CASE REPORT

Giant Prolactinoma Presenting As a Base of Skull Tumor With Nasopharyngeal Extension: A Potential Diagnostic Pitfall in Neuroendocrine Lesions of the Base of Skull

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Abstract Pituitary adenomas presenting in uncommon anatomical locations are commonly misdiagnosed. Dramatic clinical presentation with hemorrhage and infarction, along with a lack of endocrine symptoms may further confound the diagnosis in some patients as illustrated in one of our two previously reported cases of non-small cell neuroendocrine carcinoma of the sinonasal tract and nasopharynx. This report presents the clinical progress of case number 2, which has a revised diagnosis of giant lactotroph pituitary adenoma. Common clinical, radiological and pathological pitfalls in diagnosis of neuroendocrine neoplasms of the sinonasal tract and base of skull are discussed.

Introduction

Accounting for 2–3% of all prolactin-secreting tumors, giant prolactinomas are rare [1]. Characterized as large, prolactin-producing tumors with diameters of 4 cm or more, these tumors present unique diagnostic challenges [1]. Unlike typical pituitary prolactinomas that tend to present with symptoms of hyper prolactinemia, giant prolactinomas may manifest as neurologic deficits due to pressure

effects on surrounding structures such as diplopia, reduced vision, visual field defects, exophthalmos, headache, seizure, or hydrocephalus [2]. Radiologically, giant prolactinomas may mimic other neoplasms of the base of skull and sinonasal areas. Histologically, these tumors share some immuno histochemical findings with other neuroendocrine tumors, further complicating their diagnosis [3, 4]. One of us previously published a report of two cases of non-small cell neuroendocrine carcinoma of the sinonasal tract and nasopharynx [5]. Herein, we present the clinical progress of case number 2, previously diagnosed as “neuroendocrine carcinoma”, which has a revised diagnosis of giant prolactinoma, highlighting the ever-present diagnostic pitfall that neuroendocrine neoplasms involving the sinonasal tract and base of skull can represent.

Case Report

A 30 year-old man presented with severe sepsis requiring admission to the intensive care unit for circulatory support, on a background of slowly progressive proptosis, diplopia, unilaterally reduced vision and contralateral ear tinnitus. Brain imaging showed a tumor in the nasopharynx and sphenoid sinus with bilateral involvement of the cavernous sinuses (Fig. 1). The biopsy of the nasopharyngeal mass was initially interpreted as olfactory neuroblastoma (ONB). Following discussion in a multidisciplinary team meeting, the patient underwent radical combined chemoradiotherapy, with persistent disease at treatment completion. Approximately 4 years following initial diagnosis and treatment, due to slowly progressive increase in the primary mass, coupled by a cerebral spinal fluid leak complicated by meningitis prompted a secondary pathology review at our centre, where the histological diagnosis

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Fig. 1 **a, b, c** Coronal, axial and sagittal T2-weighted images **d, e, f** postgadolinium coronal, axial and sagittal T1 weighted series with fat suppression through central skull base demonstrating invasive lesion

involving sphenoid bone, including sphenoid sinus, submucosal involvement of nasopharyngeal roof, clivus and bilateral cavernous sinus

was revised to “low grade neuroendocrine carcinoma”. The mass was deemed surgically unresectable thus the patient was enrolled into a clinical trial investigating an antiangiogenic combination of sorafenib and metronomic low dose cyclophosphamide. He continued on the study for 5 years, with stable disease as best response. Approximately 7 years following study completion, the patient complained of progressive gynecomastia and presented with a self-palpated breast mass, which biopsied on two occasions revealed milky fluid, negative for malignancy. Additional investigations were significant for hyperprolactinemia at 1394 ug/L (institutional normal range for males: 2.6–18.1 ug/L). The patient was commenced on the dopamine receptor agonist Cabergoline. After 2-weeks of this therapy, his serum prolactin level decreased to 114.8 ug/L, with significant improvement in his clinical symptoms. In light of this

clinical development, the original biopsy specimen was re-examined. Following additional immunohistochemical stains, the pathologic diagnosis was revised to a lactotroph pituitary adenoma.

