



Case Report

Mixed olfactory neuroblastoma and neuroendocrine carcinoma: An unusual case report and literature review

Wilson P. Lao¹, Jordan M. Thompson¹, Lauran Evans², Yohanan Kim³, Laura Denham⁴, Steve C. Lee³

¹Loma Linda University School of Medicine, ²Department of Otolaryngology–Head and Neck Surgery, Loma Linda University Medical Center, ⁴Department of Pathology, Loma Linda University Medical Center, Loma Linda, California, ³University of Nevada, Reno School of Medicine, Reno, Nevada, USA.

Emails: *Wilson P. Lao - wplao@llu.edu; Jordan M. Thompson - jmthompson@llu.edu; Lauran Evans - Lauranevans@gmail.com; Yohanan Kim - Yohkim@llu.edu; Laura Denham - Ldenham@llu.edu; Steve C. Lee - Steele@llu.edu



*Corresponding author:

Wilson P. Lao,
School of Medicine,
Loma Linda University,
11175 Campus St, Loma
Linda - 92350, California,
United States.

wplao@llu.edu

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ABSTRACT

Background: The aim of the study was to present a case of mixed olfactory neuroblastoma (ONB) and carcinoma, an extremely rare tumor with only a few cases in the published literature.

Case Description: An otherwise healthy 27-year-old male presented with sinus complaints, headache, and unilateral eye discharge. Imaging and endoscopy revealed a mass presumed to represent a juvenile nasopharyngeal angiofibroma. Unexpectedly, the final pathology report revealed high grade mixed ONB and carcinoma. This tumor is the sixth and youngest documented patient with mixed ONB and carcinoma.

Conclusion: Physicians should remain vigilant for the possibility of malignancy in their approach to nasal cavity masses, even in young otherwise healthy patients. Careful review of the immunohistopathology should also be taken, as mixed olfactory tumors such as these are aggressive, rare entities that require multidisciplinary oncologic care.

Keywords: Diagnostic delay, Mixed tumor, Neuroendocrine neoplasm, Olfactory mixed neuroblastoma, Olfactory neuroblastoma

INTRODUCTION

Neuroendocrine neoplasms comprise a rare heterogeneous subset of tumors arising within the head and neck. Sinonasal tumors with neuroendocrine differentiation are of particular interest as its phenomenon is an infrequent occurrence. Classification of sinonasal tumors with neuroendocrine differentiation has been subdivided into neuroectodermal and epithelial origin, of which olfactory neuroblastomas (ONBs) (also known as esthesioneuroblastoma) and neuroendocrine carcinomas manifest, respectively. However, classification and nomenclature remain in constant debate. Although neuroendocrine carcinoma classification is well-established, the current nomenclature and classification of ONBs remains a challenge as its exact origin and histology are unknown partly attributed to a low incidence.^[2] In even rarer cases, sinonasal tumors with mixed neuroendocrine and nonneuroendocrine features have been described in the literature, further complicating tumor classification.

Age of the diagnosis of ONB is typically between 40 and 70 years old.^[1,6] In their retrospective case series, Bartel *et al.* reported that the mean age of diagnosis was 55 years old.^[1] The youngest

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in their series was diagnosed at 28 years old. In a study done by Joshi *et al.* with 833 histologically confirmed ONBs, the median age was found to be 54 at the time of diagnosis.^[6]

This case report exhibits a young, apparently healthy patient with a diagnosis of mixed ONB and carcinoma. To the best of our knowledge, only 12 cases of combined histopathology have been reported and only five with mixed pathology of this type.^[2,4,9]

CASE DESCRIPTION

A 27-year-old male presented to the emergency department (ED) with a right-sided nasal mass and associated progressively worsening lower right eyelid swelling over the course of several months. Medical history was insignificant. His social history was significant for a two pack-year smoking history with additional cocaine and marijuana use. Before his initial presentation, the patient had visited the ED multiple times for symptoms of intermittent epistaxis, sinus congestion, midface pressure, throbbing headaches, and ocular discharge. He had been treated with antibiotics and steroids without improvement. Due to periorbital inflammation, concern for increased intraocular pressure and decreased visual acuity at this ED encounter, the patient underwent a lateral canthotomy and cantholysis by ophthalmology, after which the patients' eye symptoms improved quickly.

