Neuroendocrine Neoplasms of the Head and Neck: Some Suggestions for the New WHO Classification of Head and Neck Tumors

Bin Xu · Runjan Chetty · Bayardo Perez-Ordoñez

Received: 1 December 2013 / Accepted: 19 January 2014 / Published online: 5 March 2014
© Springer Science+Business Media New York 2014

Abstract As knowledge and understanding in pathology evolve, classifications and nomenclature also change to reflect those advances. The 2005 World Health Organization Classification of Head and Neck Tumours was a significant step towards diagnostic standardization of head and neck neuroendocrine carcinomas; however, in the last 10 years there have been new data supporting the recognition of “large cell neuroendocrine carcinoma” as a distinctive high grade carcinoma in the head and neck, a lesion not included in the 2005 Classification. In addition, the terms “middle ear adenoma” and “carcinoid tumor of middle ear” are still widely used to describe a neoplasm that is neither a pure adenoma nor a carcinoid tumor but a lesion with variable mixed exocrine and endocrine differentiation. Largely using the diagnostic criteria of the WHO classification of neuroendocrine carcinomas of the lung, we propose the terms “neuroendocrine carcinoma, grade 1”; “neuroendocrine carcinoma, grade 2”; “neuroendocrine carcinoma, grade 3, large cell type”; and “neuroendocrine carcinoma, grade 3, small cell type” for the classification of neuroendocrine carcinomas of the head and neck in a future WHO classification. In addition, we also proposed

the term “mixed epithelial neuroendocrine tumor” of the middle ear as an alternative for “middle ear adenoma” and “carcinoid tumor of the middle ear”.

Keywords Neuroendocrine carcinoma · Middle ear adenoma · Head and neck · Salivary glands · Larynx

Introduction

Although the last 30 years have witnessed substantial progress in the classification and understanding of the clinical behavior of neuroendocrine neoplasms, many unresolved issues regarding terminology, mitotic thresholds, and the benefits of using proliferative indexes in the classification of these lesions remain. Given the heterogeneity of neuroendocrine tumors in the gastrointestinal tract and pancreas, most of these controversies are currently centered around lesions of these organs [1, 2]. Although rarer and less heterogeneous than their pulmonary and gastrointestinal counterparts; neuroendocrine neoplasms of the head and neck have not escaped these controversies. In 1988, in a seminal paper describing the clinicopathologic features of moderately differentiated neuroendocrine carcinomas of the larynx, Wenig et al. [3] remarked that the classification of the neuroendocrine carcinomas (NEC) of the head and neck (NEC-HN) was confusing and lacked standardization. The following year, Wenig and Gnepp [4] proposed a classification of laryngeal NECs as well differentiated (synonymous with carcinoid tumour), moderately differentiated (including entities previously referred to as atypical, pleomorphic, malignant, or anaplastic carcinoid), and poorly differentiated (including small cell carcinoma, both oat cell and intermediate cell variants). The 2005 World Health Organization (WHO)

B. Xu
Department of Pathology, McGill University Health Center,
Montreal, QC, Canada

R. Chetty · B. Perez-Ordoñez (✉)
Department of Pathology, Toronto General Hospital, University
Health Network, 200 Elizabeth Street, Toronto, ON M5G 2C4,
Canada
e-mail: bayardo.perez-ordonez@uhn.ca

R. Chetty · B. Perez-Ordoñez
Department of Laboratory Medicine and Pathobiology,
University of Toronto, Toronto, ON, Canada

Classification of Head and Neck Tumors lists 4 types of NECs: (a) typical carcinoid, (b) atypical carcinoid, (c) small cell carcinoma, neuroendocrine type and (d) combined small cell carcinoma, neuroendocrine type with non-small cell carcinoma [5]. This classification represented a significant step towards the standardization of diagnostic criteria of these neoplasms and although not explicitly stated, it incorporated most features of the 2004 WHO Classification for neuroendocrine carcinomas of the lung [6]. In recent years a consensus has been building in the head and neck pathology community that the current WHO Classification of Head and Neck Tumours does not adequately describe or define the clinicopathologic spectrum of NECs of the head and neck [7–10] with the most notable deficiency being the absence of a category for “large cell neuroendocrine carcinoma” (LC-NEC) [10–12]. In this short review, we visited some controversial areas in the pathology of neuroendocrine neoplasms of the head and neck which we believe should be addressed in any future WHO Classification of Head and Neck tumors.

