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Case Report

Ectopic primary olfactory neuroblastoma of the nasopharynx: A case report and review of the literature

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ABSTRACT

Olfactory neuroblastoma (ONB, also called esthesioneuroblastoma) is a rare malignant tumor of neuroectodermal olfactory cells. We report a case of an undifferentiated ONB with unfavorable histology arising ectopically in the nasopharynx. The patient was a 15-year-old male who presented with a right-sided painful neck mass, nasal obstruction, and weight loss. Awareness of the ectopic ONBs, although exceedingly rare, is important when considering differential diagnoses of sinonasal tumors as treatment and prognosis may differ from other lesions.

Introduction

Olfactory. neuroblastoma (ONB), also commonly referred to as esthesioneuroblastoma, is an uncommon neuroectodermal sinonasal neoplasm. It accounts for 3% of all intranasal tumors [1]. The tumors generally arise within the superior nasal cavity in proximity to the cribriform plate. The cell of origin is thought to be neuroectodermal olfactory cells of this cavity, specifically the basal neural cells of the olfactory mucosa [2]. ONBs can present within a wide age group of patients with a unimodal peak within the fifth and sixth decades of life [3,4]. Mass effect or local invasion of the tumor results in symptomatology based on the anatomic structures affected; nasal symptoms including obstruction and epistaxis are the most common early manifestations of tumor development with additional nasal, head, and visual symptoms occurring as the invasion progresses [5]. Typical features of these tumors include local extension into adjacent structures (paranasal sinuses, anterior cranial fossa, and orbits) with common cervical lymph node metastasis [6]. Factors used to gauge prognosis and guide therapy include Hyams grade, Kadish staging, and lymph node status [7–9].

Case report

The patient was a 15-year-old male without significant personal or family medical history who presented with an 8-week

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history of progressively worsening right-sided neck pain and swelling. This was originally treated with 2 courses of antibiotics. Clinical evaluation revealed a firm, immobile mass of the right anterior cervical chain measuring 5.5 cm by 5.5 cm along with right nasal obstruction and a 10-pound weight loss within the previous 8 weeks. Due to lack of improvement on antibiotics, an endoscopy was performed which revealed mildly asymmetric adenoid tissue which was biopsied and was otherwise unremarkable. Fine needle aspirations of the right neck mass were also performed at that time.

Immunohistochemical (IHC) staining revealed neoplastic cells diffusely positive for synaptophysin, CD56, and NSE; focally positivity for vimentin; and negative for S100, pankeratin, CD45, chromogranin, desmin, FLI1, and CD99. The tumor had an intermediate to high mitotic/karyorrhetic index displaying undifferentiation and unfavorable histology. The patient was diagnosed with undifferentiated ONB of the neck and nasopharyngeal tonsil with unfavorable histology.

Staging evaluation was undertaken. Rigid nasal endoscopy appreciated a large nasopharyngeal mass nonamenable to surgical resection. Computed tomography scanning with contrast-revealed mild nonenhancing prominence of the right adenoid tissue with extensive cervical lymphadenopathy concerning for metastatic disease. Specifically, there was no soft tissue seen in the superior nasal cavity. Metaiodobenzylguanidine (MIBG) scanning and a bone marrow scan were negative for disease. Subsequent positron emission tomography (PET) scanning revealed extensive intensely hypermetabolic cervical adenopathy (maximized standard uptake value [SUVmax] 11.6) concerning for metastatic disease and intense uptake in the region of the adenoid tissues (SUVmax 11.3; Fig. 1). The tumor was staged and diagnosed as a Kadish Stage D ONB.

The patient was treated with neoadjuvant chemotherapy and radiation therapy. End of therapy MRI was impressive for interval resolution of the initial nasopharyngeal mass and significantly decreased bilateral cervical lymphadenopathy when compared to the staging MRI. The PET/CT scan showed mild residual focal uptake of left cervical nodes (SUVmax 4.2; Fig. 2); subsequent lymph node excision and biopsy revealed only reactive lymphoid hyperplasia without any malignant cells. A plan was established to monitor the patient for recurrence, beginning with an MRI in 3 months' time.

