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Review Article

Null Cell Pituitary Adenoma of the Clivus and Sphenoid Sinus: Case Report and Systematic Review of the Literature

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Abstract

Ectopic pituitary adenomas in the sphenoid sinus and/or clivus are rare lesions with unclear etiology and clinicopathologic characteristics. Previous reports were inconsistent with regards to immunohistochemical descriptions of these lesions, and were predominantly published in the era before the recently updated molecular genetic classification of pituitary adenomas put forth by the World Health Organization in 2017. We describe a true null cell ectopic pituitary adenoma involving both the clivus or sphenoid sinus, and present a systematic review of ectopic pituitary adenomas arising in each location.

Keywords: Pituitary Adenoma; Sphenoid Sinus; Clivus; Ectopic; Sublabial; Transsphenoidal

Abbreviations

ACTH: Adrenocorticotropic Hormone; CT: Computed Tomography; FSH: Follicle Stimulating Hormone; HGH: Human Growth Hormone; IGF-1: Insulin-Like Growth Factor-1; LH: Luteinizing Hormone; MRI: Magnetic Resonance Imaging; SS: Sphenoid Sinus; TSH: Thyroid Stimulating Hormone.

Introduction

Pituitary adenomas most commonly arise in the sella turcica. They may also but rarely occur ectopically in locations such as the sphenoid sinus, clivus, suprasellar region, or nasopharynx, without direct connection to the pituitary gland. The underlying etiology and clinical characteristics of ectopic pituitary adenomas remain poorly understood. Additionally, reports of this entity must be evaluated in light of the most recent WHO classification of pituitary adenomas. Under the new system, adenoma type is primarily determined by expression of lineage-specific transcription factors that were not incorporated in the prior classification system. After determination of adenoma type (somatotroph, lactotroph, etc), lesions are sub-categorized by histologic analysis and immunohistochemical detection of adenohypophyseal hormones [7].

The new classification scheme has also refined diagnosis of tumors previously classified as hormone-negative. Indeed, up to 95% of pituitary adenomas lacking hormone expression may be positive for one or more lineage-specific transcription factors. The remaining 5% of these lesions (comprising less than 2% of all pituitary adenomas) are now designated as 'null-cell', indicating the absence of any immunohistochemical evidence of cell-type-specific differentiation. Emerging evidence suggests that true null-cell adenomas are more aggressive and invasive than other hormone-negative adenomas, perhaps comprising a distinct clinicopathologic entity [3].

We present the rare case of a null-cell ectopic pituitary macroadenoma located in the sphenoid sinus and clivus. The clinical, radiographic and histopathologic findings are discussed in the context of a comprehensive systematic review of the literature of ectopic pituitary adenomas originating in these locations.

Methods

Pathology

Fresh specimens were bisected, touched onto the surface of a glass slide and stained with hematoxylin and eosin for intraoperative analysis. They were also placed in formaldehyde for processing as a formalin-fixed, paraffin-embedded block. This was sectioned and analyzed by hematoxylin and eosin staining, as well as routine immunohistochemistry for HGH, Synaptophysin, and Chromogranin with standard protocols for the BenchMark XT Autostainer (Ventana). Immunohistochemistry for FSH, ACTH, TSH, LH, and Prolactin was performed by San Diego Pathology (San Diego, CA). Immunohistochemistry for SF-1 and Pit-1 was performed by Mayo Clinic (Rochester, MN). Slides were imaged using an Olympus BX43 microscope, and images captured using an SC30 camera and the Olympus CellSens Standard software.

Systematic review

We performed a search for all ectopic pituitary adenomas reported in the literature using the PubMed, Google Scholar, Trip and MEDLINE databases. Abstracts and full-text articles were screened to identify reports of lesions originating in the sphenoid sinus or the clivus. Four search strings were used separately: "ectopic pituitary," (("ectopic") AND ("pituitary")), (("ectopic pituitary") AND ("sphenoid")), (("ectopic pituitary") AND ("clivus")). The references listed in each study were also reviewed in order to find additional publications. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed.