Should Large Cell Neuroendocrine Carcinoma of the Head and Neck (LC-NEC) be recognized as a distinctive category of high grade neuroendocrine carcinomas?

Suggestion #1 LC-NEC of the head and neck should be recognized as a distinctive category of high-grade neuroendocrine carcinoma in any new classification of head and neck tumors.

Currently there is little doubt that LC-NECs of the head and neck [7, 11] are distinctive neoplasms, but given that it was not until 1991 that well defined criteria for the diagnosis of pulmonary LC-NEC were set forth [13], the diagnosis of LC-NEC in the head and neck lacked specificity. It was only in 2000 that Nagao et al. [14] first documented two examples of LC-NEC of salivary glands using diagnostic criteria similar to those of LC-NEC in the lung. Heretofore LC-NECs of the head and neck had been reported as “large cell carcinoma”, “atypical carcinoid tumors”, “moderately differentiated neuroendocrine carcinomas” or “large cell neuroendocrine carcinoma”. Wenig et al. [3] in a study of 54 laryngeal NEC reported that “in eight patients were mitotic figures readily identified”. In another study of 48 laryngeal paragangliomas and “neuroendocrine carcinomas”, Milroy et al. [15] used the term “large cell neuroendocrine carcinoma” and indicated that “occasional tumours had a high mitotic rate”. Woodruff et al. [16] also employed the term “large cell neuroendocrine carcinoma” in their study of laryngeal NEC and described at least 8 tumors with high mitotic rate or necrosis.

Following the report by Nagao et al. [14], others have published case reports and small series of LC-NECs in the larynx [7, 9, 12, 17–19], oropharynx and hypopharynx [17],

sinonasal tract [7], and salivary glands [20, 21] using diagnostic criteria similar to those of pulmonary NEC. Recently Kusufuka et al. [11] published a comprehensive review of LC-NEC of the head and neck using microscopic diagnostic criteria to those of lung thus putting to rest any lingering doubts regarding the existence of these tumors in the region.

Should the Classification of Neuroendocrine Carcinomas in the Head and Neck Region (Sinonasal Tract, Salivary Glands, Oral Cavity, Pharynx and Larynx) mirror the Classification of Neuroendocrine Carcinomas of Lung?

Suggestion #2 Any new classification of neuroendocrine carcinomas of the head and neck should adopt a uniform terminology and diagnostic criteria for all head and neck sites. This classification should be largely based on the current classification of neuroendocrine carcinomas of the lung.

We propose a classification of neuroendocrine carcinomas of the head and neck largely based on the 2004 WHO Classification of Tumors of the Lung [6] combined with some elements of the 2010 WHO Classification of neuroendocrine neoplasms of the digestive tract [1]. This terminology retains the microscopic criteria, including the presence of necrosis, and mitotic counts as suggested in the lung classification but incorporates the concept of grade based on mitotic activity as suggested by the 2010 classification of the digestive tract [1]. Given that all of these neuroendocrine epithelial tumors are malignant, the term “neuroendocrine carcinoma” is preferred over “neuroendocrine tumor”. There is no sufficient data to support incorporation of MIB-1 index as a component of the grading system of NEC-HN although several recent studies have reported high MIB-1 labelling indices ranging from 10 to 96 % for LC-NECs and 76–97 % for SC-NECs [7, 9, 17]. Not enough cases have been tested with Ki-67 and the labelling index might not have prognostic significance given that at least 50 % of head and neck NECs appear to be high grade [7]. The proposed terminology and definitions are listed in Table 1 and described in the paragraphs below. The classification does not include olfactory neuroblastoma (esthesioneuroblastoma) and paragangliomas given that these neoplasms represent distinctive entities that should not be confused or grouped with true neuroendocrine carcinomas.