CT and MRI obtained 3 months after the initial therapy conclusion revealed disease recurrence involving the right ethmoid air cells as well as a second foci of disease in the sphenotemporal buttress with extension into the orbit, the middle cranial fossa, and temporalis muscle. The prompted PET/CT scan revealed similar findings seen on CT and MRI (SUVmax 12.0) as well as multiple additional hepatic and osseous metastases (Fig. 3). Despite salvage therapy, patient developed cerebrospinofluid (CSF) dissemination and succumbed to his disease 15 months after initial presentation.

Discussion

Since first introduced into literature by Berger and Richard in 1924, ONB has been reported more than 945 times [1,10]. Approximately 80% of these reports have been within the past 20 years; a statistic either due to a rising incidence or more probably a result of increased awareness of the disease process. Most of these cases arise within the superior nasal cavity within the vicinity of the cribriform plate. A concise overview of the anatomy of the anterior skull base can be found in the work by Ow et al [5].

Proposed sources for the cell of origin of ONBs have included the pterygopalatine ganglion, the olfactory placode, the vomeronasal organ, the terminal nerve, autonomic ganglion in the nasal mucosa, and the olfactory mucosa. It is generally accepted that ONBs are of neuronal [11]. The best evidence to date strongly suggests the basal cells of the olfactory mucosa are the likely progenitor cells for ONB [1,12]. The olfactory epithelium stands out among the nervous system for its capability for regeneration in part due to these basal cells acting as a stem cell population [13].

The discussion of the origin of this tumor is complicated by case reports demonstrating ectopic ONBs arising in locations that lack normal olfactory neuroepithelium or locations where it is thought not to exist. As of 2016, at least 17 cases with ONB arising from outside the superior nasal cavity have been reported [14]. Reported ectopic sites include the sphenoid sinus, maxillary sinus, pituitary gland, nasopharynx, sellar region, anterior ethmoids, inferior meatus of the nasal cavity, and floor of the nose.

There have been a few proposed theories regarding the development of ONB in these ectopic sites. The 2 theories seeming the most plausible involve, firstly, the establishment of ectopic olfactory neuroepithelial cell rests during embryologic development and, secondly, the persistence of accessory olfactory systems from fetal life. First, ectopic cell rests could form as a result of impaired migration of olfactory placode neuronal cells. These cell rests are abnormally placed populations of olfactory neuronal cells capable of developing ONB in the correct conditions. This idea is best modeled by examining a case report by Zappia et al. of an ectopic maxillary sinus ONB in a patient with Kallman syndrome [15]. Kallman syndrome is caused by a genetic alteration resulting in improper migration of olfactory placode neuronal cells, leading to a lack of development of the olfactory bulb alongside hypogonadotropic hypogonadism (due to concurrent gonadotropin-releasing hormone-containing neuron migration failure). The halted migration of these neuronal cells in this syndrome provides a mechanism for the establishment of ectopic cell rests. It is theorized that even patients with lesser degrees of olfactory placode migration dysfunction could still establish ectopic cell rests capable of ONB production [16]. Second, accessory olfactory systems could be a source for ONB. This was first considered by Jakumeit in 1971 and readdressed by Morris in 2004 [16,17]. Accessory olfactory systems, like those containing the vomeronasal nerve and the terminal nerve, are present during embryonic development and typically degenerate in fetal life. Cells of the terminal nerve system specifically that persist and fail to degenerate have been theorized as possible ONB sources. Other proposed explanations for the presence of ectopic ONB include a functioning vomeronasal organ as a potential site of origin and potential submucosal spreading of tumor cells [18].

Diagnosis and staging of ONB is achieved through combined clinical, radiologic, and pathologic evaluation, although

