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Neuroendocrine Carcinoma of the Head and Neck – review of literature

Nowotwory neuroendokrynne głowy i szyi- przegląd piśmiennictwa

G.BergerMD[1]. T.Dawidziuk MD[2],Prof L.Chyczewski,MD[2]

[1]Klinika Otolaryngologii Uniwersytetu Medycznego w Białymstoku, Polska
[2]Zakład Patomorfologii Lekarskiej Uniwersytetu Medycznego w Białymstoku, Polska

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ABSTRACT: Neuroendocrine carcinoma is a rare neoplasm, and its most common location in the head and neck area is the larynx, especially the epiglottis and the supraglottic region. The first case of neuroendocrine carcinoma of the larynx was reported in 1969 by Goldman et al. Expression of the two crucial markers, synaptophysin and chromogranin, along with neural cell adhesion molecule (CD56) should be mentioned among the neuroendocrine features detected on immunohistochemistry. Human papilloma virus (HPV16/18) infection in the laryngeal neuroendocrine carcinoma can be one of the causal factors, and the detection of HPV should be considered as a standard procedure for the diagnosis and treatment..

Methods: Review of the articles published in international journals; interdisciplinary discussion between clinicians and pathologists on the topic of neuroendocrine carcinoma of the head and neck.

KEYWORDS: neuroendocrine carcinoma, head and neck

STRESZCZENIE: Nowotwory neuroendokrynne głowy i szyi stanowią rzadki rodzaj nowotworu. Najczęstszym miejscem lokalizacji nowotworów neuroendokrynnych głowy i szyi jest krtań, zwłaszcza nagłośnia i okolica nadgłośniowa. Pierwszy opisany przypadek neuroendokrynnego raka krtani został przedstawiony w 1969 roku przez Goldmana i wsp. Wśród cech guzów neuroendokrynnych, wykrywanych w badaniach immunohistochemicznych, należy wymienić ekspresję dwóch kluczowych markerów: synaptofizyny i chromograniny wraz z cząsteczką adhezji komórek nerwowych (CD56). Wykrycie zakażenia wirusem brodawczaka ludzkiego (HPV 16/18) w neuroendokrynnym raku krtani może stanowić jeden z czynników etiologicznych i powinno być traktowane jako standardowa procedura w diagnostyce i terapii.

Metody: Przegląd artykułów opublikowanych w czasopismach na całym świecie; interdyscyplinarne konsylium pomiędzy patologami a klinicystami na temat nowotworów neuroendokrynnych głowy i szyi.

SŁOWA KLUCZOWE: nowotwór neuroendokrynny, głowa i szyja

INTRODUCTION:

Neuroendocrine carcinoma (NEC) is a rare neoplasm of the head and neck area, and it appears in the paranasal sinuses, ears, nose, tongue, salivary glands, larynx and trachea. These neoplasms represent 0.5- 1% of all epithelial cancers of the larynx. The first case of neuroendocrine carcinoma of the larynx was reported in 1969 by Goldman et al. The real number of head and neck NEC cases is a matter of discussion. Tom P. van der Laan et al.[26], who performed a literature review of laryngeal NECs (MEDLINE and EMBASE databases), noticed that, amongst 436 cases of NEC in the larynx selected from 182 studies, the most frequent type of NEC was small-cell neuroendocrine carcinoma. The second most frequent lesion was the atypical carcinoid. Although small-cell neuroendocrine carcinoma of the head and neck

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is rare, roughly 75 cases of NEC located in the nasal and paranasal sinuses have been reported in the literature (in English). Moreover, it is worth mentioning that an invasion of the lamina cribrosa indicates an unfavorable prognosis of SCNEC in the region of paranasal cavities [25]. The most common location of neuroendocrine carcinomas of the head and neck is the larynx, especially the epiglottis and the supraglottic region. As Barnes et al. [2] highlighted, the most frequent type of NEC in the salivary glands is the small-cell neuroendocrine carcinoma, representing 2% of all tumors found in this location. NECs of the head and neck can be divided into two groups. One group is comprised of tumors of epithelial origin (typical carcinoid, atypical carcinoid, small-cell neuroendocrine carcinoma and large-cell neuroendocrine carcinoma), and the other group consists of tumors of neural origin (paragangliomas). In general, the most common pathological features of NECs in the head and neck include an organoid pattern of growth, absence of keratinization, granular chromatin, elevated mitotic index and expression of neuroendocrine markers, e.g. synaptophysin, chromogranin and neuron-specific enolase.