Neuroendocrine carcinoma, grade 1 (Fig. 1)

This group is equivalent to “carcinoid tumor” and “well differentiated neuroendocrine carcinoma” and is defined as “a tumor with a neuroendocrine/carcinoid morphology, mitotic rate of less than 2 mitoses per 2 mm² (10 HPF), and

Table 1 Proposed classification of neuroendocrine carcinomas of the head and neck

Proposed classification	2005 classification	Criteria for diagnosis
Neuroendocrine carcinoma, grade 1	Carcinoid tumor, well differentiated neuroendocrine carcinoma	<ul style="list-style-type: none"> • Tumor with neuroendocrine/carcinoid morphology • Mitotic rate of less than 2 mitoses per 2 mm² (10 HPF) • Absence of necrosis
Neuroendocrine carcinoma, grade 2	Atypical carcinoid tumor, moderately differentiated neuroendocrine carcinoma	<ul style="list-style-type: none"> • Tumor with neuroendocrine/carcinoid morphology • 2–10 mitoses per 2 mm² (10 HPF) and/or necrosis.
Neuroendocrine carcinoma, grade 3, large cell type	Atypical carcinoid tumor, moderately differentiated neuroendocrine carcinoma	<ul style="list-style-type: none"> • Tumor with a neuroendocrine morphology • High mitotic rate: 11 or greater per 2 mm² (10 HPF), median of 70 per 2 mm² • Necrosis • Cytologic features of non-small cell carcinoma • Staining with one or more neuroendocrine markers and/or neuroendocrine granules in electron microscopy
Neuroendocrine carcinoma, grade 3, small cell type	Small cell carcinoma, poorly differentiated neuroendocrine carcinoma	<ul style="list-style-type: none"> • Tumor cells with small size • High mitotic rate (11 or greater per 2 mm² or 10HPF), median of 80 per mm² (10 HPF) • Frequent necrosis
Combined neuroendocrine carcinoma with non-neuroendocrine carcinoma (squamous cell carcinoma, adenocarcinoma, etc.)	Combined small cell carcinoma, neuroendocrine type with non-small cell carcinoma (squamous cell carcinoma, adenocarcinoma, etc.)	

absence of necrosis”. NEC grade 1 is the least common of all NEC in the head and neck and occurs most commonly in supraglottic larynx [3, 7, 15, 22, 23], with rare examples in the parotid gland [24] and sinonasal tract [7, 25]. It is difficult to make conclusive statements regarding the clinical behavior of NEC grade 1 given their rarity and paucity of good prognostic data. Age at presentation has ranged from 23 to 71 years [7, 23, 26] with most patients being alive with no recurrent disease after follow-up periods ranging from 18 to 124 months [7, 22, 23, 27].

Neuroendocrine carcinoma, grade 2 (Fig. 2)

This group is equivalent to “atypical carcinoid tumor” and “moderately differentiated neuroendocrine carcinoma”. NEC grade 2 is defined as a tumor with neuroendocrine/carcinoid morphology with 2–10 mitoses per 2 mm² (10 HPF), and/or necrosis. In a series utilizing current diagnostic criteria, Kao et al. [7] reported that NEC grade 2 (moderately differentiated NEC) constituted 30 % (7 of 23 cases) of their neuroendocrine carcinomas of the head and neck. Most NECs grade 2 arise in supraglottic larynx and

sinonasal tract with an age at presentation ranging from 25 to 83 years [3, 7]. The differences in survival at 5 year between NEC grade 2 and NEC grade 3, large cell-type in the Kao’s series was 83 versus 21.4 % [7]. Wenig et al. [3] in their series of “moderately differentiated” NEC reported that 38 % (18/48) of patients had died with tumor. One of two patients with “moderately differentiated NEC” of parotid gland described by Said-Al-Naief [28] was alive with liver metastases whereas the patient illustrated by Modlin et al. [29] was alive with stable metastatic disease in the liver 10 years after initial diagnosis. We stress the need of collaborative studies with current diagnostic criteria to determine the differences in behavior, prognosis, and molecular genetic underpinnings between the old “atypical carcinoid tumors” and “LC-NECs” in the head and neck.

Neuroendocrine carcinoma, grade 3, large cell type (Fig. 3)

This group is equivalent to “large cell neuroendocrine carcinoma” and is defined as “(a) tumor with a neuroendocrine morphology; organoid nesting, palisading, rosettes,

Fig. 1 Neuroendocrine carcinoma, grade 1. Small submucosal NEC of larynx with solid and nested architecture (a). The tumor cells have eosinophilic cytoplasm with coarse but evenly dispersed chromatin.

Despite the variation in nuclear size, this NEC displayed no mitotic activity thus qualifying for a NEC, grade 1 (b)

Fig. 2 Neuroendocrine carcinoma grade 2 of the nasopharynx showing insular and trabecular patterns (a). The tumor is composed of cuboidal and polygonal cells with eosinophilic cytoplasm and nuclei displaying coarse chromatin and occasional mitotic figures (b).