Pathologic Findings

The biopsy was labeled “left posterior nasal fossa” and consisted of multiple fragments of tissue measuring in aggregate 2.0×1.0×0.3 cm. Approximately 70% of the sample consisted of organizing hemorrhage, blood clots and infarcted tumor (Fig. 2a). The residual viable tumor consisted of sheets of neoplastic cells with a rich vascular network. The individual neoplastic cells were relatively small, round and monotonous and exhibited scanty light

Fig. 2 Lactotroph pituitary adenoma with extensive infarction and hemorrhage. The vascular network shows fibrinoid necrosis of blood vessels and infarcted tumor in the right lower corner (**a**). The residual viable tumor cells have light eosinophilic cytoplasm with indis-

tinct cytoplasmic borders. The nuclei are round and exhibit delicate nuclear membrane with finely dispersed chromatin and inconspicuous nucleoli (**b**)

eosinophilic cytoplasm and smooth round nuclei with absent nucleoli (Fig. 1b). The mitotic rate was one mitotic figure per ten high-power fields (1 mf/10 hpf).

The tumor cells were positive for low-molecular weight keratin and pankeratin (CAM5.2, AE1:AE3),

synaptophysin, CD56, prolactin and Pit-1 (Fig. 3a–c). Epithelial membrane antigen (EMA), chromogranin, estrogen receptors (ER), growth hormone (GR), thyroid stimulating hormone (TSH), S100, HMB45, CD45 and neurofilament (NF) were negative.

Fig. 3 Lactotroph pituitary adenoma with diffuse expression of synaptophysin (**a**), prolactin (**b**) and Pit-1 (**c**)

Table 1 Selected case reports of giant prolactinomas

First author	Year	Number of patients affected	Initial impression	Reference
Mohtasebi	2015	1	Sinonasal neuroendocrine carcinoma	[4]
Care	2012	1	Olfactory neuroblastoma	[3]
Godey	1999	1	Chemodectoma	[7]
Luk	1996	3	Undifferentiated carcinoma	[8]
Van der Lely	1992	5	Undifferentiated carcinoma (3), olfactory neuroblastoma (2)	[9]

Discussion

This case illustrates some of the diagnostic difficulties presented by neuroendocrine tumors in the base of the skull. The main pathologic differential diagnosis of neuroendocrine neoplasms in this region includes olfactory neuroblastoma (ONB), neuroendocrine carcinoma (NEC) and pituitary adenoma. Pituitary adenomas presenting in uncommon anatomic locations are commonly misdiagnosed [6] and similar cases of giant prolactinoma masquerading as skull base/nasal tumors have been described in the literature (Table 1). Therefore, the immunohistochemical work-up of a well differentiated neuroendocrine neoplasm in the base of the skull should include pan-keratin, synaptophysin, chromogranin, CD56, S100 and depending on the combination of microscopic findings and initial immunohistochemical results, a panel of pituitary hormone markers and transcription factors such as prolactin and Pit-1. Certain microscopic findings such as the presence of intranuclear cytoplasmic inclusions, delicate fibrovascular stroma, variable growth pattern and plasmacytoid morphology could be helpful in raising the possibility of pituitary adenoma. Hemorrhage and necrosis do not exclude the diagnosis [6]. This patient's tumor showed some confounding features, such as being labeled "posterior fossa nasal tumor", lack of endocrine symptoms and extensive hemorrhage and infarction, which might have contributed to the initial misdiagnoses of ONB and NEC. With the increasing clinical manifestations of hyperprolactinemia and the addition of pituitary hormones markers, the revised diagnosis of lactotroph pituitary adenoma was readily established.

This case also illustrates that the imaging features of pituitary macroadenomas can be misleading if not clearly classical as seen to be centered on the sella and arising from an enlarged pituitary gland with more typical suprasellar extension. Upon review of original imaging, the infiltration of the lesion through the floor of the sella and into adjacent central bony skull base structures, submucosal nasopharyngeal tissues, sphenoid sinuses, as well as laterally into the cavernous sinuses, although rare, can be seen with pituitary tumors as ultimately, demonstrated in this case. The imaging appearance of an infiltrative central skull base tumor would include

lymphoma, meningioma as well as carcinoma given submucosal nasopharyngeal and sphenoid sinus involvement.

There needs to be a high degree of suspicion for a diagnosis of pituitary adenomas in patients with base of skull lesions and atypical clinical courses, given the good prognosis and potential for significant clinical and serological response to first-line therapy with dopamine agonists such as Cabergoline [1].

Compliance with Ethical Standards

Conflict of interest All authors declare that no conflict of interest exists related to this work.

Ethical approval Informed consent was obtained from the individual included in the study.

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