Interdisciplinary Neurosurgery: Advanced Techniques and Case Management 1 (2014) 31–33

Contents lists available at ScienceDirect

Interdisciplinary Neurosurgery: Advanced Techniques and Case Management

journal homepage: www.inat-journal.com

Cushing-type ectopic pituitary adenoma with unusual pathologic features☆

Kristopher T. Kimmell, MD [a,*], Mahlon Johnson, MD, PhD [b], Rakhil Rubinova, DO [c], G. Edward Vates, MD, PhD [a]

[a] Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY, USA
[b] Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY, USA
[c] Department of Medicine, Division of Endocrinology and Metabolism, University of Rochester Medical Center, Rochester, NY, USA

ARTICLE INFO

Article history:
Received 7 January 2014
Revised 25 March 2014
Accepted 12 April 2014

Keywords:
Pituitary
Ectopic
Cushing's syndrome

ABSTRACT

Ectopic pituitary adenomas comprise, by varying reports, approximately 1-2% of all pituitary adenomas. They are often located in the nasopharyngeal region associated with the pharyngeal pituitary. The location and pathologic features of these masses make them atypical when compared with intrasellar pituitary adenomas. A 54-year-old man presented with vertebral compression fracture and physical stigmata of Cushing's disease. Biochemical testing confirmed hypercortisolemia responsive to high dose dexamethasone suppression. MRI of the head demonstrated an enhancing mass in the posterior aspect of the sphenoid sinus not involving the sella turcica. Endoscopic biopsy followed by resection confirmed this mass to be a pituitary adenoma with unusual pathologic features. Most notably, the tumor cells demonstrated large, eosinophilic, vacuolated cytoplasm. Immunohistochemical profile of the tumor was typical of an ACTH secreting tumor, notably with positivity for ACTH. The patient did well from his surgery. Post-operatively his serum cortisol level normalized and he remains in chemical remission one year after surgery. Ectopic pituitary adenomas are an unusual manifestation of hormonally active pituitary neoplastic disease. Their atypical clinical presentations, location, and pathologic features can make them a diagnostic challenge. Clinicians should be aware of these entities, especially when considering differential diagnosis for a mass in the sphenoid sinus and nasopharyngeal region.

Introduction

Pituitary tumors represent 10–15% of all primary intracranial neoplastic disease [1]. In some instances these tumors develop in an extrasellar location. When ectopic pituitary adenomas arise, they are often located in the nasopharyngeal region and may represent neoplastic transformation of the pharyngeal pituitary. The pharyngeal pituitary, an embryologic remnant, is typically composed of cells phenotypically identical to the anterior pituitary. While once thought to be a transient structure, some scholars posit that the pharyngeal pituitary is a permanent structure arising from the embryonic craniopharyngeal duct and remnants of Rathke's pouch. We present a case of Cushing's disease caused by an ectopic pituitary adenoma with unusual pathologic features.

Case report

History

A 54-year-old male presented to the emergency department at our institution with worsening back pain and inability to ambulate for several weeks. His past medical history was notable for asthma, nasal polyps, and hypertension that had become difficult to control. During evaluation of his back pain, he was noted to have several vertebral compression fractures and bilateral adrenal nodularity. He endorsed a number of symptoms including swelling in the face, muscle weakness, bruises over the upper body and arms, abdominal bloating, indigestion, leg edema, increased exercise intolerance, decreased libido, frequent urination, dysuria and increased anxiety. Baseline hyperglycemia was evident and he required oral supplementation for hypokalemia.

Examination, laboratory, and imaging findings

Notable findings on exam at the time of presentation were upper body hyperpigmentation, round plethoric face, proximal muscle

☆ The authors have no financial relationships to disclose.

* Corresponding author at: Department of Neurosurgery, University of Rochester Medical Center, 601 Elmwood Avenue, Box 670, Rochester, NY 14642.
E-mail address: kristopher_kimmell@urmc.rochester.edu (K.T. Kimmell).

http://dx.doi.org/10.1016/j.inat.2014.04.003
2214-7519/

atrophy with ecchymosis, decreased strength, and lower extremity edema. Relevant laboratory findings included: potassium 3.7 mmol/L (normal 3.3–5.1 mmol/L) random serum cortisol 100.9 μg/dL, ACTH 240 pg/mL (normal 7–63 pg/mL), salivary cortisol 4340 ng/dL and 2950 ng/dL on two consecutive nights (normal 0–99 g/dL), aldosterone 4.1 ng/dL (normal ≤16 ng/dL), renin 0.6 ng ml^{-1} h^{-1} (normal 0.5–4.0 ng ml^{-1} h^{-1}), plasma metanephrine 0.36 nmol/L (normal 0.00-0.49 nmol/L). High dose dexamethasone (8 mg) suppressed cortisol to 25.2 μg/dL and ACTH to 99 pg/mL. The results of baseline tests suggested an ACTH-dependent Cushing's syndrome.