Laryngeal NEC grade 2 with central necrosis (c). Grade 2 NEC of larynx with high Ki-67 index. The prognostic value of Ki-index is currently unknown in NECs of the head and neck (d)

trabeculae; (b) high mitotic rate: 11 or greater per 2 mm² (10 HPF), median of 70 per 2 mm²; (c) necrosis; (d) cytologic features of non-small cell carcinoma; and (e) positive staining with one or more neuroendocrine markers and/or neuroendocrine granules in electron microscopy”. NECs grade 3, large-cell type are aggressive malignancies that need to be distinguished from NECs grades 1 and 2. In a review of 10 laryngeal LC-NECs by Lewis et al. [9], 9

patients (90 %) presented with stage IV disease and 60 % died of their disease. Kasafuka et al. [17] in a series of 8 mucosal LC-NEC reported that 7 of 8 (80 %) patients presented with regional lymph node metastases and 3 had died of disease after follow-up ranging from 15 to 90 months. Three of 4 (75 %) patients with well documented LC-NEC of the salivary glands have died of their disease [14, 20, 26].

Fig. 3 Neuroendocrine carcinoma grade 3, large cell type. At low power, the tumor is composed of well defined and confluent nests (a). The tumor cells are large with abundant eosinophilic cytoplasm with

vesicular nuclei and prominent nucleoli (b). The tumor cells are positive for chromogranin (c)

Fig. 4 Neuroendocrine carcinoma grade 3, small cell type of the parotid gland (a). The tumor cells are diffusely positive for keratin 20 (b). NEC grade 3, small cell type of oropharynx (c) with diffuse

expression of p16 (d). Linear Array confirmed the presence of human papillomavirus-16 (HPV16) in this tumor

Neuroendocrine carcinoma, grade 3, small cell type (Fig. 4)

This group is equivalent to “small cell neuroendocrine carcinoma” and is defined as: “(a) tumor cells with small

size (generally less than the diameter of 3 small resting lymphocytes), (b) scant cytoplasm, (c) nuclei: finely granular chromatin, absent or inconspicuous nucleoli, (d) high mitotic rate (11 or greater per 2 mm² or 10 HPF), median of 80 per mm² (10 HPF), and (e) frequent

necrosis”. NECs grade 3, small-cell type is the best characterized NECs of the head and neck [7, 10, 30–32]. Despite the numerous publications regarding small cell neuroendocrine carcinomas of the head and neck, one of the remaining questions include differences in behavior vis-a-vis LC-NECs. In the study by Kao et al. [7] the 5-year survival rates for LC-NEC and SC-NEC were 21.4 and 20.8 %. It is important to note the association of oropharyngeal small cell neuroendocrine carcinoma with human papillomavirus (HPV); however, the presence of HPV in these carcinomas does not change their adverse biologic behavior unlike the better overall prognosis and radiore-sponsiveness observed in HPV-associated oropharyngeal squamous cell carcinomas.

In summary we support the use of a uniform terminology and consistent standardized diagnostic criteria for all NECs of the head and neck. There is substantial evidence in the literature that NECs, including LC-NECs, of the head and neck share similar microscopic features to NECs of the lung. The adoption of uniform criteria and terminology should allow comparison and validation of study results from different investigators and institutions thus contributing to the understanding of the clinical behavior and underlying molecular abnormalities of these uncommon neoplasms.

Should Salivary Large Cell Carcinomas be divided into Neuroendocrine and Non-Neuroendocrine?

Suggestion #3 A uniform classification of neuroendocrine carcinomas in all head and neck sites should classify large cell carcinomas of salivary glands fulfilling the required microscopic criteria as neuroendocrine carcinoma, grade 3, large cell type. Those large cell carcinomas lacking the required criteria, should be classified as “large cell carcinoma NOS” or undifferentiated carcinomas.

The 2005 WHO Classification of Tumors of the Salivary Glands consists of a listing of neoplasms lacking a discrete category of neuroendocrine neoplasms. Only small cell carcinoma is recognized as a distinctive type of neuroendocrine carcinoma [5]. In contrast, large cell carcinoma is described as a heterogeneous group of high grade carcinomas with only sporadic neuroendocrine differentiation [21, 33, 34]. Large cell carcinomas also appear to include examples of poorly differentiated squamous cell carcinoma, high-grade mucoepidermoid carcinoma or undifferentiated carcinomas NOS, [35, 36]. Some of this confusion can be traced back to the inclusion of large cell carcinomas and small cell carcinomas as part of the spectrum of “undifferentiated carcinoma” [21, 35] when rigidly applying the 1991 WHO classification of salivary gland tumors [37].

