Abstract: Well-differentiated neuroendocrine carcinoma (also known as “carcinoid”) of the larynx is an exceedingly rare tumor that has an epithelial origin. These tumors are malignant and have a low, but definite, risk of metastasis. Although it can be challenging, this tumor should be differentiated from moderately differentiated neuroendocrine carcinoma (also known as “atypical carcinoid”). The clinical and pathologic features of this tumor, as well as treatment and prognosis, are reviewed in detail.

Key Words: carcinoid, atypical carcinoid, small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, well-differentiated neuroendocrine carcinoma, larynx

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CURRENT TERMINOLOGY AND CLASSIFICATION OF NEUROENDOCRINE TUMORS OF THE LARYNX

Neuroendocrine tumors (NETs) of the larynx constitute the second most common group of neoplasms of this organ, after squamous cell carcinoma. Although various classifications have been suggested, it is primarily important to differentiate the tumors based on the cell of origin into epithelial versus neural tumors. The epithelial tumors include well-differentiated neuroendocrine carcinoma (WD-NEC, also referred to as “carcinoid”), moderately differentiated neuroendocrine carcinoma (MD-NEC, also referred to as “atypical carcinoid”), and small cell neuroendocrine carcinoma and large cell neuroendocrine carcinoma. Paraganglioma is the only tumor with a neural etiology.

In the most recent WHO classification series, the suggested terminology included WD-NEC, MD-NEC, and poorly differentiated neuroendocrine carcinoma. In addition, a recent consensus group made some recommendations for terminology. Those authors advocated for the general terminology of NET for low-grade tumors and neuroendocrine carcinoma (NEC) for high-grade tumors. However, grading and classification remains organ specific. In the larynx, we advocate for the terminology in italics in Table 1, which is also the terminology proposed in the WHO.

The epithelial-derived tumors are all considered to be malignant, ranging from low-grade to highly aggressive tumors. These tumors can also be functional. Laryngeal paragangliomas are benign and are only rarely functional. Laryngeal paragangliomas can also occur as part of several syndromes, including hereditary paragangliomatosis. Although the diagnosis of laryngeal NETs is often a challenge for pathologists, surgeons, radiotherapists, and oncologists, a correct diagnosis is crucial for optimal patient management. Of the various epithelial neuroendocrine carcinomas of the larynx, WD-NECs have received the least attention, which prompted this review.

Well-differentiated Neuroendocrine Carcinoma of the Larynx: Confusion of Terminology and Uncertainty of Early Studies

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**TABLE 1. The Preferred Terminology for Epithelial-derived Neuroendocrine Carcinomas of the Larynx are Listed in Italic Font in Row 1**

<table>
<thead>
<tr>
<th>Well-differentiated neuroendocrine carcinoma</th>
<th>Moderately differentiated neuroendocrine carcinoma</th>
<th>Poorly differentiated neuroendocrine carcinoma</th>
<th>Poorly differentiated neuroendocrine carcinoma— large cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid (typical)</td>
<td>Atypical carcinoid</td>
<td>Small cell carcinoma—small cell carcinoma</td>
<td>Large cell carcinoma—large cell carcinoma</td>
</tr>
<tr>
<td>Grade I neuroendocrine carcinoma</td>
<td>Grade II neuroendocrine carcinoma</td>
<td>Small cell carcinoma</td>
<td>Grade III neuroendocrine carcinoma</td>
</tr>
</tbody>
</table>

Other terminologies used in the past are listed below for each entity.

**HISTORICAL PERSPECTIVES**

In 1980, Markel et al described a laryngeal “carcinoid,” which is regarded as one of the first histologic descriptions of the lesion in this anatomic site. However, the histologic images from that paper were later reinterpreted as being more consistent with an “atypical carcinoid tumor.”

In the same year, Gehanno et al reported another case, but this lacked thorough histologic documentation. Thus, the first well-documented case of laryngeal “carcinoid” was a case described by Duvall et al in 1983.

It should be emphasized that the literature regarding WD-NECs of the larynx is fraught with issues. The pathologic criteria for making this diagnosis have been unclear for years. This has led to probable improper classification of some of these tumors into other categories of lesions. The terminology has also shifted, which may lead to confusion in interpreting the literature. It is likely that, using current pathologic criteria and an up-to-date terminology some laryngeal WD-NECs would need to be reclassified, as discussed below.

