Neuroendocrine Neoplasms of the Sinonasal Tract: Neuroendocrine Carcinomas and Olfactory Neuroblastoma

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Received: 4 September 2015 / Accepted: 5 October 2015 / Published online: 1 February 2016
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Abstract Neuroendocrine neoplasms (NENs) can occur in organs or tissues that do not contain neuroendocrine cells normally and do not necessarily imply embryologic derivation from the neuroectoderm; but rather reflect a shared phenotype characterized by the expression of multiple genes encoding both endocrine and neuronal features. NENs are rare in the sinonasal tract and are subdivided into epithelial and neural subtypes based on the presence of keratins or neurofilaments, respectively. Although relatively rare, neuroendocrine carcinomas (NECs) and olfactory neuroblastoma (ONB) are the most common neuroendocrine neoplasms of the sinonasal tract. The focus of this review is to highlight recent developments in the pathology of sinonasal NECs and ONB in light of the upcoming update of the World Health Organization (WHO) 2005 classification of tumors of the head and neck.

Keywords Neuroendocrine carcinoma · Sinonasal tract · Nasal cavity · Olfactory neuroblastoma · Esthesioneuroblastoma

Introduction

Neuroendocrine neoplasms (NENs) can occur in organs or tissues that do not contain neuroendocrine cells normally and do not necessarily imply embryologic derivation from the neuroectoderm; but rather reflect a shared phenotype characterized by the expression of multiple genes encoding both endocrine and neuronal features [1]. NENs are rare in the sinonasal tract and are subdivided into epithelial and neural subtypes based on the presence of keratins or neurofilaments, respectively [1, 2]. Although relatively rare, neuroendocrine carcinomas (NECs) and olfactory neuroblastoma (ONB) are the most common neuroendocrine neoplasms of the sinonasal tract. The focus of this review is to highlight recent developments in the pathology of sinonasal NECs and ONB in light of the upcoming update of the World Health Organization (WHO) 2005 classification of tumors of the head and neck.

Classification

In the 2005 WHO classification of neoplasms of the head and neck, carcinoid tumor, atypical carcinoid tumor and small cell carcinoma neuroendocrine-type were identified as the three main subtypes of sinonasal NECs [3]. The term “neuroendocrine carcinoma (NEC), not otherwise specified (NOS)” was recommended for tumors with features of large cell neuroendocrine carcinoma, as defined in the respiratory tract. Tumors with predominantly neural features such as Ewing’s sarcoma/primitive neuroectodermal tumor (PNET), ONB, mucosal malignant melanoma, melanotic neuroectodermal tumor of infancy, heterotopic central nervous system tissue (nasal glioma), and ectopic pituitary adenoma were classified as neuroectodermal tumors [3].

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Table 1 Proposed terminology of neuroendocrine carcinomas of the head and neck [6, 7]

Proposed terminology	2005 classification
Neuroendocrine carcinoma, grade 1	Carcinoid tumor, well differentiated neuroendocrine carcinoma
Neuroendocrine carcinoma, grade 2	Atypical carcinoid tumor, moderately differentiated neuroendocrine carcinoma
Neuroendocrine carcinoma, grade 3, large cell type	Atypical carcinoid tumor, moderately differentiated neuroendocrine carcinoma
Neuroendocrine carcinoma, grade 3, small cell type	Small cell carcinoma, poorly differentiated neuroendocrine carcinoma
Combined neuroendocrine carcinoma with non-neuroendocrine carcinoma (squamous cell carcinoma, adenocarcinoma, etc.), grade 3	Combined small cell carcinoma, neuroendocrine type with non-small cell carcinoma (squamous cell carcinoma, adenocarcinoma, etc.)

Recently, several groups and authors have recommended the inclusion of large cell neuroendocrine carcinoma (LCNEC) as a separate entity in the classification of head and neck NECs, rather than categorizing such tumors as NEC-NOS [1, 4–7]. A proposed three-tier classification based on mitotic activity, necrosis and nuclear pleomorphism groups them into well-differentiated/grade 1, moderately-differentiated/grade 2, and poorly-differentiated/grade 3 neuroendocrine carcinoma (NEC) has also been advanced. The latter group is subdivided into small cell (SCNEC) and large cell (LCNEC) categories. The use of Ki-67 labeling index has been suggested as an additional objective criterion [6]. In this review, currently defined NECs are linked to this proposed three-tiered classification of neuroendocrine carcinomas (Table 1) [7].

