Olfactory Neuroblastoma: A Case Report

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Received: 1 June 2015 / Accepted: 17 August 2015 / Published online: 28 August 2015
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Abstract A 43-year-old female presented with persistent nasal congestion with intermittent epistaxis without resolution for the preceding 5 years. Clinical examination revealed a large pink rubbery mass, medial to the middle turbinate in the right nasal cavity extending to the choana. Radiographic images demonstrated a heterogeneously enhancing lobular soft tissue mass filling the right nasal cavity, causing lateral bowing of the right medial orbital wall and extending posteriorly to the right anterior ethmoid

sinus. The clinical, radiographic, histologic, and immunohistochemical features of olfactory neuroblastoma are discussed.

Keywords Olfactory neuroblastoma · Nasal cavity · Paranasal sinuses · Radiology · Homer Wright pseudorosettes · Flexner-Wintersteiner rosettes

History

A 43-year-old female presented to the Otolaryngology department with a mass in the right nasal cavity. Her chief complaint was persistent nasal congestion with intermittent epistaxis over the past 5 years. Three years earlier she had been treated for suspected allergic or chronic rhinitis without resolution of symptoms.

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Clinical Exam

A nasal exam was performed using rigid endoscopy, which revealed a large mass, medial to the middle turbinate in the right nasal cavity. The mass extended to the choana, but did not appear to extend into the nasopharynx clinically. It was attached superiorly with no medial or lateral attachment identified. The lesion was pink and lobulated with a rubbery, non-friable texture. No lesions were identified in the left nasal cavity.

Radiographic Features

The computed tomography (CT) scans demonstrated a heterogeneously enhancing lobular soft tissue mass that filled the right nasal cavity. Contrary to the clinical impression, the mass did extend posteriorly into the right nasopharynx, causing bowing and thinning of the right maxillary sinus wall (Fig. 1a). Opacification of the right ethmoid air cells represented either tumor or obstructive changes (Fig. 1b). The maxillary sinuses revealed mucosal thickening bilaterally with polypoid architecture. There were numerous small unremarkable cervical lymph nodes with no pathologic enlargement. No evidence of metastatic disease was seen.

Magnetic resonance image (MRI) studies revealed a heterogeneously enhancing mass centered in the posterior right nasal cavity, causing lateral bowing of the right medial orbital wall (Fig. 2a). There was no evidence of intracranial extension or adjacent dural enhancement. There was posterior extension to the right anterior ethmoid sinus (Fig. 2b). Maxillary sinuses demonstrated mucosal thickening bilaterally and additionally, there was mucosal thickening in the right frontal sinus. No pathologically

enlarged retropharyngeal or cervical lymph nodes were noted.

Diagnosis

Evaluation of the hematoxylin and eosin stained biopsy specimen revealed polypoid portions of respiratory mucosa distended by well-circumscribed nests and interconnecting tumor lobules embedded within a richly vascularized fibromyxoid stroma (Fig. 3a). Pseudorosette formation and areas of delicate neurofibrillary material was present (Fig. 3b). The tumor cells exhibited mild nuclear pleomorphism, fine chromatin, fibrillar cytoplasm, and focal scattered mitoses (Fig. 3c). The tumor cells were immunoreactive for synaptophysin (Fig. 4a), chromogranin and neuron specific enolase (NSE), but nonreactive for neurofilament protein, smooth muscle actin (SMA), and desmin. S-100 protein highlighted sustentacular cells at the periphery of the tumor cell nests (Fig. 4b). The cytomorphic and immunophenotypic features were characteristic of a Hyams grade II olfactory neuroblastoma.

Discussion

Olfactory neuroblastoma (ONB) is an uncommon malignant neuroectodermal sinonasal tumor, first described by Berger in 1924 [1, 2]. ONB represents approximately 2–3 % of all sinonasal tumors with an incidence of approximately 0.4 cases per million [3]. These tumors arise almost exclusively from the highly specialized sensory olfactory neuroepithelium normally encountered within the superior nasal vault, including the superior nasal concha, superior septum, roof of nose, and the cribriform plate of

Fig. 1 Radiology of olfactory neuroblastoma. **a** CT coronal view. **b** CT sagittal view

Fig. 2 Radiology of olfactory neuroblastoma. **a** MRI coronal view. **b** MRI sagittal view

Fig. 3 The hematoxylin and eosin aspects of ONB. **a** Rounded nests of tumor cells set within a vascularized fibromyxoid stroma. **b** Formation of pseudorosettes with scattered neurofibrillary areas.

c Tumor cells exhibit mild to moderate nuclear pleomorphism, fine chromatin, fibrillar cytoplasm, and scattered mitoses

Fig. 4 Immunohistochemical features of ONB. **a** The tumor cells are strongly positive for synaptophysin. **b** S-100 highlighting the sustentacular cells at periphery of the tumor cell nets

ethmoid [3, 4]. ONBs may occur at any age; however, a bimodal age distribution with increased occurrences in the 2nd and 6th decades is commonly accepted. There is no definitive gender or racial predilection [4, 5]. Typically, these are slow growing tumors with long-standing symptomatology, often resulting in delayed biopsy and definitive diagnosis. The primary clinical symptoms include unilateral nasal obstruction and epistaxis, but additional symptoms may include pain, excessive lacrimation, rhinorrhea, visual disturbances, and anosmia [3, 5].

Clinically, ONB presents most commonly as a large, unilateral, polypoid, glistening, red-grey mass in the superior nasal cavity. Extension into the adjacent paranasal sinuses, orbits and cranial vault is often seen. The radiographic findings may include the presence of a highly characteristic “dumbbell-shaped” occupying the superior nasal cavity and ethmoid sinus, extending through the cribriform plate and into the anterior cranial fossa with the “waist” at the level of cribriform plate [4, 6]. CT scans are useful in determining bone erosion of the lamina papyracea, cribriform plate, and fovea ethmoidalis. Contrast enhanced CT will demonstrate a homogeneously enhancing mass, while non-enhanced zones may suggest regions of necrosis. The extent and delineation of tumor is best determined by MRI with and without contrast, with T1-weighted images showing marked enhancement after gadolinium injection [4, 7].