Final inclusion criteria were any pathologically verified pituitary adenomas arising within the sphenoid sinus and/or clivus. We excluded reports with incomplete outcome description, alternative tumor types, or lacking individual case-level data. Adenomas originating in other locations such as the sella turcica or suprasellar region were excluded. Non-English language articles were also excluded.

Case Report

Clinical presentation

A 75-year-old woman presented with an incidental lesion in the sphenoid sinus in the workup for chronic left-sided tinnitus. She denied any other neurologic, visual, endocrinologic, infectious or constitutional symptoms. History was notable only for chronic allergic rhinitis and sinusitis for which she utilized Fluticasone Proprionate nasal spray, and hyperlipidemia managed with a statin. Vital signs were unremarkable. Upon examination she was neurologically intact. Complete blood count, coagulation parameters, complete metabolic panel, hemoglobin A1c, and thyroid stimulating hormone levels were within normal limits.

Imaging

Magnetic resonance imaging (MRI) scan of the sella turcica was performed with and without Gadolinium-based contrast (Figure 1). This disclosed a 1.8 x 1.6 cm soft tissue signal, mildly enhancing lesion involving the posterior sphenoid septum and right sphenoid cellule. The lesion abutted the floor of the sella turcica without definite sellar invasion; no obvious radiographic abnormality of the pituitary gland was apparent. Computed tomography (CT) scan of the sinuses showed an expansile low-density enhancing mass involving the upper clivus, eroding the sellar floor and bulging into the posterior aspect of the sphenoid sinus (Figure 2).

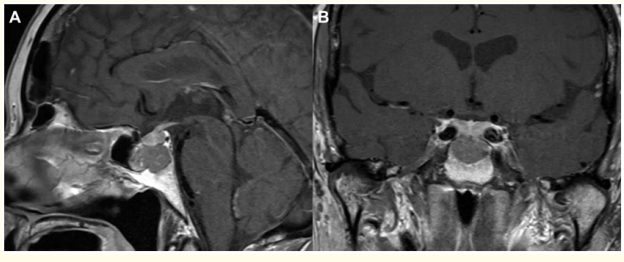

Figure 1: Pre-operative T1-weighted, contrast-enhanced sagittal (A) and coronal (B) MRI of the brain showing mildly enhancing, well-circumscribed mass in the posterior sphenoid sinus and superior clivus.

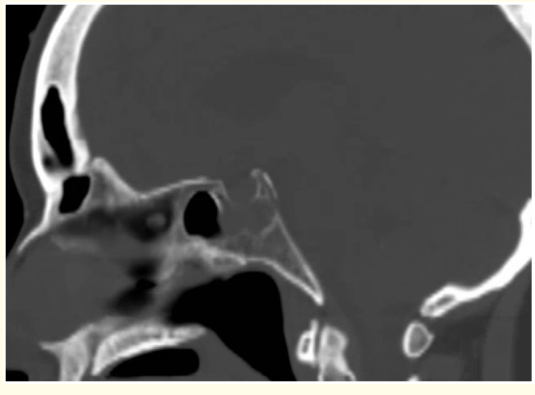

Figure 2: Pre-operative sagittal noncontrast head CT showing a midline soft tissue mass in the sphenoid sinus eroding the clivus and sellar floor.

Differential Diagnosis and Management Plan

Differential diagnosis included the following:

1. Neoplasms involving the sphenoid sinus such as neuroendocrine carcinoma, sinonasal undifferentiated carcinoma, and olfactory neuroblastoma.
2. Metastases such as melanoma.
3. Masses of the clivus such as chordoma or chondrosarcoma.
4. Hematologic malignancies involving lytic destruction of the skull base, such as plasmacytoma and lymphoma.

Given the broad differential diagnosis, the patient was offered resection of the lesion. The goal of surgery was to establish a pathologic diagnosis, and, if appropriate, achieve maximal safe resection. After discussion of risks and benefits, she provided informed consent for the procedure.

Surgical technique and intraoperative findings

Sublabial transsphenoidal microsurgical resection of the lesion was performed. The sphenoid sinus was opened widely and the mucosa removed. The tumor came into immediate view as a friable gray-purple mass. Specimen was collected for pathologic analysis. Intraoperative touch prep suggested pituitary adenoma (described below), and thus further resection was pursued.

