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Olfactory Neuroblastoma

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Abstract Few neoplasms are unique to the sinonasal tract, but sinonasal undifferentiated carcinoma and olfactory neuroblastoma are malignant tumors which require unique management. Due to the rarity of these tumors, practicing pathologists are not always aware of their distinctive clinical, radiographic, histologic, immunohistochemical, and molecular features. These cases are frequently submitted for consultation, further suggesting the diagnostic difficulties inherent to these tumors. Specifically, olfactory neuroblastoma is a neoplasm that can histologically mimic many tumors within the sinonasal tract, making recognition of this tumor important, as the management frequently requires a bicranial-facial surgical approach, a trephination procedure which can be quite technically difficult and challenging to achieve a good result. The management is therefore quite unique in comparison to other sinonasal tract malignancies, setting it apart diagnostically and managerially from other lesions.

Keywords Olfactory neuroblastoma · Esthesioneuroblatoma · Sinonasal tract · Cribriform plate · Immunohistochemistry · Synaptophysin · Chromogranin · CD56 · S-100 protein · Magnetic resonance · Cranial nerve · Lobular architecture · Homer Wright pseudorosettes · Flexner-Wintersteiner rosettes · Neurofibrillary stroma · Sinonasal undifferentiated carcinoma · Mucosal melanoma · Rhabdomyosarcoma · Extranodal NK/T-cell lymphoma, nasal type

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Introduction

Few neoplasms are unique to the sinonasal tract, but sinonasal undifferentiated carcinoma and olfactory neuroblastoma are malignant tumors which require unique management. Due to the rarity of these tumors, practicing pathologists are not always aware of their distinctive clinical, radiographic, histologic, immunohistochemical, and molecular features. These cases are frequently submitted for consultation, further suggesting the diagnostic difficulties inherent to these tumors. Specifically, olfactory neuroblastoma is a neoplasm that can histologically mimic many tumors within the sinonasal tract, making recognition of this tumor important as the management requires a bicranial-facial surgical approach, a trephination procedure which can be quite technically difficult and challenging to achieve a good result.

Background

Olfactory neuroblastoma (ONB) is an uncommon malignant neuroectodermal nasal tumor. It comprises about 2% of all sinonasal tract tumors with an incidence of approximately 0.4 per million population. Previously called esthesioneuroblastoma, olfactory placode tumor, esthesioneurocytoma, esthesioneuroepithelioma, and esthesioneuroma, these terms highlight the sensory (olfactory) and primitive neuroectodermal origins, although the use of these older terms is discouraged. ONB are thought to arise from the specialized sensory neuroepithelial (neuroectodermal) olfactory cells that are normally found in the upper part of the nasal cavity, including the superior nasal concha, the upper part of septum, the roof of nose, and the cribriform plate of ethmoid. Specifically, Jacobson's vomero-nasal

organ, sphenopalatine ganglion, ectodermal olfactory placode, ganglion of Loci (nervus terminalis), autonomic ganglia of the nasal mucosa, and the olfactory neuroepithelium (cribriform plate and superomedial surface of the superior turbinate) are all sites of origination for this malignant neural crest derived neoplasm. It is also of note that these specialized olfactory neurons are probably the progenitors of neuroendocrine carcinomas of the sinonasal tract and so called "olfactory carcinoma." The olfactory epithelium contains three cell types, which can be histologically identified in the tumor: basal cells, olfactory neurosensory cells, and supporting sustentacular cells. The basal cells are the stem cell compartment, continuously replacing the neurosensory cells throughout adult life, both physiologically and as a response to injury.

Clinical Features

ONB may occur at any age (2–94 years), but a bimodal age distribution in the 2nd and 6th decades of life are most common without a gender predilection. The tumors most commonly cause unilateral nasal obstruction (70%), and epistaxis (50%), while less common signs and symptoms include headaches, pain, excessive lacrimation, rhinorrhea, anosmia, and visual disturbances. Even though the tumor arises from the olfactory neuroepithelium, anosmia is not a common complaint (5%). Due to the non-specific nature of the initial presentation and slow growth of the tumors, patients often have a long history before diagnosis. There are isolated cases reports of ONB secreting vasopressin with resultant hypertension and hyponatremia.