Neuroendocrine carcinomas, small cell type, although relatively uncommon are well recognized and relatively

well characterized [31, 38–40]. Lower grade neuroendocrine carcinomas (“typical carcinoid” and “atypical carcinoid” tumors) of salivary gland origin are extremely rare [4, 28, 29, 41]. The recognition of LC-NEC in salivary glands was hampered by the absence of well defined microscopic criteria for their diagnosis and the lack of ancillary techniques to demonstrate neuroendocrine differentiation; however, NEC, large cell-type (LC-NEC) in the major salivary glands was recognized in 1990 by Hui et al. [21] in what is probably the most cited study of “undifferentiated” carcinomas of the salivary glands. These authors described 12 “small cell carcinomas” and 4 “large cell carcinomas” in a study of 16 “undifferentiated” carcinomas; at least one of these four “undifferentiated” large cell carcinomas had organoid architecture and neuroendocrine granules [21]. Nagao et al. [14] were the first investigators describing LC-NEC in salivary gland using the criteria for lung LC-NEC. In their review of 1,675 salivary gland tumors, 2 neoplasms were reclassified as LC-NEC. After these report, others have recognized rare LC-NEC in salivary gland highlighting the benefits of using a standard classification for neuroendocrine carcinomas [20, 26].

Should Middle Ear Carcinoids be classified separately from Middle Ear Adenomas?

Suggestion #4 The published literature indicates that “middle ear carcinoids” and “middle ear adenomas” are a single clinicopathologic entity composed of neoplasms with variable mixed exocrine (glandular) and neuroendocrine differentiation. Given that both terms “middle ear carcinoid” and “middle ear adenoma” appear to be biologically incorrect, we propose the term “mixed epithelial and neuroendocrine tumor (MENET)” of the middle ear to designate this entity.

The current WHO Classification of Head and Neck Tumours defines adenomas of the middle ear as a “benign glandular neoplasm showing variable differentiation along neuroendocrine and mucin-secreting pathways” [42] (Fig. 5). Middle ear adenoma was recognized as a distinctive “adenomatous” lesion separate from adenocarcinomas of the middle ear by Hyams and Michaels in 1976 [43]. Although some microscopic similarities of these tumors to “carcinoids” had been observed by Fayemi and Toker [43], it was until 1980 that Murphy et al. [44] documented argyrophilic granules and neurosecretory-type granules in one of these neoplasms in a manuscript entitled “Carcinoid Tumor of the Middle Ear”. Following these publications, numerous case reports and small series using immunohistochemistry and electron microscopy have confirmed a mixed or dual exocrine and neuroendocrine differentiation in these neoplasms [45–50].

Fig. 5 Mixed epithelial neuroendocrine tumor (MENET) of the middle ear showing prominent glandular and trabecular architecture (a). Keratin 7 in MENET only highlights cells with glandular differentiation. Neuroendocrine cells are negative (b). Only isolated

cells with neuroendocrine differentiation are stained with chromogranin in this MENET (c). More intense and diffuse staining of neuroendocrine cells with human pancreatic polypeptide in this example of MENET (d)

The largest clinicopathologic study of “middle ear adenoma/carcinoid tumor of the middle ear” is the report of 48 cases by Torske and Thompson [50]. These authors described the entire pathologic spectrum of these neoplasms, which includes a variety of architectural patterns: glandular, trabecular, solid, infiltrating and organoid. Although most tumors were only moderately cellular, some cases exhibited high cellularity. Other less common findings were necrosis (1 case) and moderate to severe pleomorphism (3 cases). Using a large panel of antibodies, 87.5 % of cases were positive for chromogranin, 31.3 % expressed synaptophysin, and 25 % were positive for serotonin. Human pancreatic polypeptide (HPP) staining was present in 43/48 (93 %) of cases. Keratin 7 (CK 7) was mostly expressed by cells with glandular differentiation. The authors concluded that adenomas and carcinoid tumors of the middle ear were “essentially indistinguishable benign tumors” and suggested the term “neuroendocrine adenoma of the middle ear” as an alternative name for these neoplasms to better describe their benign behavior and neuroendocrine differentiation [50–52]. But are these tumors always benign? Local recurrences have been observed in up to 20 % of adenoma/carcinoid tumors of the middle ear [53] and there are two reports of patients

developing cervical lymph node metastasis after follow-ups of 3.5 and 7 years after initial diagnosis [54, 55]. Most local recurrences have been noted in patients with incompletely resected tumors.