**INCIDENCE**

An accurate estimate of the true incidence of WD-NEC of the larynx is virtually impossible to obtain, mainly because the body of literature is significantly muddied by cases that are likely incorrectly diagnosed. For instance, and as noted above, some laryngeal WD-NECs would be reclassified as MD-NEC, whereas some MD-NECs likely represent examples of large cell neuroendocrine carcinoma. In addition, several laryngeal MD-NECs had been diagnosed in the past as metastasizing laryngeal parangangiomas. It should be noted that the same confusion exists for laryngeal parangangioma. It is likely that erroneous diagnosis has resulted in the myth that laryngeal parangangioma has a high metastatic rate. In reality, almost all alleged malignant parangangiomas of the larynx are probably examples of misdiagnosed MD-NEC.

Despite the challenges in assessing the true incidence of WD-NEC, it is by far the least common of the 4 subtypes of laryngeal neuroendocrine carcinomas. The surveillance of rare cancers in Europe clearly classifies WD-NEC as a rare cancer, that is <6 new annual cases/100,000 people. In fact, the rate of all types of neuroendocrine carcinomas (excluding those of body site C34, ie, lung and bronchus) only reaches 2.53, out of which WD-NECs are 0.37. Thus, laryngeal WD-NECs must have an incidence of well below 0.25/100,000 (Rare Care surveillance of cancer in Europe (www.rarecare.eu/rarecancer/rarecancers/asp).

**PATHOLOGY**

Macroscopically, the tumor usually presents as a submucosal or polypoid mass ranging in diameter from 0.3 to 4 cm (Fig. 1). The histology of laryngeal WD-NEC is similar to the analogous lesion in other anatomic sites of the head and neck region. WD-NEC consists of small to medium size nests and trabeculae of uniform, small- to medium-sized the throat. Despite typical expression of different hormones and peptides in the tumor cells, laryngeal WD-NECs are typically nonfunctional. Nevertheless, a single case from the files of the Armed Forces Institute of Pathology, developed carcinoid syndrome following liver metastases; raised urinary 5-hydroxyindoleacetic acid levels were detected, which dropped following chemotherapy.

**HISTOPATHOGENESIS**

Conventional views ascribe the origin of laryngeal WD-NECs to neuroendocrine cells in the lining epithelia of the organ. Experimentally, these cells do have an innate proliferative activity, as it is suggested by their increased numbers in rodents following antigenic or oxygenation challenging. However, as mentioned above, laryngeal WD-NECs are commonly supraglottic, and non-neoplastic laryngeal neuroendocrine cells are more abundant in the subglottis. Another theory of origin suggests that an altered microenvironment could cause the acquisition of “neuroendocrine” phenotypes by “reserve” progenitor, basal cells of laryngeal epithelia. On the basis of the limited experimental and anatomic data available, it is currently difficult to establish the definitive histogenesis of laryngeal WD-NEC.
cells with variably distinct boundaries (Fig. 2). The cells have moderate, pale, clear to eosinophilic cytoplasm and round or oval nuclei with speckled chromatin of “salt and pepper” appearances and inconspicuous nucleoli (Fig. 3).

Substantial pleomorphism or atypia are not seen. Mitotic activity is very low (< 2 per 10 high power fields); there is no necrosis and sparse to absent perineural and vascular invasion is noted. The overlying epithelium is usually intact. Oncocytic/oncocytoid and mucous cells may be detected as well as focal “Zellballen” arrangements. The latter account for the potential confusion with paraganglioma.

Immunohistochemically, neuroendocrine markers, such as synaptophysin, chromogranin, and CD56 are strongly positive (Fig. 4). Moreover, serotonin and various neuropeptides (bombesin, calcitonin, and somatostatin) may be present. Low–molecular-weight cytokeratins (CK7, CK8, CK18, CK19, CK20), epithelial membrane antigen and carcinoembryonic antigen are consistently expressed. Proliferative activity is generally low, and detection of MIB1/Ki67 index might be warranted in some challenging cases. There is very little literature regarding the use of Ki-67 staining in these tumors, although some studies have suggested it might be warranted to examine proliferative activity, which should be low in the setting of WD-NEC. We have previously suggested that <2 to 4 cells per 100 should be positive for Ki-67 for a diagnosis of WD-NEC, though studies are needed to determine whether this is useful clinically.