CLASSIFICATION AND BIOLOGY:

There is some confusion and ambiguity regarding the classification of NECs in the head and neck region. The recent World Health Organization's (WHO) Classification of Head and Neck Tumors, introduced in 2005, proposes the following terms, 1) typical carcinoid, 2) atypical carcinoid, 3) small-cell carcinoma neuroendocrine type, 4) combined small-cell carcinoma neuroendocrine type with non-small-cell carcinoma (e.g. adenocarcinoma, squamous cell carcinoma etc.) and 5) paraganglioma. As regards tumor differentiation, the following grading system was introduced, grade I - well-differentiated neuroendocrine carcinoma for typical carcinoid, grade II - moderately differentiated for atypical carcinoid and grade III - poorly differentiated for small-cell neuroendocrine carcinoma, undifferentiated type. The existence of large-cell neuroendocrine carcinoma was highlighted, but tumors of this kind were grouped along with atypical carcinoids. According to Lewis Jr et al.[3], a new scheme of the laryngeal NEC classification was proposed. The scheme divides epithelial NEC into the three following groups, well differentiated, low-grade NE carcinoma (i.e. typical carcinoid), moderately differentiated, intermediate grade NE carcinoma (i.e. atypical carcinoid) and poorly differentiated, high-grade NE carcinoma, consisting of small and large cell subtypes and combined small-cell neuroendocrine carcinoma. Neural-type tumors are classified separately as paragangliomas.

Typical carcinoids are built up of nests and trabeculae of bland cells with round or oval, centrally placed nuclei and granular eosinophilic cytoplasm. Neither mitotic activity (fewer than 2 mitoses per $2mm^2$ /10 high power fields), pleomorphism nor necrosis is a feature of typical carcinoid tumors. The male-to-female ratio shows a male predominance, and almost all patients are in the middle age. Typical carcinoids are recognized as well-differentiated NECs; an aggressive behavior is not common but, according to Kenneth et al. [4], tumors may metastasize in around one-third of the cases .

Atypical carcinoids, in comparison to typical carcinoids, have larger neoplastic cells with vesicular nuclei containing prominent nucleoli. Tumor cells are more pleomorphic, with areas of necrosis and mitotic activity range of 2-10 mitoses per $2mm^2$/10 high power fields. Clinically, these tumors are observed in middle–aged male patients, but unlike typical carcinoids, there are concurrent regional lymph node metastases.

According to Ferlito et al. (2009) [5] , small-cell NEC is divided into 3 types. The oat-cell type is composed of sheets of small cells that contain hyperchromatic nuclei and scant cytoplasm; cell necrosis and mitotic activity are frequent. The intermediate cell type has a similar growth pattern, but the cells are larger, polygonal-fusiform or spindle-shaped. The cytoplasm is more prominent than in the oat-cell type. The rarest type of small-cell NEC seems to be the combined type, which is a mixture of small-cell neuroendocrine carcinoma and other tumor types, commonly adenocarcinoma or squamous cell carcinoma. There is a male predominance, and patients are slightly older than patients with atypical and typical carcinoids. The survival rates are similar to those for small-cell lung cancer [6] and do not correlate with tumor size [7].