The patient underwent MRI of the head with attention to the parasellar region. This demonstrated a 38 × 31 × 40 mm mass in the sphenoid sinus isointense to brain on T1 weighted images and heterogeneous enhancement with administration of gadolinium (Fig. 1). The mass was centered in the posterior aspect of the nasopharynx with evidence of partial erosion of the clivus as well as the floor of the sphenoid sinus.

Operation and pathologic findings

The patient went to the OR for endoscopic transsphenoidal biopsy of the mass. The biopsy showed a monomorphic population of tumor cells, arranged in sheets, with abundant eosinophilic foamy cytoplasm (Fig. 2A and B) (PAS negative) and immunoreactivity for Cam 5.2, synaptophysin, and ACTH but no other pituitary hormones. TTF-1 was negative excluding nonadenomatous pituitary lesions and adenocarcinomas. CD68 and alpha 1-antichymotrypsin show scattered immunoreactivity in some macrophages but also possible tumor cells. There was no S100 immunostaining arguing against a granular cell or other neurohypophyseal tumors [2]. Neuronal transdifferentiation has been described in some adenomas but there was no Neu-N immunoreactivity [3]. The Ki-67 proliferation index was 1–2%. Electron microscopy revealed numerous cytoplasmic vacuoles and scattered secretory granules but no cell junctions (arguing against a carcinoid) (Fig. 3).

A few days later the patient underwent definitive endoscopic, transsphenoidal resection of the mass. The second pathological specimen was similar in morphology and immunohistochemical profile as the previous sample. The final diagnosis was pituitary adenoma, corticotroph cell type, with extensive vacuolar change.

Postoperative course

The patient's postoperative course was complicated by urosepsis and acute respiratory distress syndrome (ARDS) requiring hospitalization. However, he did not require any steroid replacement as a result of his systemic infection. His post-operative morning cortisol testing progressively improved. Clinically, he noted improvement in his ecchymosis, proximal muscle bulk, decreased edema as well as change in his skin hyperpigmentation. A cosyntropin stimulation test was done 60 days post-operatively to evaluate the adrenal axis. His

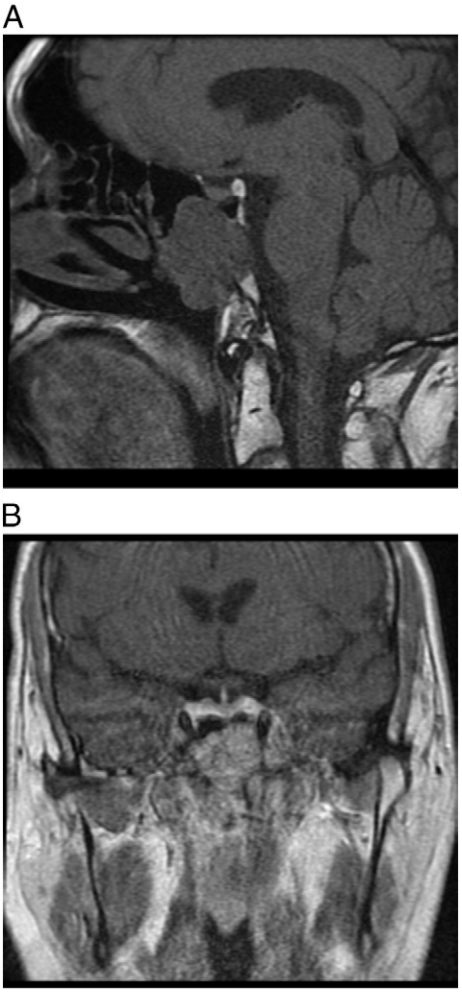

Fig. 1. T1-weighted images without (A) and with (B) contrast demonstrating isointense, heterogeneously enhancing mass in the posterior aspect of the nasopharynx. The sella appears intact.