From a review of the published literature one could reach the following conclusions: (1) “adenoma” and “carcinoid tumor” of the middle ear are indistinguishable under the microscope and therefore both terms describe the same neoplasm; (2) these tumors exhibit diverse architectural patterns and are composed of at least 2 distinctive cell types showing exocrine (glandular) and neuroendocrine differentiation; (3) the terms “adenoma” and “carcinoid” do not adequately describe the dual or mixed differentiation of the neoplastic cells, and (4) there are rare examples of so called “carcinoid” tumors of the middle ear which have developed neck lymph nodes metastases. To overcome the continuing debate surrounding terminology and clinical behavior for these neoplasm, we propose the adoption of the term “mixed epithelial neuroendocrine tumor” (MENET) of the middle ear. We believe that this term more accurately describes the dual lines of differentiation seen in these lesions and avoids the connotation of “always benign” behavior implicit in the term “adenoma”.

Conclusion

We propose to unify the classification of neuroendocrine carcinomas in the head and neck to include salivary neuroendocrine carcinomas and middle ear “adenoma/neuroendocrine” neoplasms. These two entities were previously classified under “undifferentiated carcinomas” and “middle ear adenomas”, respectively. Since the last WHO classification of head and neck tumors, there has been additional data supporting the recognition of “large cell neuroendocrine carcinoma” as a distinctive category of high grade carcinoma in the head and neck region. In addition, the importance of using uniform diagnostic criteria for neuroendocrine carcinomas in the entire region has become more evident if we are to study the underlying molecular and genetic alterations of these uncommon neoplasms. It remains unclear to us due to their rarity, if any future classification should also acknowledge the existence of “amphicrine carcinomas” in the region [56, 57].

