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Acromegaly due to an ectopic pituitary adenoma in the clivus: case report and review of literature

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Abstract Pituitary adenomas rarely originate outside the sella turcica. Ectopic locations include the suprasellar region, sphenoid sinus, cavernous sinus and clivus. We describe a 50-year-old female who presented with clinical signs and biochemical evidence of acromegaly. Pituitary MRI demonstrated a 2 mm hypointense lesion on the right side of the pituitary gland. However upon drilling of the upper clival bone to expose the sella during endoscopic transsphenoidal surgery, soft tumor-like tissue was encountered within the clivus. Exploration of the sella, including the area of hypointensity noted on preoperative imaging, did not identify any other abnormality. Immunohistochemical examination of the fully resected tumor demonstrated growth hormone immunoreactivity. Failed preoperative diagnosis of this rare ectopic GH-producing tumor was compounded by the presence of a misleading pituitary abnormality consistent with a microadenoma. The epidemiology and pertinent literature of this uncommon condition is discussed.

Keywords Ectopic pituitary adenoma · Acromegaly · Clivus · Ectopic somatotropic adenoma

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Introduction

Acromegaly is characterized by a syndrome complex due to hypersecretion of growth hormone (GH) and insuline-like growth factor 1 (IGF-1), and leads to significant morbidity and reduced life expectancy due to cardiovascular, cerebrovascular, respiratory and neoplastic disease [1–3]. It is cause by a growth hormone (GH)-secreting tumors originating in the anterior pituitary in approximately 99% of cases [3, 4]. Diagnostic studies therefore always include pituitary imaging, particularly given the fact that in 90% of cases a macroadenoma ($\geq$1 cm size) is found. In rare scenarios in which pituitary imaging is unrevealing, extrapituitary tumors are sought. Bronchial carcinoids, non-Hodgkin's lymphoma secreting GH have been reported [5, 6], as well as growth hormone releasing hormone (GHRH)-secreting states from hypothalamic, pituitary gangliocytomas, carcinoid, and pancreatic tumors [4, 7–9].

"Ectopic" pituitary tumors are another potential source of hormonal hypersecretion. These tumors are thought to arise from embryonic cell rests along the course of migration from Rathke's pouch to the sella turcica [10]. The majority of ectopic pituitary tumors are biochemically active, secreting adrenocorticotrophic hormone (ACTH) or prolactin (PRL) [11, 12]. Only eleven histopathologic confirmed cases of ectopic somatotropinomas have been reported in the literature [11–21], with most tumors located

within the sphenoid sinus [12, 14–18, 21], the suprasellar region [13], the cavernous sinus [11].

We describe a very unusual case of a GH-secreting pituitary tumor located in the clivus that was fortuitously identified during surgery. The patient had a lesion suspicious for a microadenoma identified on pre-operative imaging, which in retrospect, was misleading.

Case history

A 50-year-old female presented with a 10 year history of generalized muscle and joint pains, chronic fatigue, impaired concentration and daily headaches. On specific questioning, she reported subtle changes in the size and shape of her hands, feet and facial features, and had undergone carpal tunnel release surgery 2 years prior. On physical examination, she exhibited mild acromegalic facial features with enlarged hands, frontal bossing, widened spacing of her teeth, macroglossia and a degree of prognathism. Visual fields were normal to confrontation, as was the rest of her examination.

Table 1 Pre-surgical results of hormonal tests

Parameter	Result (age & sex-matched normal range)
IGF-1	937 ng/ml (118–298 ng/ml)
GH/OGTT	6→ 6.4→ 4.8→ 5
Prolactin	26 μg/dl (< 19 μg/dl)
Free T4	0.82 (0.8–1.6 ng/ml)
9 a.m. cortisol	10 mcg/dl (8–25mcg/dl)

Biochemical evaluation revealed a marked elevation in IGF-1 at 937 ng/ml and non-suppressed growth hormone level following a carbohydrate load (nadir GH 4.8 μg/dl after 75 g glucose). The pre-operative endocrine evaluation was within normal limits (Table 1) other than a mildly increased PRL of 26 μg/dl.

A pituitary magnetic resonance imaging (MRI) scan, performed at an outside imaging facility, identified a 2 mm hypointense lesion on the right side of the pituitary gland which was suspicious for a pituitary microadenoma. (Fig. 1, arrowed).

The patient underwent an endoscopic transsphenoidal surgery. Upon drilling of the upper clivus to expose the sella, soft tumor–like tissue was encountered within the clival bone. Intra-operative histopathologic analysis of this tissue was highly suspicious of pituitary adenoma and the entire clival tumor measuring 8–10 mm was then fully resected. Exploration of the sella, including the area of hypointensity noted on the pre-operative MRI, did not identify any other abnormality. In retrospect, an area of altered signal within the clival bone was discernible (Fig. 2, highlighted) in the region corresponding to where the intra-operative tumor tissue had been encountered.