Large-cell NEC is built up of cells that are arranged in a pattern of organoid nests, rosettes, often with palisading of the nuclei at the periphery of the nests. Large-size cells have polygonal shapes, low nuclear-cytoplasmic ratio (N/C), coarse nuclear chromatin and frequent nucleoli. Necrosis and high mitotic indices are very common (more than 10mitoses/$2mm^2$ or 10 high power fields). Expression of the two following markers, synaptophysin and chromogranin, along with neural cell adhesion molecule (CD56) should be mentioned among the neuroendocrine features detected on immunohistochemistry. Electron microscopy (EM) shows dense-core granules with diameters of 100-275 um [8], which could be considered as one of the neuroendocrine features of the tumor. It is worth to remind that Hui et al.[9] were the first authors who published a case of LCNEC of the head and neck region (tumor localized in the parotid gland). Large-cell NEC usually occurs in the lung, but it is sometimes observed as dispersed, mucosal

lesions of the salivary glands. However, Casas et al. [10], in 2005, published a case of LCNECs in the parotid gland and underlined the importance of differentiating these lesions from metastases of pulmonary LCNEC. This kind of distinction may be based on the immunoprofile of cytokeratins 7 and 20. [10] Large-cell neuroendocrine carcinoma of the head and neck is a poorly differentiated tumor; it is a high-grade neuroendocrine carcinoma with similar features to those seen in the atypical carcinoid small-cell neuroendocrine carcinoma. This makes the diagnostic process quite challenging. In 2005, the World Health Organization (WHO) introduced a new classification of head and neck neuroendocrine carcinomas in which LCNEC is considered to belong to the moderately differentiated NECs along with the atypical carcinoid. It is important to highlight the fact that the same WHO classification for pulmonary NE tumors distinguishes LCNEC from the atypical carcinoid. The aggressiveness of pulmonary LCNEC makes prognosis worse than in the case of atypical pulmonary carcinoids. Survival of patients with laryngeal LCNEC seems to be shorter than those with laryngeal atypical carcinoids [3]. That is why it is necessary to take into consideration the inclusion of LCNEC into poorly differentiated tumors, treating it as a high-grade neuroendocrine carcinoma. Hua Lin Kao et al.[11] included twenty-three (23) cases of primary head and neck neuroendocrine tumors in their study. They subdivided cases into groups of typical carcinoids, atypical carcinoids and small-cell neuroendocrine carcinomas, according to the 2005 WHO classification. Subsequently, they separated LCNECs from atypical carcinoids on the basis of the modified criteria using Ki67 labeling index and mitotic counts. In comparison to atypical carcinoids, large-cell NECs overexpressed p53 more commonly. The authors also highlighted the necessity of creating a new classification in which LCNEC would be a separate entity. The 3-year survival rates were 100%, 83.3%, 21.4% and 20.8% for the 2 typical carcinoids, 7 atypical carcinoids, 7 large cell NEC and 7 small cell NEC, respectively. Advanced stages of the disease were more common in large-cell NECs. This was accompanied by a worse prognosis (3-year survival of 21.4%). This new classification of tumors in the head and neck region, exhibiting a neuroendocrine phenotype, would provide a precise scheme for risk stratification with respect to selecting patients for more aggressive surgery or for improved chemotherapy treatments.

PATHOLOGICAL DIFFERENTIATION

Immunohistochemical analysis is essential in the diagnosis of NEC. Positive staining for chromogranin A, synaptophysin and neuron specific enolase is frequent in the head and neck NECs. Moreover, carcinoembryonic antigen (CEA) and epithelial membrane antigen (EMA) are commonly found. Atypical carcinoids and small-cell NECs often show serotonin markers, i.e. calcitonin and somatostatin.

As regards the differential diagnosis of carcinoids and atypical carcinoids of the head and neck region, it is worth to consider paragangliomas, melanomas and medullary thyroid carcinomas. Importantly, paragangliomas are always negative for cytokeratins, have a Zellballen pattern with sustentacular cells and stain positive for S-100. Positive staining for the thyroid transcription factor-1 (TTF1), carcinoembryonic antigen (CEA) and calcitonin is observed frequently in the medullary thyroid carcinoma. As regards melanomas, they can be differentiated from NEC in the head and neck by staining for HMB-45 and tyrosinase that are present in melanomas and absent in neuroendocrine carcinomas .