Diagnosis of NEC

Carcinomas are characterized as neuroendocrine when they show:

- histologic features of neuroendocrine differentiation,
- epithelial differentiation as evidenced by the tumor arising along a mucosal/epithelial site or expression of cytokeratins by immunohistochemistry, and
- immunohistochemical expression of neuroendocrine markers such as CD56/N-CAM (diffuse) together with synaptophysin and/or chromogranin (focal/variable) and dense-core, small membrane-bound cytoplasmic vesicles by electron microscopy [8].

Common histological features of neuroendocrine differentiation include architectural patterns comprising nests, ribbons, festoons, glands and rosettes; and solid. Other patterns such as papillary, pseudopapillary, and fascicular are found less frequently. Individual tumor cells are round, polyhedral or spindle-shaped and occur in a range of sizes, although cell size tends to be uniform in individual tumors. Cytoplasm may be granular, eosinophilic, amphophilic, or oncocytic. Nuclei may be small and hyperchromatic or intermediate to large with coarsely granular or speckled

chromatin [2]. Nucleolar prominence is generally confined to LCNEC.

NECs are positive for broad-spectrum keratin antibodies and often show perinuclear dot-like staining pattern. Diffuse membranous and/or cytoplasmic staining can be seen in LCNEC. Chromogranin (a major constituent of neuroendocrine secretory granules) and synaptophysin (an integral membrane constituent of neuronal synaptic vesicles) are the most widely used markers of neuroendocrine differentiation. The intensity of chromogranin staining is proportional to the number of cytoplasmic granules; diffuse cytoplasmic staining of neuroendocrine and punctate staining of neuronal cells is seen with synaptophysin. Neither neuron-specific enolase (NSE), nor CD56 are specific neuroendocrine markers and CD56 or NSE immunoreactivity alone should not be regarded as a criterion for neuroendocrine differentiation. Many non-neuroendocrine tumors including squamous cell carcinoma and adenocarcinoma focally express neuroendocrine markers; neuroendocrine features and markers should predominate to qualify as a neuroendocrine neoplasm.

Clinical Features

NECs, regardless of differentiation or subtype, account for approximately 5 % of sinonasal malignancies [9]. Sinonasal carcinoid (well-differentiated/grade 1 NEC) and atypical carcinoid (moderately-differentiated/grade 2 NEC) tumors are rare, possibly because they are underreported or have been included under other non-descriptive categories, such as “neuroendocrine carcinoma” [10]. Sinonasal NECs present with non-specific symptoms of nasal obstruction, epistaxis and/or facial pain. Extension into the nasopharynx, skull base, orbit, or brain may occur in poorly differentiated NEC with symptoms such as palpable facial mass and exophthalmos [3]. Paraneoplastic syndrome, particularly syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been reported in association with SC-NEC [11, 12].

Fig. 1 Grade 1/well-differentiated NEC composed of monotonous small to medium size cells arranged in trabeculae and vague nests. The nuclei contain stippled chromatin and there are no visible

nucleoli (a). The tumor cells are diffusely positive for synaptophysin (b). The differential diagnosis of this tumor includes pituitary adenoma and low-grade ONB

Carcinoid Tumors/Well-Differentiated NEC/Grade 1 NEC

These have been described in the nasal cavity, nasal septum, sphenoid sinus, nasopharynx and the frontal sinus, occurring over an age range of 13–83 years [13]. Resembling carcinoid tumors elsewhere, they are composed of cords, nests of cells with glandular or rosette-like structures (Fig. 1) [14]. They have uniform nuclei with stippled chromatin and clear or eosinophilic cytoplasm; tumors with oncocyctic cytoplasm have also been described [15]. There is no cytologic atypia or necrosis. Mitoses are rare (<2 per $2 \text{ mm}^2/10 \text{ HPF}$) and the Ki-67 labeling index is $\leq 2\%$ [6, 7], although Ki-67 labeling index is currently not needed for classification or prognosis. An important differential of this uncommon tumor in the sinonasal tract is pituitary adenoma, which can arise in an ectopic location in the nasal cavity, nasopharynx, sphenoid, and ethmoid sinuses, or can occur as a downward extension of a sellar tumor [3].