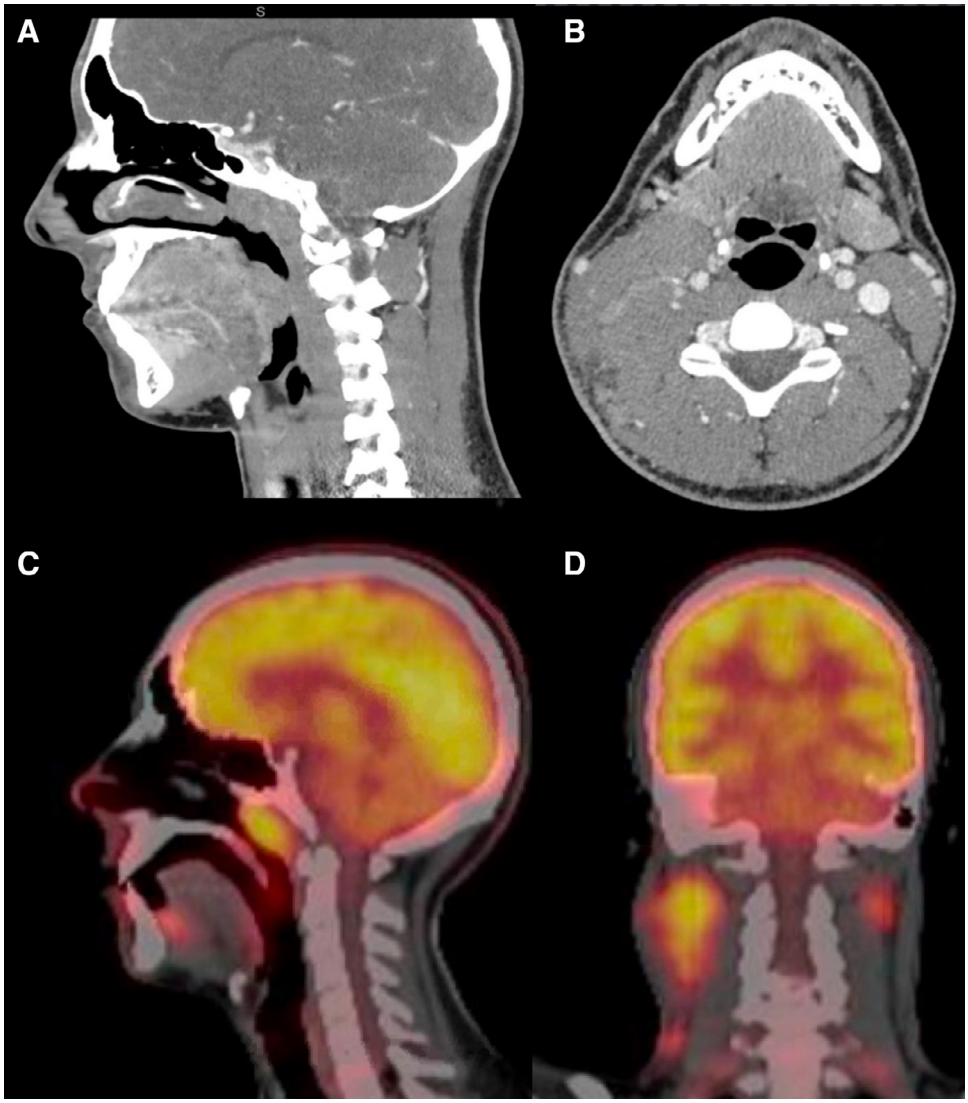

Fig. 1 – A 15-year-old male with ectopic olfactory neuroblastoma. Initial contrasted CT images (A and B) revealed a mild prominence of the adenoid tissue as well as significant right-sided lymphadenopathy. Note absence of soft tissue seen in the superior nasal cavity. Sagittal and coronal PET/CT (C and D) demonstrated increased metabolic activity in the nasopharynx (SUVmax 11.3) as well as the cervical lymph nodes (SUVmax 11.6).

pathologic evaluation remains the primary modality for definitive diagnosis of ONB. The tumor typically presents in patients with nonspecific symptomatology. Mass effect or local invasion of the tumor results in symptomatology based on the anatomic structures affected; nasal symptoms including obstruction and epistaxis are the most common early manifestations of tumor development with additional nasal, head, and visual symptoms occurring as the invasion progresses [5]. Typical features of these tumors include local extension into adjacent structures (paranasal sinuses, anterior cranial fossa, and orbits) with common cervical lymph node metastasis [6]. The primary imaging modalities for ONB staging include complementary use of MRI, CT, and PET/CT. A brief discussion regarding imaging for ONB follows.