Contrast-enhanced computed tomography (CT) at that time showed a 4.0 × 2.2 cm mass in the right nasal cavity, deviation of the nasal septum to the left, erosion of most of the ethmoidal air cells, and possible extension through the cribriform plate. There was near total opacification of the right frontal sinus, maxillary sinus, and ethmoid air cells with right preseptal soft-tissue edema [Figure 1]. Given the patient's gender, age, and imaging evidence at the time, there was a high suspicion for juvenile nasopharyngeal angiofibroma (JNA). The patient was admitted and elective interventional radiology (IR) embolization was scheduled.

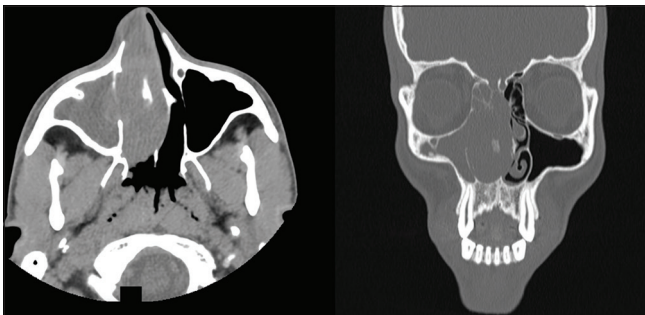


Figure 1: CT image (coronal and axial) of a 27-year-old male found to have a mixed olfactory neuroblastoma and carcinoma. Tumor appears to fill the right nasal cavity and extend into the right maxillary sinus, with erosion of bone and ethmoid air cells on the right.

During his admission, the patient became febrile. Subsequently, embolization of the mass/maxillary artery was cancelled to avoid seeding of intravascular coils with bacteria, as the patient's fever was felt to be secondary to bacteremia. Furthermore, the patient exhibited a declining serum sodium concentration from 133 mMol/L to 118 mMol/L, and syndrome of inappropriate antidiuretic hormone secretion (SIADH) was suspected. He received salt tablets and several doses of demeclocycline with subsequent improvement.

For the treatment of the presumed JNA, otolaryngology performed a right medial maxillectomy, right nasal endoscopy with debridement, total ethmoidectomy, and removal of the intranasal mass. The patient recovered appropriately and was discharged on postoperative day 2. Unexpectedly, the pathology from the right maxilla revealed a high grade malignant neoplasm, most consistent immunophenotypically and histologically with high grade "mixed" ONB and carcinoma [Figure 2]. The tumor was comprised nests of poorly differentiated cells with hyperchromatic nuclei, coarse chromatin, and minimal cytoplasm that was continuous with areas of typical neuroblastoma including neuropil formation. Foci of both squamous differentiation and nonenteric glandular differentiation were also noted. Lymphovascular and bone invasion were present. Immunohistochemical staining of the tumor showed positivity for the following markers, which differed slightly depending on the area of tumor that was stained: synaptophysin, CD56, chromogranin (rare/focal), S100 peripherally, Pan CK, CAM 5.2, CK7, p16, p63, CK 5/6, and p40 [Table 1, Figure 2]. After recognizing the nasal cavity mass as a malignancy, the tumor was staged as T4aN0Mx.

During postoperative follow-up, the patient reported improved right periorbital swelling and erythema, decreased serosanguinous drainage from right nares. No purulent nasal drainage was noted and he remained afebrile. Based on the results of pending magnetic resonance imaging (MRI) and positron emission tomography scans, the patient is expected to undergo further resection of residual tumor versus chemotherapy and radiation.

DISCUSSION

ONB is itself a rare entity. Therefore, the presence of a histologically mixed tumor is noteworthy. Cases of mixed neuroendocrine with nonneuroendocrine tumors have been previously reported 12 times,^[2] but specifically mixed ONB with carcinoma has been reported only 5 times as of 2017.^[4,9] The previous studies report that the age of diagnosis ranges from 40 to 70 years old with a peak incidence of 55 years old. Of interest is the unusually young age of this 27-year-old patient compared to previously reported ages. To the best of our knowledge, the youngest reported age of ONB is 28 years old.^[1]