Imaging Studies

A "dumbbell-shaped" mass extending across the cribriform plate is one of the most characteristic imaging findings for this tumor. The observation depends on the size of the tumor and the duration of symptoms. The upper portion is a mass in the intracranial fossa, while the lower portion is in the nasal cavity, with the "waist" at the cribriform plate. CT will show speckled calcifications and bone erosion of the lamina papyracea, cribriform plate and/or the fovea ethmoidalis by non-contrast methods. Contrast enhanced CT will show homogenously enhancing mass, with non-enhancing areas suggesting regions of necrosis. MRI images with and without contrast will delineate the extent of the disease (Fig. 1), with T1-weighted images showing hypointense-to-intermediate signal intensity within the mass compared to the brain, while areas of necrosis will be hypointense. T2-weighted images may show hyperintense regions which correlate to the cystic regions at the advancing edge. There is often marked tumor enhancement after gadolinium. ONB may rarely present with only an intracranial (frontal lobe) mass. Ectopic tumors within the paranasal sinuses (not ethmoid) are vanishingly rare, except in recurrent tumors.

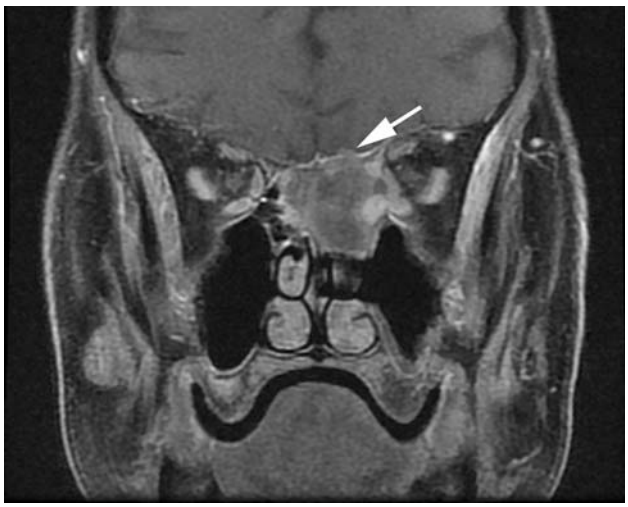

Fig. 1 An MRI shows a mass expanding and filling the upper portion of the nasal cavity, extending through the cribriform plate (*arrow*), showing early intracranial extension

Pathology Features

Macroscopic

For practical purposes, the cribriform plate region is involved by the tumor to some degree or another. The tumor is usually a unilateral, polypoid, glistening, soft, red–grey mass with an intact mucosa (Fig. 2). The cut

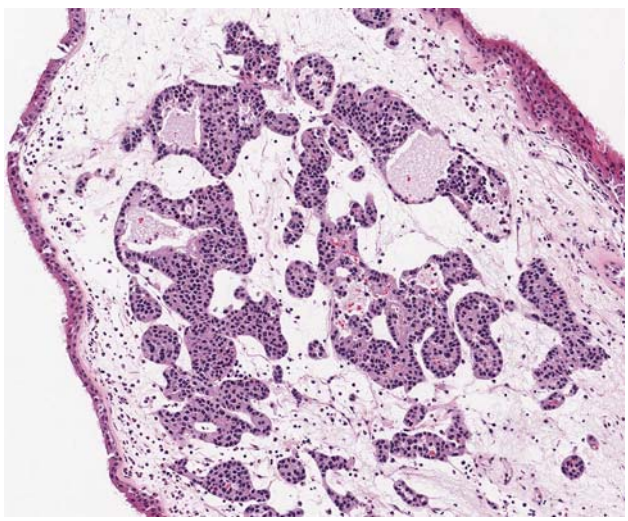

Fig. 2 This polypoid projection shows an intact respiratory epithelium. There are lobules or islands of tumor in the edematous stroma

surface appears grey-tan to pink-red and hypervascular. Tumors range from <1 cm up to large masses involving the nasal cavity and intracranial region. Tumors frequently expand into the adjacent paranasal sinuses, orbits and cranial vault. From a practical perspective, the tumors may not have a specific appearance, making it indistinguishable from other nasal tumors.

