinomas comprise >50% of 'typical' diagnosed sellar adenomas, followed by non-functioning adenomas (<40%), GH-secreting adenomas (11%–13%), ACTH-secreting adenomas (1%–2%) while TSH-secreting adenomas are rare (<1%) [16]. EPA invasion of bone either on imaging or apparent during resection was reported in 36% of EPAs of all locations but more common in clival tumors (93%) [1].

Imaging

Yang et.al [7] reviewed the radiographic features in a comparative study of eight individuals with histologically confirmed EPAs arising in the sphenoid sinus. On non-contrast CT imaging, EPAs typically appeared isodense compared to adjacent grey matter and moderately enhanced with contrast. EPAs typically appeared isointense on both T1 and T2-weighted MRI with moderate enhancement post contrast administration [7]. In comparison with the case we report, which demonstrated a lesion that appeared isointense on T1-weighted MRI and hyperintense on T2-weighted with avid enhancement. Molecular imaging in the management of EPAs warrants further evaluation. One recent case report demonstrated the diagnostic utility of [⁶⁸Ga]-DOTA-Tyr3-octreotate (DOTATATE) PET/CT in localizing an ectopic TSH-producing adenoma occurring in

the nasopharynx which could not be localized initially with anatomical imaging (MRI) [17].

Treatment

Currently there are no EPA management guidelines, due to their low incidence. Ectopic prolactinomas have been successfully treated with dopamine agonists such as bromocriptine and cabergoline in the primary setting [9] and as adjuvant treatment following debulking surgery [9]. Unfortunately, EPAs may be belatedly diagnosed following transsphenoidal resection, pursued due to the (appropriate) clinical or radiographic concern for a more sinister lesion such as a chordoma. Such circumstances deprive the individual of the opportunity for a diagnostic trial of medical therapy.

Chordoma

Chordomas are a rare form of bone malignancy that present as locally destructive midline lesions. They are typically diagnosed late due to their indolent nature, leading to a poor prognosis [18,19]. Chordomas originate from remnants of the notochord and approximately 35% of chordomas arise in the spheno-occipital area, with most arising from the clivus [20]. Radiographically, chordomas classically appear as a clival lytic lesion with periosteal elevation [20]. They most often appear isointense on T1 weighted MRI and hyperintense on T2, as reported in our case [20]. Patients with chordomas most commonly present with headache, followed by visual disturbance, then abducens palsy [20].

Conclusion

Ectopic pituitary adenomas are a rare clinical entity. Detection of a skull base lesion should prompt anterior hormone testing as this may provide an opportunistic diagnostic trial for medical therapy. In patients with hyperprolactinemia and no radiographic features of malignancy, consideration should be made to treat with low-dose dopamine agonist therapy for 3 months before evaluation with repeat hormone panel +/- imaging. In those awaiting surgery, consideration can also be made to treat with medical therapy. However, given the varying clinical presentation of ectopic pituitary adenomas and lack of diagnostic certainty without tissue biopsy, management will be guided by the combination of clinical, biochemical and radiographic evidence and clinical discretion. All cases should be assessed within a multi-disciplinary setting at a center with a high level of experience in skull base and pituitary lesions.

Patient consent statement

We thank our patient for providing consent to the publication of all materials presented in this case.

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