Histopathological and immuno-histochemical analysis of paraffin-embedded resected clival tissue confirmed a pituitary adenoma (Fig. 3a), that was immunoreactive for both growth hormone (Fig. 3b) and prolactin (Fig. 3c). Immunohistochemistry for the proliferative marker Ki-67

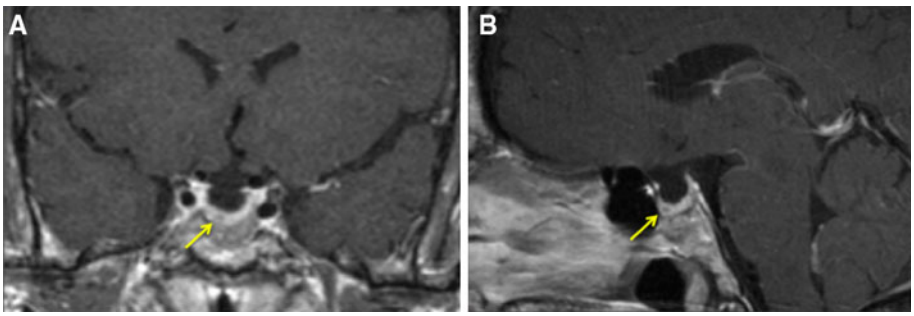

Fig. 1 Preoperative MRI. **a** Coronal T1-weighted image with gadolinium demonstrating a 2 mm hypointense lesion on the right side of a small pituitary gland with partial empty sella. **b** Sagittal gadolinium-enhanced image confirmed the small hypo-enhancing pituitary lesion

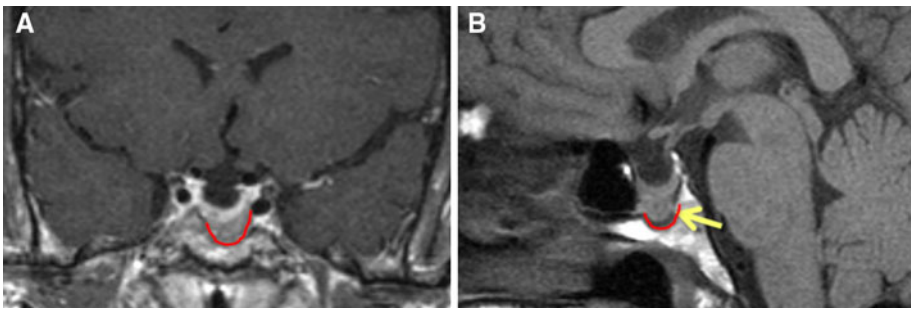

Fig. 2 Preoperative MRI. **a** Coronal and **b** sagittal T1-weighted with gadolinium showing mass at the clivus

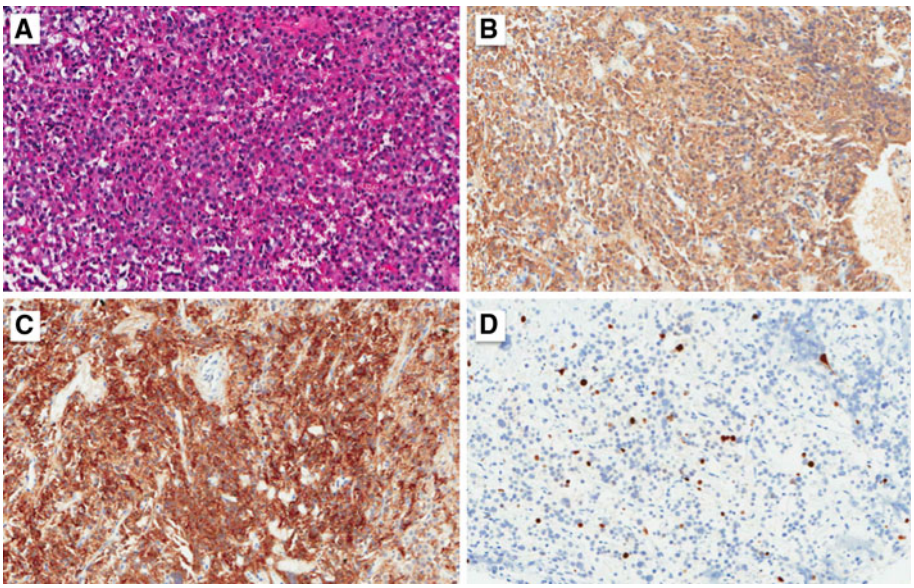

Fig. 3 **a** Hematoxylin and eosin stain of the resected clival tissue demonstrating sheets of monotonous cells with uniform round nuclei. Immunohistochemical stain showing positive immunostain for GH (**b**) and PRL (**c**). **d** Ki-67 immunopositivity was positive in 3–4% of cells. (×200 magnification)

demonstrated that this was slightly increased at 3–4% (Fig. 3d) and expression of p53 was estimated at <1%.