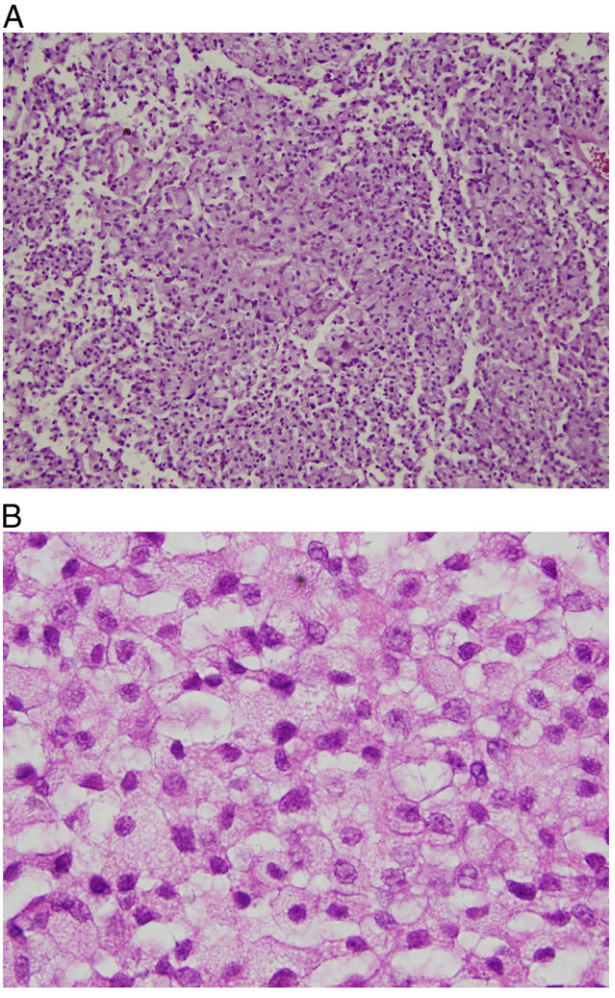

Fig. 2. Low- (A) and high-powered (B) micrographs of H&E stains of the mass demonstrating a bland, monomorphic population of tumor cells arranged in sheets with eosinophilic cytoplasm and evidence of vacuolar change.

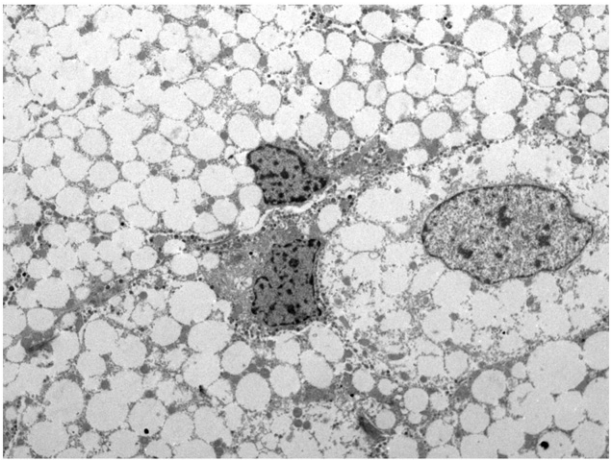

Fig. 3. Electron microscopic examination of tumor demonstrates fine nuclear chromatin and multiple vacuolar cytoplasmic bodies with absence of cell junctions.

baseline cortisol was 7.3 μg/dL and at 60 minutes increased to 29.5 μg/dL, demonstrating a complete normalization of his adrenal function. One year after surgery, the patient had no physical stigmata of endocrinopathy, and he remains in chemical remission from ACTH-dependent hypercortisolemia.

Discussion

Ectopic pituitary adenomas are an unusual manifestation of pituitary neoplastic disease. They have a long history in the literature the first report of an ectopic pituitary was by the Austrian pathologist Jakob Erdheim in 1909 [4]. Harvey Cushing also reported a likely ectopic pituitary in his chapter "The Chiasmal Syndrome" in 1930 [5].

It has been thought that a pituitary adenoma arising outside the sella represents neoplastic transformation of rests of pituitary cells deposited during the migration of Rathke's pouch. Indeed, Hori has analyzed adult and fetal meninges at the time of autopsy and found evidence of adenohypophysis ectopia without neoplastic transformation [6].

Hori and others have also described an entity known as the pharyngeal pituitary [7–9]. McGrath performed a number of studies of the pharyngeal pituitary in human fetuses and neonates as well as other mammals. She observed that the pharyngeal pituitary was typically found within the mucoperiosteum of the posterior nasopharynx. Others have confirmed the presence of adenohypophyseal tissue in this location [10]. Fuller and colleagues contend that the pharyngeal pituitary is a result of incomplete obliteration of the craniopharyngeal duct after the migration of Rathke's pouch [7]. Hori and coauthors suggest that extra-cranial ectopic pituitary adenomas arising in the nasopharyngeal region could represent neoplastic transformation of the pharyngeal pituitary [8]. In terms of development, the pharyngeal pituitary is believed to grow in the fetal period and in the first few months after birth. The pharyngeal pituitary produces the same hormones as does the anterior pituitary; however, due to its extremely small size (approximately one-thousandth the size when compared to the anterior pituitary) the impact of its hormone production is thought to be of no clinical significance. Anatomically, the structure has no direct connection to the hypothalamus and, in contrast to the anterior pituitary, does not possess a portal system. Pathologically, ectopic pituitary adenomas can display features atypical for intrasellar pituitary adenomas. Thompson et al, present the most comprehensive review of the pathological characteristics of ectopic pituitary adenomas, specifically of the sphenoid sinus region [11]. Of their series of 32 ectopic pituitaries arising in the sphenoid sinus, several tumors had unusual morphology, such as oncocytic change and prominent eosinophilic cytoplasm. The authors of this review do not offer an explanation for the increase in atypical features in this set of tumors. Nevertheless, Thompson et al point out the importance of careful pathologic examination of such tumors, as the differential for a sphenoid sinus or nasopharyngeal mass is broad. A careful, high-powered microscopic examination of these tumors by a neuropathologist, coupled with analysis of the immunohistochemical profile in these cases, is critical to make the correct diagnosis. In the current case, the adjunct electron microscopic examination proved very useful in helping to define the large vacuolar cytoplasmic structures in these tumors cells, as such vacuolar change is not typical for pituitary adenomas.