The mass was carefully resected using a combination of ring curettes, rongeurs and suction. The superior portion of the mass had eroded the sellar floor and abutted normal-appearing pituitary gland. The mass extended posteriorly to the ventral aspect of the clivus. A gross total resection was achieved; this was confirmed by intraoperative neuronavigation. No cerebrospinal fluid leak was noted.

Pathology

Representative pathologic images are shown in Figure 3. Intraoperative touch prep showed monomorphous cells with bland, round to ovoid nuclei suggestive of adenoma. Hematoxylin and eosin preparation was notable for sheets and ribbons of round and polygonal cells with stippled chromatin and small nucleoli. The specimen stained strongly for synaptophysin and minimally for chromogranin. Scattered islands of cells stained positive for the PIT-1 transcription factor, which was otherwise predominantly negative. Immunohistochemistry for the transcription factor SF-1 and hormones FSH, LH, ACTH, TSH, HGH, and Prolactin showed only rare, weakly staining cells. Taken together, the findings were suggestive of null cell pituitary adenoma arising from a small island of ectopic pituitary tissue.

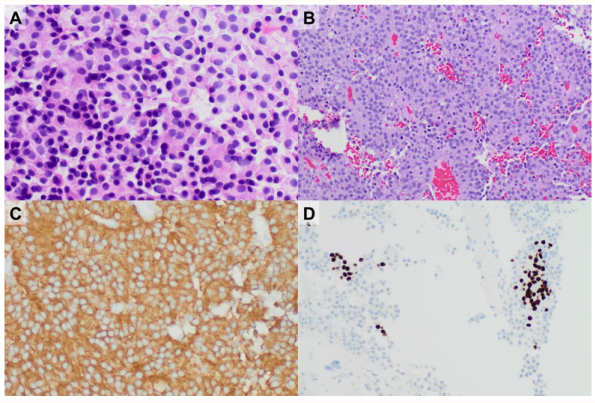

Figure 3: Histopathology. (A) Intraoperative touch prep displayed at 400x magnification. (B) Hematoxylin and eosin, 200x. Immunohistochemistry for synaptophysin (C) and PIT-1 (D), 200x.

Postoperative course

The patient had a benign postoperative course and was discharged two days after the procedure. MRI during the postoperative stay showed total excision of the lesion. Fasting levels of FSH, LH, cortisol, TSH, free thyroxine, growth hormone, prolactin and IGF-1 on post-operative day 1 were within normal limits. She remained asymptomatic at 2-week neurosurgical follow-up and one-month endocrine assessment. She reported no change in her prior allergic rhinitis and sinusitis symptoms postoperatively.

Systematic literature review

We performed a systematic literature review of ectopic pituitary adenomas arising from the sphenoid sinus (SS) (Table S1) and clivus (Table S2). A total of 75 cases originating in the SS and 24 in the clivus were found. A minority of lesions extended into adjacent skull base structures or the nasopharynx. Empty sella turcica was observed in 29.3% of SS lesions and 8.3% of clivus lesions, respectively. Gender was male in 36.5% and 54.2%, respectively. Ages ranged from 15 to 82 years, with median age 53.5 years in both cohorts. Clinical presentations were diverse, including endocrinopathies such as Cushing syndrome, headache, nasal obstruction and neurological deficit. Three cases were associated with multiple endocrine neoplasia (MEN) syndrome type 1. Hormone production included ACTH (31.1% and 4.2%, respectively), Prolactin (29.7% and 50%), Growth Hormone (13.5% and 25%). Tumors were non-functioning in 29.7% and 33.3% of cases, respectively.

Management was primarily with surgical resection, and rarely radiation or pharmacologic dopamine agonist. Immunohistochem-

istry results showed positivity for one or more markers in a majority of cases, while 9.6% of SS lesions and 16.7% of clivus lesions were histologically hormone-negative. Gross total resection, oncologic remission and endocrinologic cure were achieved in most cases.