It is obligatory to differentiate small-cell NEC from basaloid squamous cell carcinoma, malignant lymphoma and metastatic carcinomas of the lung. Malignant lymphomas can be detected using typical markers of hematopoietic cells such as CD 20, CD3, CD43 and LCA. A typical staining for NEC is not observed in the basaloid squamous cell carcinoma. According to Stacey E. Millis[12], misdiagnosing a small-cell NEC for a basaloid squamous cell carcinoma can result from the presence of a prominent, pleomorphic basaloid cell component in some cases. The presence of overlying squamous dysplasia is strongly suggestive of the basaloid variant. Moreover, as clinical observations indicate, basaloid squamous cell carcinoma, as a laryngeal NEC, shows a marked predilection for the supraglottic region. It is difficult to differentiate between primary neuroendocrine tumors in the head and neck and to rule out metastases from more frequent NEC sites, including the lung, thyroid or skin. An elevated expression of calcitonin, which is frequently observed in primary NECs of the larynx, is also commonly observed in metastases of the medullary cancer of the thyroid gland. To rule out the possibility of metastasis, it is necessary to obtain a negative immunohistochemical reaction for TTF1. Moreover, a negative TTF-1 staining in tumor cells excludes metastatic NECs of the lung. Also, small-cell NEC of the lung is positive for TTF-1 in up to 90% of cases, according to Folpe et al. [13] On the other hand, Oliveira et al. mentioned that TTF-1 is not a useful marker for the differentiation between metastatic pulmonary small-cell carcinoma and primary head and neck NEC, since up to 50% of extrapulmonary small-cell carcinomas are positive for TTF-1. Tumors of the head and neck, which exhibit various degrees of neuroendocrine differentiation, are difficult to differentiate. For instance, the olfactory neuroblastoma, having a well-developed neuroendocrine differentiation, almost invariably arises from the olfactory mucosa and typi-

cally exhibits low-grade cytological features and may have a protracted clinical course with overall 5-year survival of approximately 50%. Moreover, microscopically, the sinonasal undifferentiated carcinoma is a high-grade neoplasm with a few neuroendocrine features but a very aggressive clinical course and almost 100% mortality. [12]

CLINICAL TREATMENT

Accurate classification and differentiation of NECs are essential for treatment planning. The typical carcinoid is not considered to be the most aggressive disease and is classified as a well-differentiated NEC requiring radical surgery. A good example of this treatment approach in the head and neck region is supraglottic laryngectomy. The larynx, especially the supraglottis, is considered to be the most common site of tumor expansion. An alternative approach may be trans-oral CO_2 laser surgery in some cases. Cevizci et al. [14] highlighted the advantages of laser excision in cases of typical carcinoids and reported good functional results and lower morbidity in comparison to standard methods. According to Ferlito et al., an elective neck dissection is not obligatory, but all clinically or pathologically proven cervical metastases require a bilateral selective neck dissection (levels II and III) [15].

All cases of atypical carcinoids require surgical resection as the primary mode of treatment. Usually, atypical carcinoids are malignant, high-grade neoplasms that should be treated aggressively. Radiation therapy does not improve survival considerably. It is obligatory to distinguish these tumors from more radiation-sensitive squamous cell carcinomas. The larynx is considered to be the most common site for atypical carcinoid of the head and neck region, and in the case of supraglottic tumor location, it is recommended to perform supraglottic laryngectomy. Good oncological results can be achieved with trans-oral laser CO_2 surgery as well. The involvement of cervical lymph nodes and frequent early infiltration of local tissues require an elective neck dissection. As mentioned by Ferlito et al. [15], a bilateral dissection of level IIA and level III is only adequate for elective surgical treatment in supraglottic tumors of the larynx. Moreover, Ferlito et al.[15] highlighted the importance of performing bilateral selective neck dissection (levels II and III) for therapeutic purposes, if metastases occur. In the case of lymph node metastases, post-operative radiotherapy is indicated. For small-cell neuroendocrine carcinoma (SCNEC) in the head and neck (a poorly differentiated carcinoma), the therapeutic plan should contain a combination of local irradiation and chemotherapy. The most common agents used for chemotherapy are cyclophosphamide, doxorubicin, vincristine, methotrexate and lomustine. However, Cymerman et al.[23] recommend aggressive surgical resection with margins for SCNEC of the tongue, similarly to that recommended for Merkel's skin cell carcinoma. Also, Cymerman et al.[16] advocated a 20-mm margins to maintain clearance; neck dissection should be performed in order to grade this type of cancer. Moreover, Cymerman et al. suggested that surgery is the mainstay of treatment for NEC, including Merkel's cell carcinoma in all body sites, which significantly improves survival in comparison to other treatment modalities. [17]. Radiochemotherapy may be advised in patients who cannot undergo major surgery. [16]