ONB typically presents as a soft tissue mass centered at the superior olfactory recess, often demonstrating local extension into the ethmoid sinuses, and well as localized invasion in any direction. Given the typical site of origin for ONBs, there is often extension intracranially through the cribriform plate resulting in a "dumbbell" shaped appearance of the mass. The waist of this "dumbbell" sits at the cribriform plate. On MRI, the tumor is typically T1-hypointense to gray matter but can be T1-hyperintense when hemorrhagic; it is T2-isointense or T2-hyperintense, with avid homogeneous enhancement with contrast. These are nonspecific findings and can be noted in a variety of other sinonasal tumors. MRI is the modality of choice when evaluating the extension of the tumor to sinonasal, intraorbital, or intracranial spaces [19,20]. Marginal cysts and speckled calcifications are not pathognomonic features of ONB, but are often seen in these tumors and can help aid in diagnosis [21,22]. CT is valuable when evaluating bone erosions; special attention should be paid to potential ero-

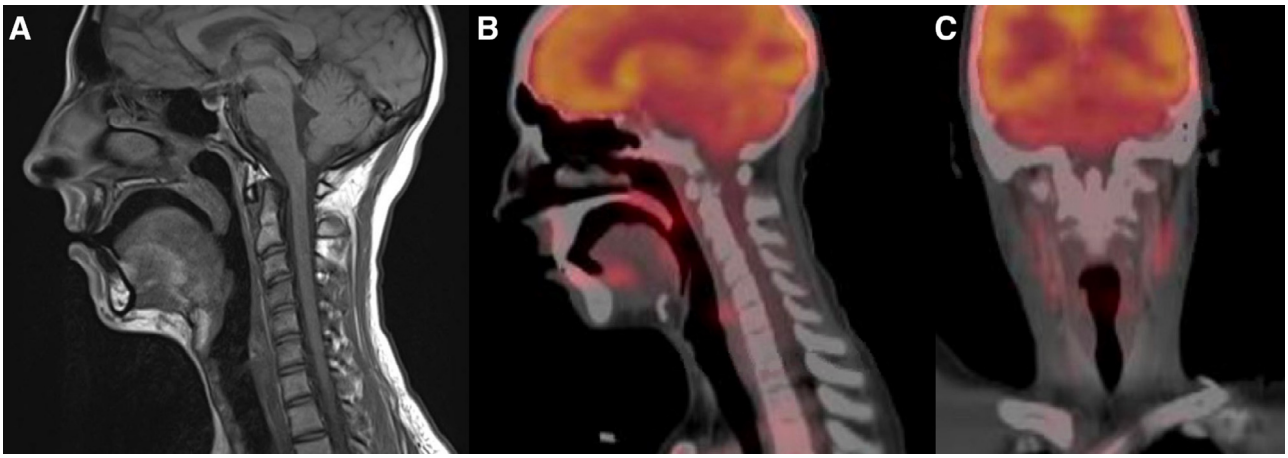

Fig. 2 – Initial post-therapy MRI (A) and PET/CT (B and C) revealed resolution of nasopharyngeal mass and significant improvement in cervical lymphadenopathy (SUVmax 4.2).

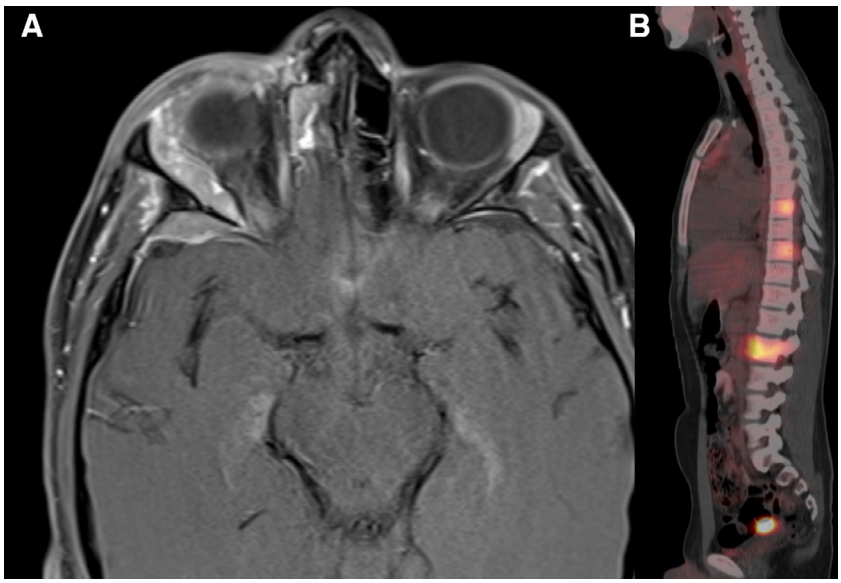

Fig. 3 – A 3-month follow-up contrast-enhanced MRI (A) revealed recurrent disease in the right ethmoid, as well as the sphenotemporal buttress with local extension into the orbit, temporal fossa, and middle cranial fossa. PET/CT (B) at that time also demonstrated multiple osseous metastatic lesions (SUVmax 12.0).

sion at the fovea ethmoidalis, cribriform plate, and lamina papyracea [20,23].