Microscopic

One of the most important histologic features is a *lobular* architecture comprised of "primitive" neuroblastoma cells (Fig. 3). These circumscribed lobules or nests of tumor are identified below an intact mucosa separated by a vascularized fibrous stroma. While in situ tumor is theoretically possible, by the time the tumor reaches clinical attention, in situ disease alone is no longer appreciated. The tumor cells are "small, round, blue" cells slightly larger than mature lymphocytes, with a very high nuclear to cytoplasmic ratio (Figs. 4 and 5). The nuclei are small and uniform with hyperchromatic, albeit delicate, uniform, "salt-and-pepper" nuclear chromatin distribution. Nucleoli are inconspicuous. The cells are often in a syncytial arrangement with a tangle of neuronal processes forming the background. Cellular nests are surrounded by fine fibrovascular septa in an organoid fashion. The matrix is finely fibrillar. While high grade lesions exist (discussed below), for the most part, nuclear pleomorphism (Fig. 6),

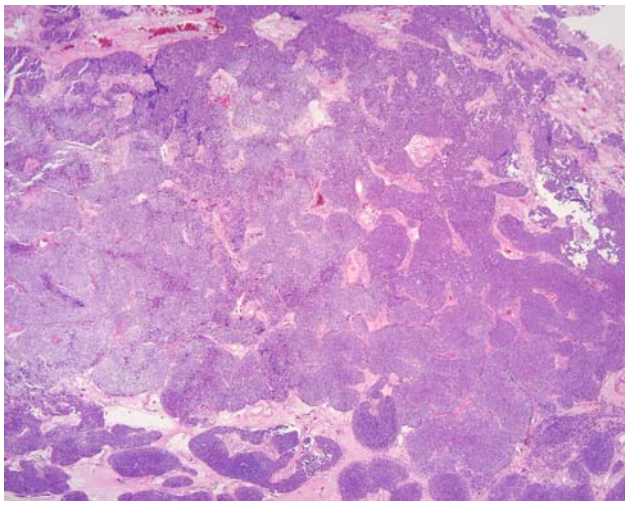

Fig. 3 A low power magnification demonstrates numerous lobules or islands of interconnecting tumor cells. There is a fibrotic to edematous vascularized stroma in the background

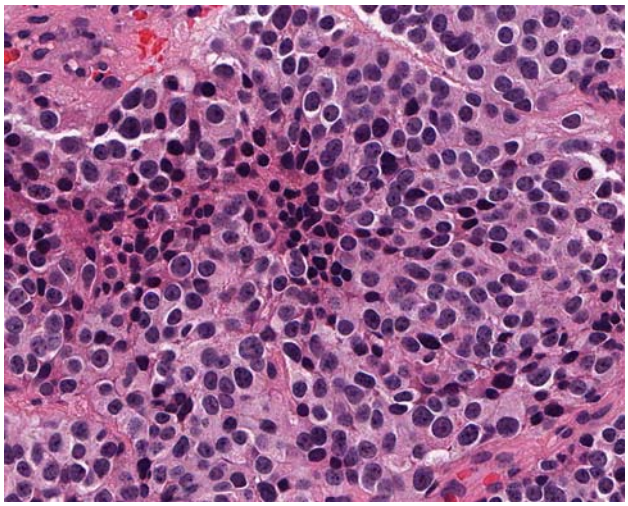

Fig. 5 Anisocytosis and anisonucleosis is noted in this Grade II lesion. Areas of pyknosis are also present. However, there is still a lobular architecture maintained

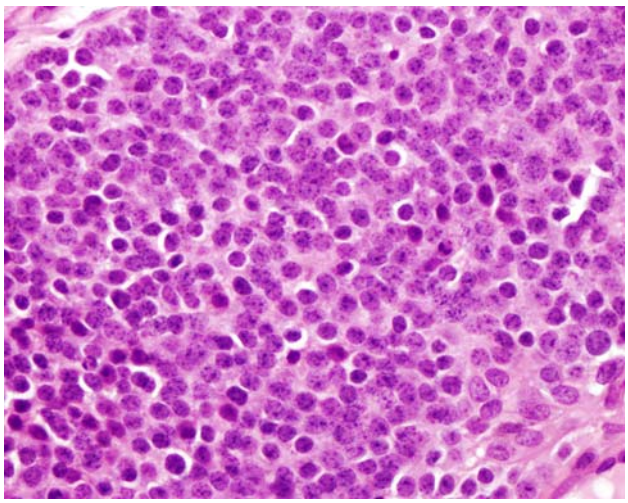

Fig. 4 There is a sheet of neoplastic cells with a very high nuclear to cytoplasmic ratio. The cells are arranged in a syncytium. The nuclear chromatin is even to delicate in this Grade I tumor