A total of 14 cases involving both the SS and clivus were found (cases 1-10 in Table S1 and cases 1-4 in Table S2). Tumors secreted prolactin in 8 of these cases (57.1%), ACTH in 1 case (7.1%), and growth hormone in 1 case (7.1%); the remaining 4 cases (28.6%) were nonfunctioning. Only one case was histologically hormone-negative, while the remainder expressed various combinations of markers.

Table 1

Table 2

Discussion

Less than 150 total cases of ectopic pituitary adenoma have been reported over the last century. The etiology and clinicopathologic characteristics of these rare lesions remain poorly understood. During normal development, an evagination of the oral ectoderm forms Rathke's pouch. The connection with the pharynx is then severed, giving rise to the anterior pituitary gland. Remnants of the pouch due to aberrant migration or severing may result in islands of ectopic pituitary tissue that may proliferate and form adenomas. The general features and function of ectopic adenomas resemble those of tumors originating in the pituitary gland itself [5]. However, the factors influencing adenoma formation from ectopic pituitary tissue remain unknown [1].

Tumors involving the SS and/or clivus pose unique challenges due to the broad differential diagnosis of lesions in these locations (outlined above) that have drastically different implications for further management and prognosis. In view of the potential diverse lesions in these locations, the initial workup may include metastatic screening, endocrinologic workup, blood counts and chemistries. Evaluation by neurosurgery, otolaryngology, endocrinology and oncology specialists should be pursued. Surgical resection should be strongly considered in order to establish a pathologic diagnosis. Intraoperative surgical pathology capability is critical to determine whether aggressive surgical resection should be undertaken.

We have performed a systematic review of ectopic pituitary adenomas originating in the SS or clivus. Interestingly, SS lesions more commonly occurred in female patients, were associated with empty sella, and secreted ACTH. Clivus lesions, however, were more common in male patients and secreted prolactin or growth hormone. Lesions involving both structures were most commonly prolactin-secreting or nonfunctioning, and only rarely secreted ACTH or growth hormone. It is possible that unique microenvironmental cues determine the pathophysiology and terminal differentiation of adenoma cells in these different locations. Alternatively, these observed differences may be due to publication bias and the relatively small number of reported cases.

Following surgical resection, histopathology and immunohistochemical analysis are necessary for accurate molecular classification of pituitary adenomas. Importantly, the classification system has been updated in the latest system put forth by the World Health Organization in 2017. Expression of transcription factors such as PIT-1, SF-1 and T-PIT determine the lineage and cellular subtype of adenohypohyseal cells comprising the lesion. Final determination of adenoma subtype also requires morphologic characterization and staining for pituitary hormones such as ACTH, GH, PRL, and TSH [6]. The rarest molecular subtype is a null cell adenoma, comprising less than 2% of overall lesions. Although the terms hormone-negative and null-cell adenoma were previously used interchangeably, it is now clear that the former may still be positive for transcription factors such as SF-1, whereas true null cell adenomas are negative for all transcription factors as well [7].

Only one prior case of ectopic pituitary adenoma involving both the SS and clivus was found to be hormone-negative [4]. Other reports have described hormone-negative lesions involving the sphenoid sinus [2,9,10]. However, it is unclear whether these were true null cell lesions because no transcription factor analysis was reported. There is only one prior report of true null cell ectopic adenoma in the SS or clivus, in a 78-year-old patient presenting with apoplexy due to a clival null cell adenoma [8]. As such, our report of a true null cell ectopic pituitary adenoma in the sphenoid sinus or clivus is unique.

Conclusion

Ectopic pituitary adenomas remain rare lesions with unclear etiology and clinicopathologic characteristics. Surgical management is indicated when these lesions are in the differential diagnosis of skull base lesions. Accurate molecular genetic subtyping incorporating the latest WHO classification scheme may influence the understanding of these tumors. Under the new system, true null-cell designation requires negative immunohistochemical staining for both classic adenohypophyseal hormones as well as the newly incorporated lineage-specific transcription factors. We report a unique case of a true null-cell ectopic pituitary adenoma involving both the sphenoid sinus and clivus. The analysis of this

unique case and our attendant systematic review of lesions arising from each location may provide a useful reference for future studies of this rare, enigmatic entity.

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