References

- Rindi G, Arnold R, Bosman FT, et al. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, et al., editors. WHO classification of tumours of the digestive system. Lyon: International Agency for Research on Cancer; 2010. p. 13–4.
- Klimstra DS, Modlin IR, Coppola D, et al. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas*. 2010;39:707–12.
- Wenig BM, Hyams VJ, Heffner DK. Moderately differentiated neuroendocrine carcinoma of the larynx: a clinicopathologic study of 54 cases. *Cancer*. 1988;62:2658–76.
- Wenig BM, Gnepp DR. The spectrum of neuroendocrine carcinomas of the larynx. *Semin Diagn Pathol*. 1989;6:329–50.
- Barnes L. Tumours of the hypopharynx, larynx, and trachea: neuroendocrine tumors. In: Barnes L, Eveson JW, Reichart P, et al., editors. Pathology and genetics head and neck tumours. Lyon: IARC Press; 2005. p. 135–9.
- Brambilla E, Pugatch B, Geisinger KR, et al. Large cell carcinoma. In: Travis WD, Brambilla E, Muller-Hermelink HK, et al., editors. Tumours of the lung, pleura, thymus, and heart. Lyon: IARC Press; 2004. p. 45–50.
- Kao HL, Chang WC, Li WY, et al. Head and neck large cell neuroendocrine carcinoma should be separated from atypical carcinoid on the basis of different clinical features, overall survival, and pathogenesis. *Am J Surg Pathol*. 2012;36:185–92.
- Chetty R, Shah KA, Perez-Ordóñez B. Large cell neuroendocrine carcinoma of the head and neck. *Am J Surg Pathol*. 2012;36:1102–3.
- Lewis JS Jr, Spence DC, Chiosea S, et al. Large cell neuroendocrine carcinoma of the larynx: definition of an entity. *Head Neck Pathol*. 2010;4:198–207.
- Lewis JS Jr, Ferlito A, Gnepp DR, et al. Terminology and classification of neuroendocrine neoplasms of the larynx. *Laryngoscope*. 2011;121:1187–93.
- Kusafuka K, Ferlito A, Lewis JS Jr, et al. Large cell neuroendocrine carcinoma of the head and neck. *Oral Oncol*. 2012;48:211–5.
- Greene L, Brundage W, Cooper K. Large cell neuroendocrine carcinoma of the larynx: a case report and a review of the classification of this neoplasm. *J Clin Pathol*. 2005;58:658–61.
- Travis WD, Linnoila RI, Tsokos MG, et al. Neuroendocrine tumors of the lung with proposed criteria for large-cell neuroendocrine carcinoma: an ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. *Am J Surg Pathol*. 1991;15:529–53.
- Nagao T, Sugano I, Ishida Y, et al. Primary large-cell neuroendocrine carcinoma of the parotid gland: immunohistochemical and molecular analysis of two cases. *Mod Pathol*. 2000;13:554–61.
- Milroy CM, Rode J, Moss E. Laryngeal paragangliomas and neuroendocrine carcinomas. *Histopathology*. 1991;18:201–9.
- Woodruff JM, Huvos AG, Erlandson RA, et al. Neuroendocrine carcinomas of the larynx: a study of two types, one of which mimics thyroid medullary carcinoma. *Am J Surg Pathol*. 1985;9:771–90.
- Kusafuka K, Abe M, Iida Y, et al. Mucosal large cell neuroendocrine carcinoma of the head and neck regions in Japanese patients: a distinct clinicopathological entity. *J Clin Pathol*. 2012;65:704–9.
- Chung EJ, Baek SK, Kwon SY, et al. Moderately differentiated neuroendocrine carcinoma of the larynx. *Clin Exp Otorhinolaryngol*. 2008;1:217–20.
- Halmos GB, van der Laan TP, van Hemel BM, et al. Is human papillomavirus involved in laryngeal neuroendocrine carcinoma? *Eur Arch Otorhinolaryngol*. 2013;270:719–25.
- Casas P, Bernaldez R, Patron M, et al. Large cell neuroendocrine carcinoma of the parotid gland: case report and literature review. *Auris Nasus Larynx*. 2005;32:89–93.
- Hui KK, Luna MA, Batsakis JG, et al. Undifferentiated carcinomas of the major salivary glands. *Oral Surg Oral Med Oral Pathol*. 1990;69:76–83.
- Bapat U, Mackinnon NA, Spencer MG. Carcinoid tumours of the larynx. *Eur Arch Otorhinolaryngol*. 2005;262:194–7.
- Duvall E, Johnston A, McLay K, et al. Carcinoid tumour of the larynx: a report of two cases. *J Laryngol Otol*. 1983;97:1073–80.
- Nicod JL. Carcinoid of the parotid gland. *Bull Assoc Fr Etud Cancer*. 1958;45:214–22.
- Siwersson U, Kindblom LG. Oncocytic carcinoid of the nasal cavity and carcinoid of the lung in a child. *Pathol Res Pract*. 1984;178:562–9.
- Kawaratan H, Tsujimoto T, Yoshikawa M, et al. Large cell neuroendocrine carcinoma presenting with neck swelling in the submandibular gland: a case report. *J Med Case Rep*. 2013;7:81.
- Weinreb I, Perez-Ordóñez B. Non-small cell neuroendocrine carcinoma of the sinonasal tract and nasopharynx: report of 2 cases and review of the literature. *Head Neck Pathol*. 2007;1:21–6.
- Said-Al-Naief N, Sciandra K, Gnepp DR. Moderately differentiated neuroendocrine carcinoma (atypical carcinoid) of the parotid gland: report of three cases with contemporary review of salivary neuroendocrine carcinomas. *Head Neck Pathol*. 2013;7:295–303.
- Modlin IM, Shapiro MD, Kidd M. Primary carcinoid tumor of the parotid gland: a case report and review of the literature. *Ear Nose Throat J*. 2006;85:533–9.
- Gnepp DR, Corio RL, Brannon RB. Small cell carcinoma of the major salivary glands. *Cancer*. 1986;58:705–14.
- Chan JKC, Suster S, Wenig BM, et al. Cytokeratin 20 immunoreactivity distinguishes Merkel cell (primary cutaneous) neuroendocrine carcinomas and salivary gland small cell carcinomas from small cell carcinomas of various sites. *Am J Surg Pathol*. 1997;21:226–34.
- Perez-Ordóñez B, Caruana SM, Huvos AG, et al. Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses. *Hum Pathol*. 1998;21:826–32.