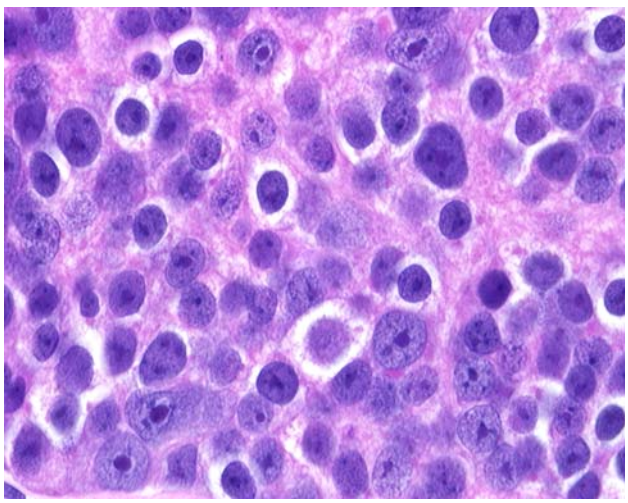

Fig. 6 There is quite a bit of pleomorphism with easily identified prominent nucleoli in this Grade III tumor. Note the suggestion of a Flexner-Wintersteiner rosette

mitotic figures (>2/HPF), and necrosis are uncommon. Two types of rosettes are recognized: pseudorosettes (Homer Wright) seen in up to 30% of cases, and true rosettes (Flexner-Wintersteiner) seen in about 5% of cases. The delicate, neurofibrillary and edematous stroma forms in the center of a cuffing or palisaded arrangement of cells in Homer Wright pseudorosettes (Fig. 7), while a "gland-like" tight annular arrangement is seen in Flexner-Wintersteiner rosettes. The latter is comprised of gland-like spaces lined by non-ciliated columnar cells with basally placed nuclei (Fig. 8). Peritheliomatous "rosettes" are of no diagnostic utility. Variable amounts of calcification may be seen, although they are not usually present in higher grade tumors (Grades III and IV). Exceedingly uncommon, vascular invasion, ganglion cells, melanin-containing cells and rhabdomyoblastic cells can be identified.

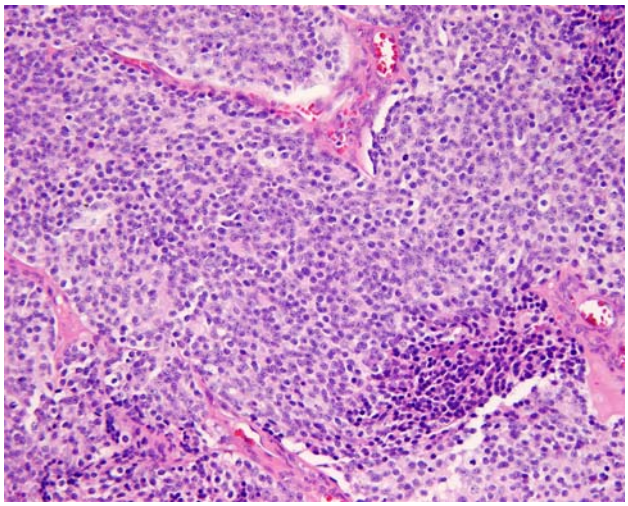

Fig. 7 The tumor nests are arranged in small pseudorosettes with faint eosinophilic, fibrillar material in the center of pseudorosettes. There is a vascularized stroma

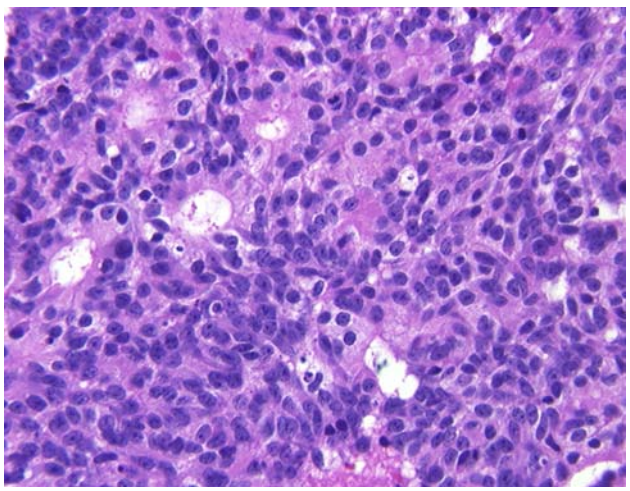

Fig. 8 There are numerous "duct-like" spaces with non-ciliated columnar cells arranged around a central lumen: these are Flexner-Wintersteiner rosettes in a Grade III neoplasm