Close correlation with imaging findings and immunohistochemistry for pituitary hormones (ACTH, prolactin, TSH, FSH, GH and LH) should be considered on encountering tumors with such morphology.

Prognostic information in sinonasal well-differentiated NEC is based on isolated case reports. Recurrence was reported in one patient whose tumor involved nasal cavity, ethmoid sinus, and sphenoid sinus [16]. A disease free follow-up of 4 years has been recorded in another case [17].

Atypical Carcinoid Tumors/Moderately-Differentiated NEC/Grade 2 NEC

As at other sites, these tumors occur as sheets or nests of cells with trabecular, glandular, acinar, and organoid formations (Fig. 2) [14]. The cells are larger compared to those of carcinoid tumor with eosinophilic cytoplasm, speckled chromatin, variable small eosinophilic nucleoli,

Fig. 2 Grade 2/moderately-differentiated NEC with trabecular and nested architecture in a myxoid background. Isolated mitoses and apoptotic cells are noted in the center of the field (a). Tumor cells are positive for chromogranin (b)

mild to focal nuclear pleomorphism, mitoses, and necrosis. Necrosis and/or presence of between 2 and 10 mitoses per 2 mm²/10 HPF separate these tumors from typical carcinoid and the Ki-67 labeling index is between 3 and 20 % [6, 7]. Similarly to WD-NEC, Ki-67 labeling index is not needed for classification or prognosis. These tumors lie in the morphologic spectrum between typical carcinoid/well-differentiated NEC and LCNEC.

The prognosis of patients affected by MD-NEC is variable. In a study of 7 patients with sinonasal disease, 2 died of disease at 56.2 and 119 months, and in the remaining 5 patients, the median disease free follow up was 107 months (range 16.6–172 months) [18]. In another study, five patients with sinonasal atypical carcinoid/MD-

NEC were alive at a median follow-up of 60 months (range 50–78 months), two with recurrent disease [6].

Small Cell NEC/Poorly-Differentiated NEC Small Cell Type/Grade 3 NEC Small Cell Type

This resembles small cell carcinoma of the lung containing sheets, cords or ribbons of undifferentiated small cells with high nucleocytoplasmic ratio showing prominent mitotic activity, >11 per 2 mm² or 10 HPF. The Ki-67 labeling index is >20 % (Fig. 3) [6] but is not routinely used for grading or prognosis. The nuclei may be hyperchromatic or open with delicate nuclear chromatin. Individual cell apoptosis and areas of necrosis are present and often

Fig. 3 Grade 3/poorly-differentiated NEC, small cell-type with prominent nuclear molding (a), dot-like keratin (b), weak chromogranin (c), and diffuse expression of CD56 (d)