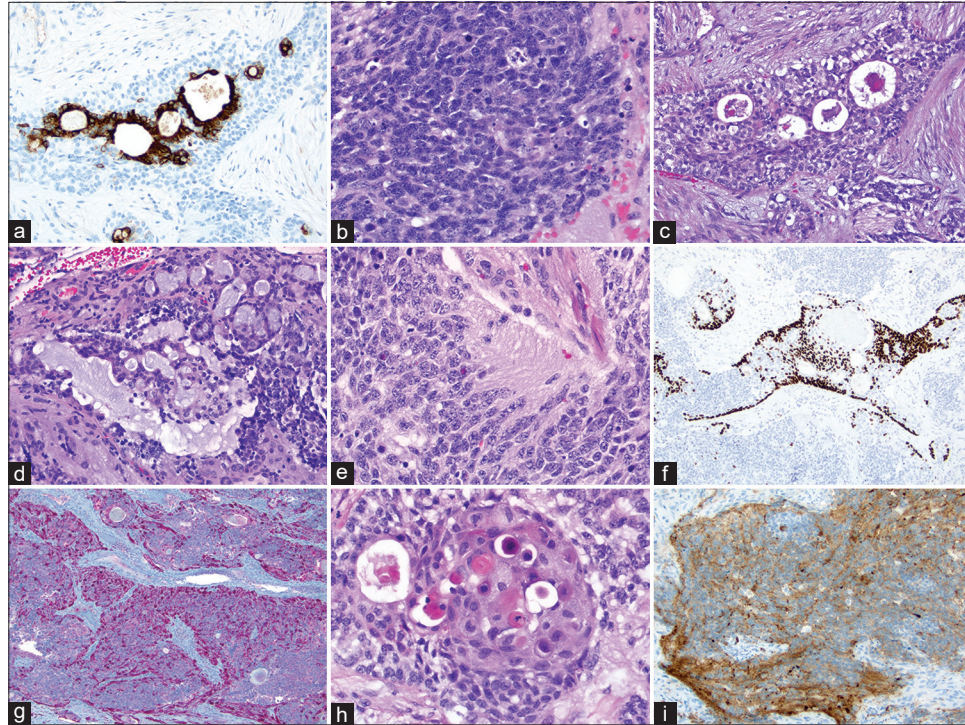


Figure 2: (a) CK7 highlights the glandular component $\times 200$, (b) Cytologically the majority of cells have high nuclear to cytoplasmic ratios coarse chromatin and display frequent mitoses and apoptotic bodies H&E $\times 400$, (c) Glandular component corresponding to CK7 image H&E $\times 200$, (d) Glandular component merging into poorly differentiated carcinoma H&E $\times 200$, (e) Neuroblastoma component with neuropil formation H&E $\times 400$, (f) p40 is positive in a subset of cells and is negative in glandular and neuroblastoma components $\times 200$, (g) S100 is positive mainly at the periphery of nests $\times 100$, (h) Squamous component with single cell keratinization H&E $\times 400$, (i) Synaptophysin is positive in majority of cells $\times 200$.

This patient was diagnosed with JNA based on his presenting symptoms, imaging, exam, and age. However, a few features of this case are unusual for JNA in retrospect. First, the patient's age is somewhat advanced for JNA, although reports of JNA in older patients and even in an elderly female have been reported.^[10] Second, on careful review, there was subtle evidence for erosion of the cribriform plate on preoperative CT that was not noted by radiology or the surgical team preoperatively. While intracranial involvement is not unheard of in JNA, it is usually the middle cranial fossa rather than the anterior cranial fossa which is involved. Finally, the patient had SIADH which would be unusual in the setting of JNA. We proceeded to surgery for resection and pathologic analysis, as in-office biopsy of highly vascular tumors, such as JNA, is a known contraindication. If the lesion was determined to be a JNA as we expected, the surgery would be definitive therapy; otherwise, the surgery would be therapeutic in terms of the obstructive infection and compressive symptoms as well as diagnostic.