Tumors are separated into four grades, although sometimes a definitive separation between grades is arbitrary. There is a continuum from Grade I to Grade IV (see Table 1), with grade based on the degree of differentiation, presence of neural stroma, mitotic figures, and necrosis. Lobularity is present in all tumors, although better developed in Grade I tumors, but still present in Grade IV lesions. Grade I includes the majority of tumors and is the most differentiated. The cells are syncytial, have cytoplasmic neurofibrillary extensions, and are uniform, with small round nuclei and evenly disbursed nuclear chromatin. Surrounding fibrous stroma is quite vascular. Mitotic activity and necrosis is absent. Grade II tumors show less neurofibrillary stroma and slightly more pleomorphism, with isolated mitoses. Grade III tumors show more pleomorphism, coarse chromatin distribution, hyperchromasia, with increased mitotic activity and necrosis. Flexner-Wintersteiner rosettes may be seen and calcifications are absent. Grade IV neoplasms are the most anaplastic, showing pleomorphic nuclei with prominent eosinophilic nucleoli. Necrosis (Fig. 9), increased mitotic figures, including atypical mitotic forms are common. Neurofibrillary material is absent, as are calcifications. The grade correlates with prognosis, although not as sensitively as tumor stage. As the grade of the tumor increases so does the difficulty in diagnosis, often requiring ancillary studies to confirm the diagnosis.

Special Studies

Histochemical studies

The increased utilization of immunohistochemistry studies has made histochemical reactions less valuable, but occasionally the silver stains such as Bodian, Grimelius and Churukian-Schenk may still be of assistance in highlighting the neurosecretory granules.

Ultrastructural features

Membrane-bound dense core neurosecretory granules are present in the cytoplasm and in nerve processes, which additionally contain neurotubules and neurofilaments. The diameter of the granules is from 50 to 250 nm. Olfactory differentiation with olfactory vesicles and microvilli or apical cilia on apical borders may be seen in Flexner-Wintersteiner rosettes. The fibrillary stroma corresponds to the immature nerve processes. Schwann-like cells are uncommon.

Table 1 Olfactory neuroblastoma grading (based on Hyams' grading system) [12]

Microscopic features	Grade I	Grade II	Grade III	Grade IV
Architecture	Lobular	Lobular	±Lobular	±Lobular
Pleomorphism	Absent to slight	Present	Prominent	Marked
NF matrix	Prominent	Present	May be present	Present
Rosettes	HR	HR	FW	FW
Mitoses	Absent	Present	Prominent	Marked
Necrosis	Absent	Absent	Present	Prominent
Glands	May be present	May be present	May be present	May be present
Calcification	Variable	Variable	Absent	Absent

NF neurofibrillary, *HR* Homer Wright pseudorosettes, *FW* Flexner-Wintersteiner rosettes

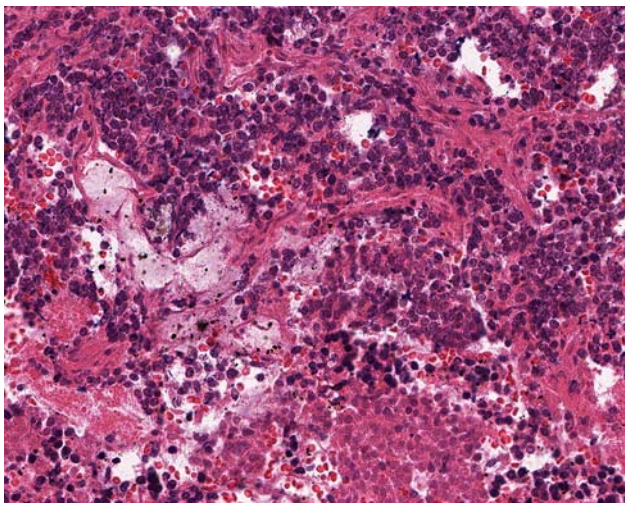

Fig. 9 Tumor necrosis (lower part of field) and a lack of organoid growth are noted in this Grade IV ONB