Table 2 Differential diagnosis of sinonasal neuroendocrine neoplasms

Entity	Selective diagnostic features
Olfactory neuroblastoma	Lobules of uniform cells with indistinct cell borders and background fibrillary material Homer-Wright (pseudo-) or Flexner–Wintersteiner (true) rosettes +/– Synaptophysin+, Chromogranin+, CK variable S-100 at periphery of lobules in most tumors
Sinonasal undifferentiated carcinoma	Malignant tumor with no squamous or glandular differentiation Nuclei are medium to large but uniform Mitoses and necrosis are prominent CK+, chromogranin/synaptophysin variable but focal
NUT midline carcinoma	Sheets of monotonous, small to medium “undifferentiated” cells Abrupt and focal squamous differentiation CK+, NUT antibody+ <i>BRD4-NUT, BRD3-NUT, NUT-variant</i>
Malignant melanoma	Atypical melanocytes/pagetoid change/in situ melanoma in intact respiratory epithelium is a useful diagnostic feature Anisonucleosis, nucleolar prominence S-100+, HMB45+, Melan A+
Rhabdomyosarcoma (RMS)	Both embryonal (ERMS) and alveolar (ARMS) variants are observed EMRS has primitive mesenchymal cells in loose stroma ARMS contains sheets/nests of monomorphic small round cells Rhabdomyoblasts are variable Desmin+, myogenin+, MyoD1+ <i>PAX3-FOXO1/PAX7-FOXO1</i> in ARMS
Ewing’s/PNET	Nests/cords/sheets of uniform cells with bland nuclei and cytoplasmic glycogen Occasional pseudorosettes CD99+, vimentin+ CK+in up to 30 % <i>EWSR1 abnormalities</i>
Extranodal NK/T cell lymphoma, nasal type	Generally diffuse infiltrate of medium or small and large cells, but can show wide cytologic spectrum Angiocentric/angiodestructive infiltrate with necrosis CD2+, CD56+ EBER+

prominent. The differential diagnosis of this “small round blue cell tumor” includes lymphoma, melanoma, rhabdomyosarcoma, sinonasal undifferentiated carcinoma, olfactory neuroblastoma, Ewing’s/PNET, and NUT midline carcinoma (Table 2) [8, 10, 19, 20]. The age range is 26–77 years (mean 49 years) and tumors commonly arise in superior or posterior nasal cavity; maxillary or ethmoid sinuses without nasal involvement account for 45 % of cases.

SC-NECs are aggressive neoplasms with a local recurrence rate of 45 % and a metastasis rate of 35 %. Common sites of metastasis include cervical lymph nodes, lungs, liver, bone marrow, and vertebrae [3]. In a recent study of head and neck NEC, the 5-year survival of patients with SCNEC was 20.8 % [6]. The presence of human papillomavirus (HPV) has been described recently in rare examples of SC-NEC of the sinonasal tract [21, 22]. The

prevalence and clinical significance of HPV in SC-NEC is unclear and needs further study.

Large Cell NEC/Poorly-Differentiated NEC, Large Cell Type/NEC Grade 3, Large Cell Type

As defined in the respiratory tract [23], these are composed of organoid nests, trabeculae and rosettes, often with peripheral palisading of nuclei (Fig. 4). The cells are large with relatively low nucleus/cytoplasm ratio, nucleoli or vesicular chromatin and >11 mitoses per 2 mm² or 10 HPF. Although not used for grading or prognosis, Ki-67 labeling index is >20 % [6]. Neuroendocrine features are seen on immunohistochemistry or electron microscopy. Differential diagnoses include sinonasal undifferentiated carcinoma (SNUC), malignant melanoma, and lymphoma. Rarity of cases and overlapping morphologic and immunohistochemical features pose a

Fig. 4 Grade 3/poorly-differentiated NEC, large cell-type displaying nested architecture (a), Flexner–Wintersteiner rosettes and frequent nucleoli (b)

conceptual challenge in the diagnosis of LCNEC and its differentiation from SNUC and high-grade olfactory neuroblastoma (ONB) [8].

LCNEC has an aggressive behavior, similar to that of small cell carcinoma and a poorer prognosis when compared to atypical carcinoid tumors; 5 year survival rates of atypical carcinoid tumor, LCNEC, and SCNEC were 83.3, 21.4, and 20.8 %, respectively in a study of 23 NEC, 11 of which occurred in the sinonasal tract [6].