Kovać et al. reported a case of small-cell neuroendocrine carcinoma in the petrous apex of the temporal bone, in which treatment options were radical surgery followed by radiotherapy and chemotherapy. Aggressive treatment is necessary, as shown by the study on extrapulmonary small cell carcinomas performed in the Mayo Clinic. The study revealed that the median survival in a group of 14 patients with primary head and neck SCNEC was about 14.5 months. [18]

The treatment approach in large-cell NECs is not clear because of the lack of standardized treatment schemes. Barker et al.[19] advocate chemotherapy as a crucial element of therapy for high-grade neuroendocrine carcinomas of the head and neck. Because of the rarity of LCNEC in the head and neck, it is difficult to establish a specific treatment approach.

It is interesting that Kraft et al.[20] published a rare case of an HPV-associated neuroendocrine carcinoma of the oropharynx , with high-grade histological features and aggressive clinical behavior. Currently, squamous cell carcinoma is the most common malignancy of the head and neck in the oropharyngeal region and is recognized to be associated with human papilloma virus infection (HPV). However, HPV-associated neuroendocrine carcinomas have not been previously described in the oropharynx. Kraft et al.[20] reported of eight oropharyngeal neuroendocrine carcinomas, of which all were classified as poorly differentiated neuroendocrine carcinomas with immunoreactivity for synaptophysin and chromogranin. Moreover, 7 out of 8 cases showed an expression of p16, a surrogate marker for high-risk HPV infections. Despite a HPV16/18 infection in the head and neck, SCC is considered to have a favorable prognosis associated with a good response to radiotherapy [21], HPV-associated neuroendocrine carcinoma cases developed aggressive behavior. As the incidence of HPV-associated SCC has increased even to the level of an epidemic, it is important to realize that HPV infections can coexist with both squamous cell cancer (SCC) and neuroendocrine carcinoma, although this is rare in the

head and neck area. Hallmos et al. [24] also detected human papilloma virus (HPV) infection in the laryngeal neuroendocrine carcinoma. In 2 out of 10 cases, a high-risk HPV type was found; the atypical carcinoid was positive for HPV16 and large-cell neuroendocrine carcinoma for HPV18, respectively. As part of a more detailed investigation, immunohistochemical staining was performed for Ki67, p16 and p53 expression. In both HPV-positive cases, a high Ki67 labeling index was seen, thereby further characterization of tumor proliferation was enabled. One has to keep in mind that Hallmos et al. were the first to describe a detection of a high-risk HPV in a laryngeal neuroendocrine carcinoma and confirmed that laryngeal NECs positive for a high-risk HPV had a better response to therapy and a good prognosis.

CONCLUSION

Neuroendocrine tumors usually occur in the gastrointestinal tract or in the respiratory system. The aggressive nature of these tumors at sites other than the head and neck area requires precise diagnosis and aggressive surgical resection or chemoradiotherapy. Management and prognostic implications are deeply dependent on an accurate diagnosis, which is challenging for both pathologists and surgeons. The majority of neuroendocrine carcinomas in the head and neck region arise from the larynx, and the second most common location are major salivary glands and seromucinous glands. As the number of neuroendocrine carcinomas of the head and neck region is increasing, with clinical behavior ranging from benign to rapidly lethal, it is necessary to perform long-term clinical studies. The detection of HPV16/18 infection in neuroendocrine carcinomas of the head and neck should be considered as a standard procedure for diagnosis and therapy.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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Corresponding author: Medical University of Białystok, ul. Waszyngtona 13, 15-269 Bialystok , Poland, e-mail:greta.ewa.berger@gmail.com?

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