Electron-microscopically, the characteristic dense-cored “neurosecretory-type” cytoplasmic granules can be seen, but the very few cases thus examined largely showed oncocyte-like phenotypes and various numbers of mitochondria.

The TNM staging is performed as with any laryngeal primary tumor.

DIFFERENTIAL DIAGNOSIS

It must be re-emphasized that the histologic distinction between WD-NEC and MD-NEC is important, but often difficult. It is usually based on mitotic rates, size of tumor cells, prominence of nucleoli, and presence of necrosis. In terms of specific histologic criteria for distinguishing WD-NEC and MD-NEC, mitotic counts (< 2 per high power field) and the absence of necrosis are the most reliable features for WD-NEC. It must also be appreciated that in small, incisional biopsies, these features may not be well represented. The distinction from paraganglioma is relatively straightforward, as the latter is negative for cytokeratins and includes a subpopulation of peripheral S100-positive, sustentacular cells around tumor nests.

MOLECULAR PATHOLOGY AND GENETICS

Little is known about the molecular pathology and genetics of laryngeal WD-NEC. Most patients have a history of heavy tobacco use. Like MD-NEC and high-grade laryngeal neuroendocrine carcinomas, WD-NEC seems to be HPV and p53 negative. It should, however, be emphasized that very few cases of WD-NEC have so far been analyzed at the molecular level, and additional molecular genetic
studies would be needed to draw firm conclusions as to the molecular pathogenesis of these tumors.

MANAGEMENT

The treatment of choice is surgical excision. In appropriate cases, this should be minimally invasive (transoral CO2 laser or transoral robotic approach), because of desirable functional results and lower morbidity.22 If transoral surgery is not an option, then open surgery would be the viable alternative. Again, to preserve organ function, a conservative procedure is preferable (eg, supraglottic laryngectomy). Total laryngectomy should be reserved for cases when a functional larynx cannot be achieved through conservative approaches, or when marked tumor extension or patient-related factors complicate the surgery (eg, excessively high aspiration risks). Elective neck dissection is not warranted.26 Bilateral selective neck dissection (levels II and III) is indicated when metastatic disease is suspected clinically or radiologically.27 Chemotherapy and/or radiotherapy have not been effective in the limited number of patients treated.28

PROGNOSIS

The reported 5-year disease-specific survival of 100%28 should be interpreted with caution. The critical question is what percentage of laryngeal WD-NECs will metastasize? This same controversy and clinical dilemma exists in other organ systems. For example, ileal and gastric “carcinoids” are known to have different metastatic rates. Therefore, it is important to define the true metastatic potential in WD-NEC of the larynx. Soga et al29 observed that 33% of 42 patients with so-called typical “carcinoid tumor” of the larynx developed metastases (cases from the Niigata Registry of Gut-Pancreatic Endocrinomas).30 However, reviewing those publications in the light of current knowledge, one might speculate that the estimated metastatic rate has been influenced by the aforementioned difficulty in accurately differentiating between WD-NEC and MD-NEC. This seems likely, given the large number of laryngeal WD-NECs, which are now regarded as rare, that were reviewed in that series. Again, this illustrates how the value of retrospective published data regarding the long-term behavior of laryngeal WD-NEC is limited due to the rarity of the tumor and the historical debate on precise histopathologic diagnostic criteria.

On the basis of our collective experience we believe that laryngeal WD-NEC is a low-grade malignancy. It should not, however, be considered to be a uniformly indolent or nonaggressive tumor. WD-NEC of the larynx has a low, but definitive risk of regional lymph node and distant metastases.16,31 Death attributed to the neoplasm has been reported.31,32

CONCLUSIONS

Current classifications and diagnostic criteria should be used by pathologists to differentiate WD-NEC from MD-NEC. In diagnosing and treating laryngeal WD-NEC, it should not be regarded as an indolent neoplasm,33 but as a low-grade carcinoma that has potential for metastasis (though the risk of metastasis is currently not quantifiable). Although the term “carcinoid” is historically entrenched, it should be abandoned for the more clinically and pathologically appropriate form of WD-NEC. Older publications should be carefully interpreted, especially in the setting of reviews and meta-analyses, as the diagnostic tools and definitions at the time were less available and less clear.

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