Olfactory Neuroblastoma

Clinical Features

Olfactory neuroblastoma (ONB) also known, as esthesioneuroblastoma is an uncommon neoplasm thought to arise from basal reserve cells (olfactory stem cells) found in the olfactory mucosa lining the superior portion of the nasal vault. ONB was first described by Berger in 1924 [24]. ONB constitutes about 3–6 % of all malignancies in the sinonasal tract [25]. These tumors arise almost exclusively in the superior portion of the nasal cavity in the region of the cribriform plate/olfactory nerve. There is no race or gender predilection. ONB is seen in a broad age range (3–90 years) with most cases presenting in the fourth and fifth decades [26]. The most common symptoms at presentation are nasal obstruction, epistaxis, and anosmia. Rare patients have presented with production of ectopic adrenocorticotrophic hormone (ACTH) and inappropriate secretion of antidiuretic hormone secretion [27, 28]. A complete physical and radiological examination—including CT and MRI—are essential for diagnosis, staging, and proper treatment planning [10]. In 1976, Kadish et al. [29] proposed a staging system for these neoplasms, which was

later modified by Morita et al. [30] (Table 2). Most tumors are in stage B and C at presentation with less than 10 % of patients having nodal or distant metastasis at presentation [26, 31].

Pathologic Features

Microscopically low-grade ONBs consist of well-circumscribed cell nests and lobules separated by fibrovascular stroma (Fig. 5a, b). The lobules may coalesce and interconnect, forming sheets of cells with a prominent capillary network. Approximately 60 to 70 % of tumors have a variable amount of fibrillary stroma, which in some cases is only a focal finding (Fig. 5c). True rosettes (Flexner–Wintersteiner rosettes, indicative of olfactory differentiation) and pseudorosettes (Homer Wright rosettes) are also typical (Fig. 5b, d), but like the fibrillary stroma, they may also be found only in small foci or may be completely absent. Pseudorosettes are most common in cases with a prominent fibrillary background (Fig. 5d). The neoplastic cells are small or medium-sized and have pale eosinophilic cytoplasm with indistinct borders. The nuclei are round, somewhat vesicular, with fine chromatin and absent or inconspicuous nucleoli in low-grade cases (Fig. 5b). Most cases are low-grade and show only mild to moderate nuclear pleomorphism and low mitotic rate with necrosis being uncommon [26, 30]. True glandular, squamous, or myogenic differentiation (Fig. 6) and melanin are distinctively rare in ONB as is maturation to ganglioneuroblastoma [32, 33].

ONBs express NSE, CD56, calretinin, synaptophysin (Fig. 5e), and chromogranin [8, 34]. The periphery of the cell nests show S-100 protein positive spindle or stellate sustentacular cells (Fig. 5f) which may be sparse in high-

Fig. 5 Low-grade ONB composed of individual and confluent nests of small round cells in a slightly hyalinized or edematous stroma (**a**). Low-grade ONB with Flexner–Wintersteiner rosettes (**b**). ONB with abundant neurofibrillary matrix (**c**). High-grade ONB with

hyperchromatic nuclei with molding and pseudorosettes (Homer Wright rosettes) (**d**). Low-grade ONB with strong and diffuse expression of synaptophysin (**e**) and numerous sustentacular cells highlighted by S-100 (**f**)

grade ONB. Neurofilament protein is seen in the cytoplasm and fibrillary matrix. ONB are usually negative for keratin, however, focal or strong patchy staining may be found in up to 30 % of tumors [35]. The distinction between high-grade ONB and high-grade NEC can be difficult, particularly in small biopsies. Careful attention to architectural and cytologic features and judicious use and interpretation of immunohistochemical stains, particularly expression and

distribution of keratins and neuroendocrine makers, is necessary for the accurate diagnosis of ONB (Table 3).

Partly due to its rarity, little is known about the molecular and genetic abnormalities of ONB. Weiss et al. [36] using paired samples of a primary and metastatic high-grade ONB from a single patient described mutations in *KDR*, *MYC*, *SIN3B*, *NLRC4*, *TP53*, *TAOK2*, and *MAP4K2* genes. Mutations of *KDR*, *MYC*, *SIN3B*, and *NLRC4* were

Fig. 6 Rhabdomyoblastic differentiation in ONB characterized by large round cells with deep eosinophilic cytoplasm

Table 3 Modified Kadish staging of olfactory neuroblastoma [29, 30]

Stage A	Tumor confined to the nasal cavity
Stage B	Tumor confined to the nasal cavity and paranasal sinuses
Stage C	Tumor extent beyond nasal cavity and paranasal sinuses, including involvement of the cribriform plate, base of the skull, orbit, or intracranial cavity
Stage D	Tumor with metastasis to cervical lymph nodes or distant sites

found only in the metastatic lesion. In a different study using array comparative genomic hybridization of 13 ONBs, the most frequent changes included gains at 7q11.22-q21.11, 9p13.3, 13q.10p/q, and Xp/q; and losses at 2q31.1, 2q33.3, 2q37.1, 6q16.3, 6q22.1, 22q11.23, 22q12.1 and Xp/q. High-stage ONBs showed more genetic abnormalities than low-stage tumors [37]. Clearly there is a need for more research if we are to understand the biology of these neoplasms and better treat patients affected by ONB.