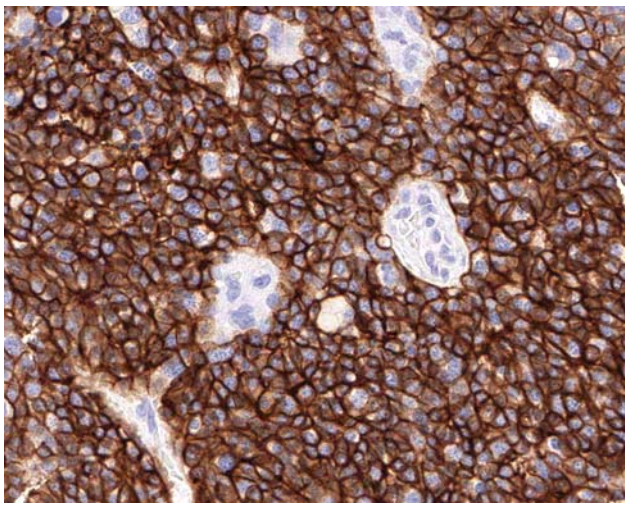

Fig. 11 CD56 gives a strong and heavy membrane-type staining

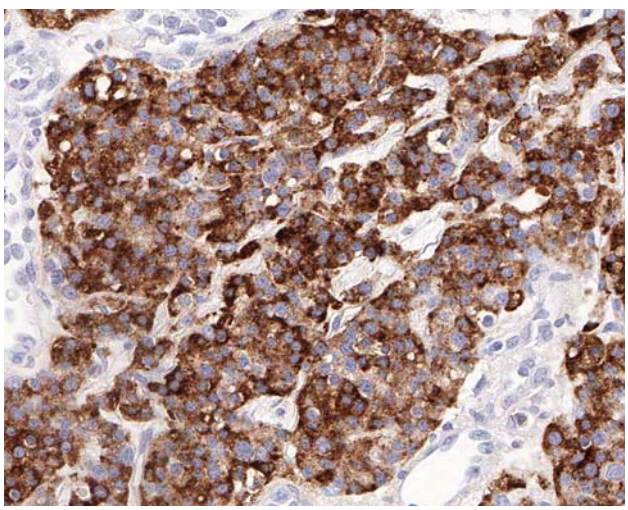

Fig. 10 Chromogranin yields a granular reaction in the cytoplasm of the neoplastic cells, giving a variable reactivity in each tumor cell

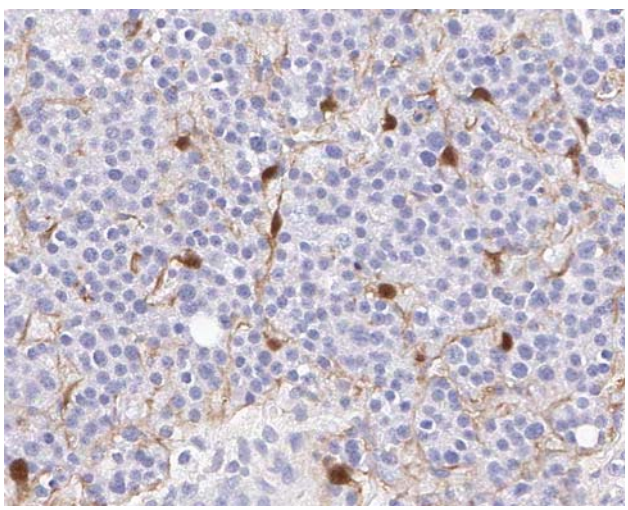

Fig. 12 A delicate sustentacular reaction with S-100 protein (nuclear and cytoplasm) highlights the supporting framework cells of an ONB

Immunohistochemical features

ONBs are positive for synaptophysin, chromogranin (Fig. 10), CD56 (Fig. 11), neuron specific enolase, NFP and S-100 protein (Fig. 12). The small round cells are usually positive for the first five markers whereas the S-100 protein-positive cells are found at the periphery of the tumor lobules and correspond to Schwann (sustentacular) cells. These same peripheral cells may be positive with glial filament acidic protein (GFAP). Class III beta-tubulin and EPCAM are positive. A few ONBs may also stain focally for low molecular weight cytokeratin (Cam 5.2). They are negative, however, for desmin, myogenin, CD45RB (leukocyte common antigen), as well as CD99 (MIC2 antigen). Proliferation marker studies using Ki-67 reveal a high proliferative index of 10–50%. Aneuploidy and polyploidy is frequent, but not germane in diagnosis.

