Large cell neuroendocrine carcinoma of the head and neck: a distinct clinicopathologic entity

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Head and neck cancers account for approximately five percent of all cancers, and the majority are squamous cell carcinoma. Neuroendocrine carcinomas of the head and neck are uncommon and present unique challenges both in diagnosis and treatment. Tumors with neuroendocrine morphology are a distinct subset of neoplasms that share specific morphologic, histochemical, immunohistochemical, ultrastructural, and molecular characteristics. These tumors include paraganglioma, well-differentiated neuroendocrine carcinoma (or typical carcinoid), moderately differentiated neuroendocrine carcinoma (or atypical carcinoid), small cell neuroendocrine carcinoma (SCNC), and large cell neuroendocrine carcinoma (LCNC). Staging, treatment, and prognosis vary widely among the five neuroendocrine

neoplasms of the head and neck, thus accurate histologic classification is essential.

LCNC is a high-grade malignant neuroendocrine tumor that was first defined in the lungs by Travis et al. [1] in 1991. This tumor accounts for approximately 3 % of all lung cancers [2], and the prognosis is poor. The diagnosis of LCNC is based on high-grade features, and the presence of both neuroendocrine morphology as well as immunohistochemical evidence of neuroendocrine differentiation. LCNC is a poorly differentiated neuroendocrine neoplasm that has several morphological and biologic features in common with both moderately differentiated neuroendocrine carcinoma (atypical carcinoid) and SCNC. However, the prognosis of pulmonary LCNC and SCNC is significantly worse than for moderately differentiated neuroendocrine carcinoma.

The 2005 World Health Organization Classification of Head and Neck Tumours [3] was a significant step towards diagnostic standardization of head and neck neuroendocrine carcinomas. It did not specifically include LCNC as a distinct tumor type, however. In the last 10 years, though, there have been new data supporting the recognition of “large cell neuroendocrine carcinoma” as a distinctive high-grade carcinoma in the head and neck, an entity not included in the 2005 Classification [4]. By the 2005 WHO classification, laryngeal LCNCs would actually be classified as variants of moderately differentiated neuroendocrine carcinoma (atypical carcinoid), whereas the pulmonary WHO classification considers LCNCs as poorly differentiated neuroendocrine carcinomas essentially grouping them with SCNC. The proper distinction among these entities is of paramount importance as it has significant therapeutic and prognostic implications.

The first report of LCNC in the head and neck was published by Hui et al. [5] in 1990 and at that time the authors

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used the term undifferentiated carcinoma. As a highly aggressive malignancy, this tumor attracts a significant attention and is in focus of considerable discussion recently also in head and neck area [6–17].

There are reports of these tumors arising in a variety of the head and neck subsites, the most common being the larynx [14, 17–24]. The parotid gland is the second most common site [5, 11, 12, 25]. LCNCs are increasingly being recognized in other sites and have been reported in sinonasal tract [9, 26], oral cavity [27], oropharynx [8, 28], hypopharynx [8], and submandibular gland [10, 29]. Given the limitations of the current WHO classification, which does not make a distinction between moderately differentiated neuroendocrine carcinoma and LCNC, a reliable estimate of the true incidence of LCNC is not possible.

Macroscopically, the tumor presents as a submucosal unencapsulated mass. The tumor cells have relatively abundant, eosinophilic cytoplasm and a neuroendocrine architecture (organoid nesting, palisading, trabecular growth and/or rosette-like structures). Their nuclei display coarse or fine chromatin, frequently having a “salt and pepper” appearance as in other neuroendocrine tumors, and usually also have prominent nucleoli. The tumor often shows large areas of coagulative necrosis, and by definition, has a high mitotic rate (>10 mitotic figures in 2 mm^2 of viable tumor). The cells are positive for one or more neuroendocrine markers (synaptophysin, chromogranin A, CD56) other than neuron-specific enolase. The tumor may be immunopositive for thyroid transcription factor. Cytokeratin subsets are of limited utility in diagnosing this tumor. Immunohistochemistry for Ki-67 usually shows a very high proliferative fraction. Electron microscopy shows numerous neurosecretory granules in the cytoplasm of the cells.

LCNC has to be distinguished from SCNC and moderately differentiated neuroendocrine carcinoma. The differential diagnosis may be difficult in small biopsies and can be especially challenging in cytologic specimens. Currently there is no immunohistochemical stain for discrimination between SCNC, moderately differentiated neuroendocrine carcinoma, and LCNC. The major feature that distinguishes between LCNC and moderately differentiated neuroendocrine carcinoma is the mitotic activity which is very abundant in LCNC, being defined specifically in the lung as >10 mitoses per ten high-power fields, whereas moderately differentiated neuroendocrine carcinoma is between two and ten mitoses per ten high-power fields. The neoplastic cells are generally small in SCNC and large in LCNC. However, the critical distinction is not in the overall cell size, but in the nuclear to cytoplasmic ratios (“high” in small cell and “lower” in large cell). In an attempt to differentiate between SCNC and LCNC, a panel of three markers, BAI3, CDX2, and VIL1, was suggested as an adjunct in the distinction amongst these tumor subtypes [30].

In a recent meta-analysis on the neuroendocrine carcinoma of the larynx by van der Laan et al. [14], median age of the LCNC patients was found comparable to those with SCNC, although the proportion of female patients was somewhat larger in the former group (29.6 vs. 18.6 %). In addition, median duration of symptoms, history of tobacco smoking, and stage distribution were also similar between the two. Significantly more supraglottic primaries (81.5 vs. 57.9 %) have been reported in LCNC of the head and neck than for SCNC [14], and no association with paraneoplastic syndromes has been reported for LCNC.

The treatment of LCNC is controversial and not standardized, even when it occurs in the lung [15]. Because of its rarity of LCNC in head and neck, there are no clinical trials that define the optimal treatment approach for either localized or advanced disease.

In above cited meta-analysis with 29 laryngeal LCNC included, the 5 years disease-specific survival was 15.3 % for LCNC, the worst among all four histological subtypes from the neuroendocrine tumor group (typical carcinoids 100 %, atypical carcinoids 52.8 %, small cell neuroendocrine tumors 19.3 %) [14]. When treatment results between SCNC and LCNC were compared, regional control (84 vs. 34.6 %) and distant-metastasis free survival (46.5 vs. 34.7 %) at 5 years were worse in the LCNC patients, whereas local control seemed comparable between the two (91.6 vs. 88.2 %). However, when SCNC and LCNC were analyzed by the treatment that was used, it appears that in patients with LCNC, chemotherapy was administered significantly less frequently and that a larger proportion of these patients had only locoregional treatment, i.e. surgery, radiotherapy or combination of the two (75 vs. 42 %). In tumors with high propensity for distant dissemination, like LCNC, shortage of chemotherapy implementation could be one of the reasons for poor treatment results and short survival [14] in the current literature.

Some authors believe that a treatment approach similar to that of SCNC of the lung may be indicated. However, there is no standardized therapy, even in lung LCNC. Combined cisplatin-based chemotherapy, similar to the one used for small-cell counterpart, seems to be most effective [31]. For LCNC of the head and neck, aggressive trimodality therapy seems to be the most effective treatment option although survival remains poor. In these tumors, surgery supplemented with postoperative radiotherapy or concomitant chemoradiotherapy is accepted as the primary treatment modality for localized disease. It appears that in all but the most early-stage tumors, some forms of systemic therapy acting against possible micrometastases should be part of the treatment regimen. For patients with systemic disease, palliative chemotherapy or best supportive care remain appropriate options.

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