33. Ueo T, Kaku N, Kashima K, et al. Carcinosarcoma of the parotid gland: an unusual case with large-cell neuroendocrine carcinoma and rhabdomyosarcoma. *APMIS*. 2005;113:456–64.
34. Larsson LG, Donner LR. Large cell neuroendocrine carcinoma of the parotid gland: fine needle aspiration, and light microscopic and ultrastructural study. *Acta Cytol*. 1999;43:534–6.
35. Hatta C, Terada T, Okita J, et al. Clinicopathological study of undifferentiated carcinoma of the parotid gland. *Auris Nasus Larynx*. 2003;30:273–7.
36. Nagao K, Matsuzaki O, Saiga H, et al. Histopathologic studies of undifferentiated carcinoma of the parotid gland. *Cancer*. 1982;50:1572–9.
37. Seifert G, Sobin LH. Histological classification of salivary gland tumours. Berlin: Springer; 1991:1–38.
38. Scher RL, Feldman PS, Levine PA. Small-cell carcinoma of the parotid gland with neuroendocrine features. *Arch Otolaryngol Head Neck Surg*. 1988;114:319–21.
39. Huntrakoon M. Neuroendocrine carcinoma of the parotid gland: a report of two cases with ultrastructural and immunohistochemical studies. *Hum Pathol*. 1987;18:1212–7.
40. Gnepp DR, Wick MR. Small cell carcinoma of the major salivary glands: an immunohistochemical study. *Cancer*. 1990;66:185–92.
41. Wenig BM. Neuroendocrine tumors of the larynx. *Head Neck*. 1992;14:332–4.
42. Michaels L, Soucek S. Adenoma of the middle ear. In: Barnes L, Eveson JW, Reichart P, et al, editors. *Pathology and genetics: head and neck tumours*. Lyon: IARC Press; 2005. p. 345.
43. Fayemi AO, Toker C. Primary adenocarcinoma of the middle ear. *Arch Otolaryngol*. 1975;101:449–52.
44. Murphy GF, Pilch BZ, Dickersin GR, et al. Carcinoid tumor of the middle ear. *Am J Clin Pathol*. 1980;73:816–23.
45. McNutt MA, Bolen JW. Adenomatous tumor of the middle ear: an ultrastructural and immunocytochemical study. *Am J Clin Pathol*. 1985;84:541–7.
46. Riches WG, Johnston WH. Primary adenomatous neoplasms of the middle ear: light and electron microscopic features of a group distinct from the ceruminomas. *Am J Clin Pathol*. 1982;77:153–61.
47. Azzoni C, Bonato M, D'Adda T, et al. Well-differentiated endocrine tumours of the middle ear and of the hindgut have immunocytochemical and ultrastructural features in common. *Virchows Arch*. 1995;426:411–8.
48. Ketabchi S, Massi D, Franchi A, et al. Middle ear adenoma is an amphicrine tumor: why call it adenoma? *Ultrastruct Pathol*. 2001;25:73–8.
49. Medina EA, Arias VL. Middle ear adenoma. *Biomedica*. 2009;29:348–53.
50. Torske KR, Thompson LD. Adenoma versus carcinoid tumor of the middle ear: a study of 48 cases and review of the literature. *Mod Pathol*. 2002;15:543–55.
51. Wassef M, Kanavaros P, Polivka M, et al. Middle ear adenoma: a tumor displaying mucinous and neuroendocrine differentiation. *Am J Surg Pathol*. 1989;13:838–47.
52. Hale RJ, McMahon RF, Whittaker JS. Middle ear adenoma: tumour of mixed mucinous and neuroendocrine differentiation. *J Clin Pathol*. 1991;44:652–4.
53. Saliba I, Evrard AS. Middle ear glandular neoplasms: adenoma, carcinoma or adenoma with neuroendocrine differentiation: a case series. *Cases J*. 2009;2:6508.
54. Mooney EE, Dodd LG, Oury TD, et al. Middle ear carcinoid: an indolent tumor with metastatic potential. *Head Neck*. 1999;21:72–7.
55. Pellini R, Ruggieri M, Pilch B, et al. A case of cervical metastases from temporal bone carcinoid. *Head Neck*. 2005;27:644–7.
56. McCluggage WG, Napier SS, Primrose WJ, et al. Sinonasal neuroendocrine carcinoma exhibiting amphicrine differentiation. *Histopathology*. 1995;27:79–82.
57. McCluggage WG, Bharucha H, Cameron CH, et al. Amphicrine carcinoma of the larynx. *Histopathology*. 1994;24:182–5.