Molecular-Cytogenetic studies

Cytogenetic studies of a few ONBs have shown multiple aberrations. Among these include DNA overexpression of chromosomal material on the entire chromosome 19, partial gains of the long arm of chromosomes 8, 15 and 22 and deletion of the entire long arm of chromosome 4. Several gains and loses have also been described on 3p, 6q, 9q, 10q, 9q, 13q and 17q. Specifically, deletions of 11 and gains of 1p are associated with an increased risk of developing metastases and with a less favorable prognosis. The absence of *EWS/FLI-1* gene fusion, t(11;22)(q24;q12) translocation and CD 99 (MIC 2, 12E7, HBA-71, 0–13) expression indicate that ONB is definitely not related to nor should be included in the Ewing/PNET group of tumors.

Differential Diagnosis

The differential diagnosis of ONB includes the group of "small round blue cell" malignant neoplasms that can occur in the sinonasal tract, i.e. squamous cell carcinoma, sinonasal undifferentiated carcinoma, extranodal NK/T cell lymphoma, nasal type, rhabdomyosarcoma, Ewing/PNET, mucosal malignant melanoma and neuroendocrine carcinomas (NEC). Of course, a metastic adrenal gland neuroblastoma to the sinonasal tract would present with histologically identical findings—but a lack of *MYCN* amplification would help to make this separation. Interestingly, NEC tend to be high grade lesions, with necrosis, high mitotic figures, and apoptosis. These tumors will show a punctate paranuclear cytokeratin immunoreactivity that is not seen in the cases of ONB that react with keratin. ONB is also non-reactive with TTF-1, while NEC can be positive. Immunoperoxidase stains that are helpful in separating some of these neoplasms are shown in Table 2, as are a selection of other features that are useful. Other tumors considered in the differential diagnosis are paraganglioma, extramedullary plasmacytoma, pituitary adenoma, extracranial meningioma, mesenchymal chondrosarcoma, and granulocytic sarcoma. In a small biopsy with crush artifact, misinterpretation is common, especially as edge effect and diffuse artifacts with immunohistochemistry may not resolve the differential. As an example, keratin reactions can be positive in up to one-third of ONBs and in a well defined subset of alveolar rhabdomyosarcomas, besides being positive in the epithelial neoplasms mentioned above. Therefore, extra caution should be employed when making an interpretation on limited material.

Management

Most curious for modern staging systems, the Kadish et al. proposed staging system from 1976 is still used, even though others have proposed a TNM-type classification (Dulgeuerov and Calcaterra) for ONBs. The Kadish system includes: A: tumor limited to nasal cavity; B: nasal cavity and paranasal sinuses; C: beyond nasal cavity and sinuses (see Table 3). While variably employed in clinical practice, most tumors are in Stage C (about 50%), and there is an associated decrease in survival as the stage increases: 75–91% for Stage A, 68–71% for Stage B and 41–47% for Stage C. Overall, there is a 60–80% 5-year survival (stage and grade dependent). Low grade tumors have an 80% 5-year survival while high grade tumors have a 40% survival.

Due to potentially significant bleeding, biopsy should be used with caution. Complete surgical elimination frequently requires a bicranial-facial approach (trephination) which removes the cribriform plate, and is usually followed by a course of radiotherapy as the treatment of choice to achieve the best long term outcome. Occasionally, endoscopic resection for limited tumor can achieve similar results. An elective neck dissection is not warranted. Palliation with chemotherapy is achieved for advanced unresectable tumors or for disseminated disease. Autologous bone marrow transplantation has achieved long term survival in limited cases. The tumors tend to be locally aggressive, involving adjacent structures (orbit and cranial cavity). Depending on stage and grade of tumor, patient survival ranges from 78% at 5 years to 68% at 15 years. As a point of comparison, low grade tumors have a reported 80% 5-year survival compared to 40% 5-year survival for high-grade tumors. Recurrences develop in about 30% of patients (range 15–70%), usually within the first 2 years after initial management. Cervical lymph node metastasis