Despite the abundance of literature on the use of 18F-fluorodeoxyglucose (FDG) PET/CT in the work-up of malignancy, there is relatively little research concerning the utility of this modality in cases of ONB. Howell et al conducted a retrospective review evaluating the utility of 18F-FDG PET/CT to effectively demonstrate cervical lymph node metastasis [6]. The study was consistent with the established literature in showing that approximately 20%-30% of patients with ONB will present with cervical lymph node metastasis; of those with nodal disease, almost all patients had level II nodes and approximately 50% of patients had Level I, III, or retropharyngeal nodes. This highlights the importance of careful radiologic consideration of these areas during staging. Other studies have evaluated the magnitude of the SUVmax in ONBs. There does not appear to be any relationship between SUVmax and ONB tumor size [24]. Furthermore, there appears to be no relationship between tumor grade and uptake among primary, recurrent, and metastatic tumor foci [25]. There may be utility in using SUVmax in differentiating ONBs and sinonasal undifferentiated carcinoma, which is a tumor arising from the sinonasal cavity with similar histopathological features but differing behavior and management than ONB [26]. Overall, current research suggests that 18F-FDG PET/CT has utility in detecting primary disease, recurrence, metastasis, and unsuspected lesions following MRI/CT staging [6,24,26].

Pathologic evaluation of ONB primarily involves diagnosis and grading of the tumor. IHC staining plays a crucial role in

differentiating ONBs from other sinonasal small round blue cell tumors. IHC profiles for ONB have been proposed. Broadly, ONBs will have consistent neuroendocrine marker positivity, frequent focal nonspecific pancytokeratin- and squamous marker-positivity, and variable S100 positivity. IHC plays a crucial role in differentiating ONBs from other sinonasal small round blue cell tumors, including rhabdomyosarcoma, melanoma, lymphoma, pituitary adenoma, small cell carcinoma, sinonasal neuroendocrine carcinoma, and sinonasal undifferentiated carcinoma [5,27].

The most widespread grading method of these tumors is Hyams grading [28]. It utilizes a 4-tier system which scores tumors based on factors implicating tumor maturity. These factors are the presence of lobular architecture, mitotic activity, nuclear polymorphism, fibrillary matrix, calcification, Flexner-Wintersteiner or Homer-Wright rosettes, and necrosis. Updated histologic grading systems have been developed in attempts to provide more reliable prognostic information, although the Hyams grading continues to be the most recognizable system [29].

Varying staging methods have been proposed over the last few decades. Questions over the most useful staging protocol for prognosis and treatment planning are still being evaluated. The staging method proposed by Kadish was the first introduced and is frequently applied although it only classifies local disease [30]. Morita et al propose utilization of a “modified Kadish” staging, which adds a class for nodal disease and regional and distant metastasis [31]. Classifications devised by Dulguerov et al and Biller et al consider lymph node and distant metastasis separately from local tumor involvement [32,33]. Considering the variability in locations of ectopic ONB, the utilization of modified Kadish staging should be questioned when it is applied to ectopic ONB cases.

Recent research has offered several reviews evaluating prognostic tools for patients with ONB; the most commonly used tools include staging, Hyams grading, and cervical lymph node status [2,31]. In particular, Hyams grade and the presence neck lymph node metastasis provide the best predictors of survival [9,34].

A prominent concern for this disease is local and regional recurrence. Treatment modalities involve surgical removal, if feasible, and adjuvant radiation therapy; the role of chemotherapy should also be considered [35]. Lifelong follow-up of patients with clinical and radiographic imaging has been proposed [36].

Accurate grade and stage assignment are crucial for assessing prognosis and guiding treatment options. There are notable behavioral differences between ONB and other neuroendocrine tumors; misdiagnoses of these tumors are possible without proper clinical, radiographic, and pathologic consideration, particularly consideration of ectopic ONB [37,38]. Knowledge of the rare ectopic presentation of ONB is useful in diagnosing sinonasal masses.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.radcr.2019.05.031.

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