Prognostic Factors

The outcome of ONB is variable. In a population-based analysis of survival and prognostic factors, Jethanamest et al. [25] reported overall 5- and 10-year survival rates of 61.1 and 45.6 % respectively. In a single institution

experience of 35-years, which included 95 patients with different treatment modalities, Rimmer et al. [38] described overall survival rates of 83.4 and 76.1 % at 5- and 10-years with disease specific survival rates of 80 and 62.8 %, respectively. The modified Kadish staging system, Hyams histologic grade, lymph node status at presentation, treatment modality, and age have been found to be useful predictors of patient outcome and survival [25, 26, 31, 38, 39]. Hyams et al. [40] introduced a four-tier histologic grading system based on architectural and cytologic parameters, and the presence of mitoses, rosettes, neurofibrillary stroma and necrosis with the better differentiated tumors being grade I and the most poorly differentiated tumors with high mitotic rate and necrosis tumors being grade IV (Table 4). Hyams grading system has evolved into a two-tier system with grade I–II being low-grade and grade III–IV tumors being classified as high-grade. Approximately 60 % of ONB are low-grade [26, 31]. Although imperfect and initially controversial, many studies have confirmed the prognostic utility of the Hyams grading system [26, 30, 31, 39]. In a study of 109 patients with ONB, Van Gompel et al. [39] the median survival for low-grade tumors was 9.8 years compared to 6.9 years in those with high-grade lesions ($p = 0.02$). Somewhat similar findings have been reported in a study of 124 patients by Bell et al. [26].

Age at presentation greater than 65 years also has an adverse impact on overall survival [26, 39]. Kaplan–Meier analysis have shown overall and disease specific survival rates at 10 years to be 83.4 and 90 % for Kadish stage A disease, 49 and 68.3 % for those with stage B, 38.6 and 66.7 % for those with stage C, and 13.3 and 35.6 % for those with stage D [25]. In a different study, the disease free survival dropped from 221 months for Kadish A to 33 months for Kadish D cases [38]. Approximately 25 % of patients with ONB develop local recurrences and 20 % develop cervical lymph node or distant metastases [31, 38]. Most metastases are intracranial but spine, liver, skin, and lung metastases also occur. Local recurrences and distant metastases can occur 10 years after initial diagnosis and treatment; therefore long term follow-up of patients affected by ONB is strongly advisable [30, 38].

Table 4 Hyams' microscopic grading of ONB

Grade	Lobular architecture	Mitotic index	Nuclear pleomorphism	Fibrillary matrix	Rosettes	Necrosis
I	+	No	No	Prominent	HW rosettes	No
II	+	Low	Moderate	Present	HW rosettes	No
III	±	Moderate	Prominent	Low	FW rosettes	Rare
IV	±	High	Marked	Absent	No	Common

HW Homer Wright rosettes, FW Flexner–Wintersteiner rosettes

Conclusions

The 2005 WHO classification of head and neck needs to be updated to properly recognize the occurrence of NECs with the features of LCNEC as defined in other sites such as lung. The optimal terminology for grading and classification of head and neck and sinonasal NECs remains controversial and not universally accepted with the historical terms “carcinoid tumor” and “atypical carcinoid tumor” remaining in wide use. Unlike the controversies surrounding NECs, the pathologic features and grading of ONB have been well characterized and are widely used; however, in this era of personalized medicine there is a need for additional research into the molecular and genetic abnormalities of ONB to devise effective treatments for patients with recurrent and metastatic disease.

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