Of reported cases, ONBs make up $<5\%$ of malignant tumors found in the nasal fossa and paranasal sinuses.^[1,4] Other malignancies which may arise within the same anatomical space include squamous cell carcinoma, neuroendocrine

carcinoma, rhabdomyosarcoma, melanoma, intestinal-type adenocarcinoma, undifferentiated carcinoma, and metastasis. As previously described, the reported patient interestingly exhibited both ONB and carcinoma histologically.^[11,12] Immunohistochemical staining in the current case revealed similarities with the previously reported mixed olfactory tumors, including positivity with S100, CD56, synaptophysin, and chromogranin.^[4,8] In addition to ONB, this patient's tumor also exhibited divergent differentiation in the form of both squamous carcinoma and adenocarcinoma, resulting in a rare mixed neuroendocrine and nonneuroendocrine olfactory neoplasm [Figure 2].

Common presenting symptoms in ONBs throughout the literature include epistaxis, nasal obstruction, anosmia, headache, rhinorrhea, lacrimation, visual disturbances, and SIADH.^[4] Our patient presented quite typically for an ONB, with epistaxis, headache, eye discharge, and even SIADH. Imaging of ONBs can typically reveal a mass of "dumbbell shape" crossing the cribriform plate or cysts at the junction of the tumor and brain tissue.^[3,4] The reported patient's CT did not demonstrate this "dumbbell" imaging pattern, though MRI has not yet been obtained to definitively determine the extent of anterior cranial fossa involvement.

Table 1: Immunohistochemical staining of the “mixed” olfactory neuroblastoma and carcinoma, with foci of squamous cells and glandular cells in the carcinoma component, which was continuous with typical neuroblastoma cells.

Stain	Squamous cells (A5)	Glandular cells (A1)
Chromogranin	Positive	Negative
CD56	Rare positive	Negative
CK 5/6	Positive	Negative
S-100	Scattered cells positive (The peripheral staining with S100 was in the ONB component)	Positive, mainly at periphery
NFP	Negative	Negative
Pan CK	Focally positive, mostly in glands	Focally positive
CAM 5.2	Patchy positive, mostly in glands	Patchy positive
CK7	Negative	Positive
CK20	Negative	Negative
CDX2	Highlights squamous foci	Negative
p16	Patchy positive	Patchy positive
p40	Positive	Negative
p63	Patchy positive	Negative
Desmin	Negative	Negative
Calponin	Negative	Negative
NUT	Negative	Negative
INI	Maintained staining	Maintained staining
EBER	Negative	Negative

The diagnostic protocol of ONB begins with a histologically confirmed positive biopsy usually, followed by classification. However, the classification of these tumors continues to remain in debate. At present, the Kadish clinical system appears to be the most commonly used classification system for ONBs, apart from traditional tumor-node-metastasis, Dulguerov, and Hyams classification systems.^[1,2,6] Kadish *et al.* actually proposed the first staging system for these tumors based on a series of 17 patients in 1976: A – within the nasal cavity, B – nasal cavity and at least one paranasal sinus, and C – extending past the sinonasal cavities.^[7] The Hyams system was then developed in 1988 and instead of gross anatomical classification utilized histological grading to categorize the tumor into one of four distinct categories. Hyam’s criteria include features such as lobular architecture, pleomorphism, neurofibrillary matrix, rosettes, mitotic index, necrosis, and calcification; grades three and four indicate poor prognosis.^[5] In addition, staging of mixed tumors are not well established secondarily due to the rarity of such a tumor.

In the previous series, intended curative surgical resection with an endoscopic approach was performed on patients with ONBs regardless of staging. Although surgery is still considered first-line treatment, multidisciplinary

management of such tumors is crucial. Grandhoke *et al.*’s patient did not undergo adjuvant radiation or chemotherapy and had a fast-growing recurrence only 2 months after total resection.^[4] Combined adjuvant radiotherapy or adjuvant chemotherapy in addition to surgery increase overall survival, compared to surgery or adjuvant therapy alone.^[1] Similarly, our patient was presented at our institution’s multidisciplinary tumor board, following the unexpected diagnosis of mixed ONB/carcinoma. As described, our patient underwent surgery and is being referred for possible adjuvant chemotherapy and radiation therapy.

CONCLUSION

Providers should be aware of this rare sinonasal mixed neuroendocrine malignancy and the management of such a histologically diverse tumor. In addition, diagnostic caution should be practiced when considering a sinonasal mass in a young adult, as more aggressive malignancies may mimic benign conditions such as JNA. Finally, further studies are necessary to develop a more standard classification system and treatment modality.

Declaration of patient consent

Patient’s consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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