In the present case, there was some diagnostic uncertainty based on the patient's precipitous presentation with Cushing's syndrome, the anatomic location of the tumor, and the pathologic features of the tumor at the time biopsy. Because the patient had evidence of adrenal nodularity on CT at the time of presentation, there was some concern about an extra-hypophyseal source of ACTH causing his hypercortisolemia. However, the tumor sample was negative for TTF-1, a marker frequently used to identify neuroendocrine tumors or adenocarcinoma, especially of pulmonary origin. The lack of S100 and Neu-N expression argued against other diagnostic possibilities such as primary olfactory neuroblastoma, sinonasal neuroendocrine carcinoma, granular cell or other neurohypophyseal tumors, or malignant melanoma. The absence of cell junctions on electron microscopic examination argued against carcinoid as a possible diagnosis. These findings, coupled with the classical findings of positive expression of Cam 5.2, synaptophysin, ACTH, and low Ki-67 index, confirmed the diagnosis of ectopic pituitary adenoma.

This case also highlights the challenges in the evaluation of a patient presenting with cushingoid features, which requires careful biochemical work-up along with appropriate imaging modalities. As previously mentioned, the patient's precipitous presentation was concerning for a more aggressive source of his hypercortisolemia, necessitating careful consideration of all possible causes of Cushing syndrome.

The differential diagnosis for a nasopharyngeal mass is also broad, and careful attention must be paid to the imaging, clinical, and pathologic characteristics. Biopsy with detailed pathologic examination by a neuropathologist is warranted to accurately determine the morphology and immunohistochemical expression. It should be noted that a sphenoid sinus mass in a patient presenting with endocrine dysfunction may be a red herring. Such complexities necessitate a multi-disciplinary approach to these patients.

References

[1] Sanno N, Teramoto A, Osamura RY, et al. Pathology of pituitary tumors. Neurosurg Clin N Am 2003;14:25–39 [vi].
[2] Kleinschmidt-DeMasters BK, Lopes MB. Update on hypophysitis and TTF-1 expressing sellar region masses. Brain Pathol 2013;23:495–514.
[3] Johnson MD, Fan X, Bourne P, Walters D. Neuronal differentiation and expression of neural epitopes in pituitary adenomas. J Histochem Cytochem 2007;55:1265–71.
[4] Erdheim J. Uber einen Hypophysentumor von ungewohnlichem Sitz. Beitr Pathol Anat 1909;46:233–40.
[5] Cushing H. The chiasmal syndrome. Arch Ophthalmol 1930;3:505–51.
[6] Hori A. Suprasellar peri-infundibular ectopic adenohypophysis in fetal and adult brains. J Neurosurg 1985;63:113–5.
[7] Fuller GN, Batsakis JG. Pharyngeal hypophysis. Ann Otol Rhinol Laryngol 1996;105:671–2.
[8] Hori A, Schmidt D, Rickels E. Pharyngeal pituitary: development, malformation, and tumorigenesis. Acta Neuropathol 1999;98:262–72.
[9] Melchionna RH, Moore RA. The pharyngeal pituitary gland. Am J Pathol 1938;14:763–72 [761].
[10] Noronha BE, Panda NK, Mann SB, Mehra YN, Banerjee CK. Incidence of pharyngeal hypophysis in neonates a histologic study. Ann Otol Rhinol Laryngol 2001;110:364–8.
[11] Thompson LD, Seethala RR, Muller S. Ectopic sphenoid sinus pituitary adenoma (ESSPA) with normal anterior pituitary gland: a clinicopathologic and immunophenotypic study of 32 cases with a comprehensive review of the english literature. Head Neck Pathol 2012;6:75–100.