Table 2 Sinonasal tract small blue round cell tumor differential

Feature	Olfactory neuroblastoma	Sinonasal undifferentiated carcinoma	Melanoma	Extranodal NK/T cell lymphoma, nasal type	Rhabomyosarcoma	Ewing sarcoma/PNET	Neuroendocrine carcinoma
Mean age	40–45 years	55–60 years	40–70 years	50–60 years	<20 years	<30 years	50 years
Site	Roof of nasal cavity	Multiple sites usually	Anterior nasal septum > maxillary sinus	Nasal cavity > paranasal sinuses > nasopharynx	Nasopharynx > sinonasal tract	Maxillary sinus > nasal cavity	Superior/posterior nasal cavity, ethmoid, maxillary sinuses
Imaging studies	"Dumbbell-shaped" cribriform plate mass	Marked destruction/ spread	Central destructive mass	Early changes are non-specific; midline destruction later	Size, extent of tumor	Mass lesion with bone erosion	May invade skull base or orbit
Prognosis	60–80% 5-year survival	<20% 5-year survival	17–47% 5-year survival	30–50% 5-year survival (stage dependent)	44–69% (age, stage, subtype dependent)	60–70% 5-year (stage, size, *FLI1*)	>60% die of disease
Cranial nerve involvement	Sometimes	Common	Uncommon	Sometimes	Uncommon	Sometimes	Uncommon
Pattern	Lobular	Sheets and nests	Protean	Diffuse	Sheets, alveolar	Sheets, nests	Ribbons, islands
Cytology	Salt and pepper chromatin, small nucleoli (grade dependent)	Medium cells, inconspicuous nucleoli	Large, rhabdoid, polygonal, epithelioid, plasmacytoid, spindle, pigment	Polymorphous, small to large, folded, cleaved and grooved nuclei	Round, strap, spindled, rhabdomyoblasts, primitive	Medium, round cells, vacuolated cytoplasm, fine chromatin	Salt and pepper, granular chromatin
Anaplasia	Occasionally and focally	Common	Common	Common	Common	Minimal	Moderate
Mitotic figures	Variable	High	High	High	Variable	Common	High
Necrosis	Occasionally	Prominent	Limited	Prominent	Limited	Frequent	Prominent
Vascular invasion	Occasionally	Prominent	Rare	Prominent	Rare	Rare	Present
Neurofibrillary stroma	Common	Absent	Absent	Absent	Absent	Absent	Absent
Pseudorosettes	Common	Absent	Rare	Absent	Absent	Present	Present
Keratin	Focal, weak	>90%	Negative	Negative	Negative	Rare	Positive
CK 5/6	Negative	Negative	Negative	Negative	Negative	n/a	n/a
EMA	Negative	50%	Rare	Negative	Negative	n/a	n/a
NSE	>90%	50%	Negative	Negative	Negative	Positive	Positive
S-100 protein	+ (sustentacular)	<15%	Positive	Negative	Negative	Rare	Positive
Synaptophysin	>90% (can be weak)	<15%	Negative	Negative	Negative	Positive	Positive
In situ EBER	Absent	Absent	Absent	Positive (nearly 100%)	Absent	Absent	Absent
Neurosecretory granules (EM)	Numerous	Rare	Absent	Absent	Absent	Absent	Present

EBER Epstein barr virus encoded RNA (EBV-encoded RNA)

Table 3 Clinical staging for olfactory neuroblastoma [15]

Stage	Extent of tumour	5-Year survival (%)
A	Tumour confined to the nasal cavity	75–91
B	Tumour involves the nasal cavity plus one or more paranasal sinuses	68–71
C	Extension of tumour beyond the sinonasal cavities	41–47

(up to 25%) or distant metastases (approximately 10%) develop irrespective of the grade of the tumor. The most frequent sites of distant metastasis are the lungs and bones. Overall survival is adversely affected by female gender, age <20 or >50 years at initial presentation, high tumor grade, extensive intracranial spread, distant metastases, tumor recurrence, a high proliferation index, and polyploidy/aneuploidy.

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