The post-operative course was unremarkable, including an MRI obtained 12 h after surgery showing no evidence of residual tumor. At 3 months, the IGF-1 level had normalized at 227 ng/ml (NR 94-252) and GH suppressed normally to 0.3 μg/dl after a 75 g glucose load in keeping with disease remission.

Discussion

Pituitary adenomas are the most common lesion found in the sellar space and they constitute 10–15% of primary brain tumors. However, an ectopic location of pituitary adenoma is rare, and since its first description in 1909 [22] approximately 100 cases have been reported [11, 13].

The location of ectopic pituitary tissue bears a close correlation with the embryological formation and involution of the craniopharyngeal duct. At the 8th week of gestation, a series of intricate neuroembryological events herald the beginning of the separation of the primitive pituitary gland into its pharyngeal and distal parts. Incomplete separation results in distribution of ectopic so-called ''pharyngeal pituitary'' tissue along the pharyngeal mucosa over the posterior vomerosphenoidal articulation [10]. This pharyngeal pituitary can be "stranded" in the walls of the nasal cavity, craniopharyngeal canal, or sphenoid sinus [20] and has been found incidentally at autopsy but these cells can also develop into ectopic pituitary adenomas.

A diagnosis of ectopic pituitary adenoma can only be made after careful intraoperative exploration confirms that the adenoma bears no direct communication with the sella itself and takes into consideration the relationship between the adenoma, the diaphragma sellae, pituitary stalk and normal pituitary gland. The location and radiologic appearance of ectopic pituitary adenomas can mimic a variety of skull base lesions including chordomas and meningiomas and accurate histopathologic assessment is key to confirming a diagnosis of pituitary adenoma and ascertaining the potential functional nature of these neoplasms [20].

In the largest series of 86 ectopic pituitary tumours [11], ACTH-secreting adenomas were most frequently (37.2%) encountered, followed by prolactinomas (25.6%) and endocrine inactive tumors (23.3%). GH-secreting adenomas accounted only for 10 (5%) of the series [11]. Additionally, of 11 previously reported ectopic intracranial GH-secreting pituitary adenomas (Table 2), seven were located in the sphenoid sinus and only two were located in the clivus [19, 20].

Clival tumoral masses are unfrequent and radiologic appearances are not specific. Differential diagnosis includes chordoma (~40% of cases) and less frequently meningioma, astrocytoma, germ cell tumors, lymphoma and metastases [23]. Ectopic clival pituitary adenomas are very uncommon and most reported cases were PRL-secreting or non-functional adenomas [23]. This case represents the third reported case of ectopic clival somatotropinoma.

The availability of advanced MRI imaging techniques, including dynamic acquisition studies, has greatly improved the ability to identify pituitary abnormalities. The presence of a small intrasellar hypointensity in this case was misleading. In the pre-operative evaluation, there was some concern that a 2 mm lesion might be inconsistent with an IGF-1 level of 937 ng/ml. To our knowledge, a high correlation between pituitary tumor size and IGF-1

Table 2 Reported histological confirmed cases of ectopic intracranial growth hormone-secreting pituitary adenomas

Series (ref. no)	Location	Elevated hormone levels
Corenblum et al. [21]	Sphenoid sinus	GH
Matsuno et al. [16]	Sphenoid sinus	GH and PRL
Madonna et al. [18]	Sphenoid sinus	GH and TSH
Hori et al. [14]	Sphenoid sinus	GH and PRL
Godim et al. [15]	Sphenoid sinus	GH
Mitsuya et al. [11]	Cavernous sinus	GH and PRL
Chan et al. [17]	Sphenoid sinus	GH
Choin et al. [19]	Clivus	GH
Guerrero et al. [13]	Suprasellar	GH and PRL
Bhatoe et al. [20]	Clivus	GH and PRL
Kurowska et al. [12]	Sphenoid sinus	GH and PRL

levels has not been reported, and in our own experience, we have witnessed paradoxical increases in IGF-1 levels following near complete resections of GH-secreting macroadenomas. Because a partially empty sella, like our patient, has been reported to harbor small GH-secreting adenomas within the compressed rim of pituitary tissue [14], we did not seek extrasellar lesions and proceeded to surgery. Fortunately, the clival tumor was found and resected.

Conclusion

Pituitary adenomas are common intracranial tumors, and the diagnosis is made by interpretation of clinical symptoms and signs in combination with biochemical and radiologic findings. GH-secreting adenomas are nearly invariably localized in the sella and are $\geq$1 cm in diameter in 90% of cases. Ectopic hormone-secreting adenomas are rare and the diagnosis may be difficult. Careful interpretation of MR images is required to avoid an unnecessary surgical dissection of inappropriate tissues, especially in situations where abnormalities are subtle, uncharacteristic or not adequately visualized.

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