ONBs behave in a locally aggressive manner, often involving contiguous vital, anatomic structures, to include the orbit and cranial cavity. Extreme caution should be used with the approach to the biopsy, due to the risk of significant potential bleeding. Based upon the clinical and radiographic extent of tumor, Kadish et al. [8] proposed a staging system for these neoplasms: Stage A, disease confined to the nasal cavity; Stage B, disease confined to the nasal cavity and paranasal sinuses; Stage C, lesions with distant spread from the nasal cavity, usually involving the base of skull, orbit or intracranial cavity. Currently, this is the most widely utilized staging system in an effort to stratify ONB and continues to serve as a reliable prognosticator of outcome and long-term patient survivability [9]. Hyams et al. developed a four-tiered grading system, which has also shown good overall correlation with outcome, demonstrating a histologic continuum from Grade I to Grade IV [9, 10]. Definitive separation between histologic grades can, at times, be somewhat arbitrary and subject to inter-observer variability. Therefore, it may be more reliable to separate tumors into low or high grade for prognostic purposes [5, 9, 10]. Grade I tumors are the most differentiated and often demonstrate sheets of “small, round, blue cells” with a high nuclear to cytoplasmic ratio. The cells have a syncytial quality, cytoplasmic neurofibrillary extensions, and uniform, small round nuclei with a

“salt and pepper” nuclear chromatin appearance. The tumor cells are set within a vascularized fibromyxoid stroma. Mitotic activity and necrosis are absent. Grade II tumors reveal less neurofibrillary stroma with mild nuclear pleomorphism and scattered, focal mitoses. Both Grade 1–2 tumors (low grade) maintain an overall lobular architectural growth pattern and may also present with calcifications and focal Homer Wright pseudorosettes. As ONB progress to Grade 3–4 (high grade), the lobular growth pattern, pseudorosettes and the neurofibrillary background stroma are less conspicuous to absent. Flexner-Wintersteiner rosettes may be seen and calcifications are absent. The nuclei become more pleomorphic with prominent eosinophilic nucleoli. Necrosis and markedly increased mitotic figures, to include atypical mitoses, are common observations. As one might expect, the increased grade of tumor often correlates with the difficulty in achieving definitive diagnosis, often requiring ancillary immunohistochemical and molecular studies, flow cytometry, and electron microscopy to confirm the diagnosis.

The clinical and radiographic presentation often suggests a broad and complex differential diagnosis including both benign and malignant epithelial, lymphoid, and mesenchymal tumors [11–13]. Histologically, the differential diagnosis of ONB encompasses the myriad of “small round blue cell” tumors that may arise within the sinonasal tract. This differential includes, but is not necessarily limited to, squamous cell carcinoma, sinonasal undifferentiated carcinoma, sinonasal small cell neuroendocarcinoma, rhabdomyosarcoma, Ewing sarcoma/PNET, lymphoma, malignant melanoma, synovial sarcoma, extramedullary plasmacytoma, paraganglioma, pituitary adenoma and extracranial meningioma. To further complicate matters, many of the aforementioned tumors share a similar immunohistochemical profile. The unique staining pattern of ONB, however, provides an important diagnostic clue into the underlying diagnosis. ONB is usually diffusely positive for synaptophysin, chromogranin, CD56, and NSE [3, 5]. S-100 protein-positive sustentacular cells characteristically highlight the periphery of the tumor lobules. Occasionally, the dendritic processes of these cells may be noted within the tumor lobules. In high grade tumors, the sustentacular cells may be sparse or absent [14]. Of note, approximately 30 % of ONBs will exhibit focal staining for cytokeratins, including low molecular weight cytokeratins (Cam 5.2) [5, 14]. This staining pattern may occur in areas of obvious divergent glandular differentiation; however, the cytokeratin immunoreactivity is never diffuse throughout the tumor cell population. ONB is negative for desmin, myogenin, actin, CD99 (MIC2 antigen), EBER, TTF1, and CD45RB (common leukocyte antigen). Succinctly, the presence of primitive appearing “small round blue cells” with finely granular chromatin, a distinctive lobular and often coalescing

architectural growth pattern, neuroendocrine immunophenotype without significant cytokeratin expression and the presence of S-100 positive sustentacular cells at the periphery of tumor lobules, essentially confirms the diagnosis of ONB.

Complete surgical eradication of tumor, to include the removal of the cribriform plate, is often followed by a full course of radiotherapy and is considered the treatment modality of choice for most ONBs [4, 5]. Palliative chemotherapy may be reserved for advanced, surgically inoperable tumors or for disseminated disease. Prognosis is largely dependent upon the inter-relationship of tumor stage and grade with a 5 year overall survival rate of 70 % [13, 15]. Under the Kadish staging system there are diminished survival rates as the clinical stage increases: 75–91 % for Stage A, 68–71 % for Stage B, and 41–47 % for Stage C [4]. With respect to the histologic grading of ONBs, low grade tumors have an 80 % 5 year survival rate while high grade tumors exhibit a dismal 40–25 % survival rate [4, 13, 15]. The presence of cervical lymph node metastases (35 %) and distant metastases (10 %) may occur, and as expected, serve as a poor prognostic indicator [13, 15]. Additional negative prognostic indicators include female gender, ages of <20 or >50 years at initial diagnosis, extensive intracranial involvement, recurrence, and high proliferation index [4, 13, 15].

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