

Profile of Head and Neck Neuroendocrine Carcinoma at Hasan Sadikin General Hospital Bandung from 2016 to 2020

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ABSTRACT

Neuroendocrine carcinoma (NEC) is a type of malignancy that affects the nerve and endocrine systems and secrete neuropeptides into the bloodstream. Because there are significant treatment differences between primary NEC of the head and neck and typical squamous cell carcinoma, it is critical to distinguish between the two types of cancer. Primary NEC of the head and neck is rare cancer that should be distinguished from typical squamous cell carcinoma. Therefore, this study aimed to present the characteristic of head and neck neuroendocrine carcinomas at Hasan Sadikin General Hospital Bandung for 2016 to 2020. This is a descriptive retrospective study with head and necks neuroendocrine tumor patients at Hasan Sadikin General Hospital Bandung from 2016 to 2020. Demographic, clinical, and histopathological characteristics were obtained through the medical record data of patients. Samples were taken through consecutive sampling methods. This is a descriptive retrospective study with head and necks neuroendocrine tumor patients at Hasan Sadikin General Hospital Bandung from 2016 to 2020. Demographic, clinical, and histopathological characteristics were obtained through the medical record data of patients. Samples were taken through consecutive sampling methods. Head and neck neuroendocrine carcinomas have distinct characteristics and histopathological entities. Positive immunohistochemistry assay was significant findings to establish the diagnosis

Keywords: *Clinical Characteristic, Head and Neck, Histopathological Characteristic, Neuroendocrine Carcinoma.*

1. INTRODUCTION

Having structures complexity within the region of the head and neck, a variant of neoplasm with neuroendocrine differentiation might emerge. These tumors are exceedingly are in many cases, and their biological behavior in this part is different from another origin [1].

Neuroendocrine carcinoma (NEC) is a malignancy and aggressive epithelial neoplasm that secretes neuropeptides that affect nervous or endocrine systems. Small-Cell NEC (SCNEC) usually comes from the pulmonary tract, but it rarely also arises from genitourinary, gastrointestinal, breast, neck, also head

areas. It mainly occurs in the larynx, salivary gland, nose, and paranasal sinuses [2]. The oral cavity accounts for 9 percent, the oropharynx for 12 percent, the larynx for 35 percent, the hypopharynx for 4 percent, the nasopharynx for 10 percent, and approximately 30% of the total is comprised of the sinonasal [3].

NECLs (neuroendocrine cell-derived lesions) are a heterogeneous category of neuroendocrine cell-derived lesions that These tumors include non-carcinoid “gastroenteropancreatic tumor”, “well-differentiated” NEC (WDNEC), “moderately differentiated” NEC (MDNEC), and poorly differentiated NEC (WDNEC). Among the many forms of NEC, the largest is large-cell

carcinoma (LCC), and the smallest is small-cell carcinoma (SCC) [4].

The PDNEC subtype of NEC is the most common in the head and neck region. When it manifests up in the lungs, instead of being referred to as small-cell carcinoma, it is referred to as an example, oat-cell carcinoma is a type of cancer. It is more aggressive and cancerous to the extreme than well and moderately differentiated subtypes [5]. Males got affected often than females, they are on average 60 years old. Patients who smoke account for around 85 percent of the population. The lesion has a significant likelihood of spreading because of its aggressive clinical history and tendency to early wide metastasis. Metastasis occurs frequently in cancer patients in the brain, bone, skin, and kidneys, to name a few locations. Metastatic head and neck NEC can be fatal in a very short amount of time make it a particularly concerning disease. Primary head and neck NEC is a rather uncommon occurrence in the general population [4].

LCNEC is a prevalent form of malignancy of the lung that affects both men and women. There have only been five cases of LCNEC in the head and neck area that have been recorded, with four of those cases emerging from the parotid gland and the tongue mucosa [6].

SCC is a form of malignancy that affects the cells of the skin most commonly bronchogenic in origin and is known for its aggressive clinical behavior. Extrapulmonary SmCC is now thought to account for 2.5 to 5% of all SmCCs [7]. Olofsson and Nostrand published in 1972, there was the first report of SmCC in the head and neck region, identifying it as in primary tumor in the larynx. In part due to the rarity of This tumor in the neck and head is a kind of cancer., it has been impossible for any single group of researchers to examine and publish anything more than a few personal experiences for collected series specific to tumors in these sites. However, while SmCC originating in the head and neck shares many similarities with SmCC of bronchogenic origin in terms of appearance, the evidence collected to date suggests some differences when evaluating these tumors in distinct subsites [7].

This review focuses on specific issues about NEC involving the head and neck. This article describes 2 cases of small cell neuroendocrine tumors of the head and neck.

2. METHODS

The participants in this study were two patients who had been diagnosed with neuroendocrine carcinoma in the head and neck. The study was conducted retrospectively. All cases of “NEC of the head and neck in adults” who presented between 2016 and 2020 at Hasan Sadikin Hospital in Bandung, Indonesia, were compiled from the pathology database of the hospital. After reviewing the pathology slides from these patients, the pathologist made a recommendation. The presence of positive staining for CK20, synaptophysin, chromogranin, or NSE was required for inclusion in this study.

The methods that must be followed in order to color the biopsied tissue are listed below. Deparaffinized paraffin-embedded tissue slices were soaked in ethanol at 100 percent and 95 percent concentrations for 15 minutes before being heated for antigen retrieval in 0.01 in citrate buffer for 25 minutes under pressure in a pressure cooker inside a microwave oven for 25 minutes, according to the results of the study. Sections were treated for 1 hour at room temperature with primary antibodies after they had been dried with hydrogen peroxide. After that, they were stained with secondary antibodies. Ventana Medical Systems, Inc. is supplying all of the antibodies that will be used in this inquiry on behalf of the researchers. (Tucson, AZ). To bind into the primary antibody, The usual streptavidin-biotin-peroxidase complex technique was employed in this investigation, together with Multilink concentrated biotinylated anti-IgG as in secondary antibody. The reaction products were envisioned by counterstaining using the 3,3'-diaminobenzidine reagents set (Kirkegaard & Perry Laboratories, Gaithersburg, MD). Hematoxylin was used to counterstain the sections. Sections were treated with phosphate-buffered saline without the primary antibody as a negative control.

3. RESULTS AND DICUSSION

3.1 Results

Two head and neck NEC cases were identified for patients who underwent surgical resection in Hasan Sadikin Hospital, Bandung, Indonesia. The clinicopathological data are summarized in table 1.

All patients were male with a mean image of 61 ± 13.44 years. Each was diagnosed with malignant neoplasm of accessory sinuses and carcinoma sinonasal.

Subtype analysis revealed that all patients had small cell neuroendocrine carcinomas. Immunohistochemistry (IHC) of patient 1 was positive for chromogranin and negative for synaptophysin and CK20. Patient no. 2 had undergone therapy. He had been given 30x radiotherapy and 10x booster therapy by the end of October 2020. It is scheduled for Etoposide and Cisplatin (3 cycles /4 weeks). The rest of the patients have not received any treatment.

Table 11. Pathological, Stadium and therapy of neuroendocrine Carcinoma Patients

No	Age	Gender	Immunohistochemical staining				Diagnosis	Types	Therapy
			CK20	Chromogranin	Synaptophysin	NSE			
1	70	M	-	+	-	N/A	Malignant neoplasm of accessory sinuses T3N0M0 stg. III	SCNEC	Uncontrolled
2	52	M	N/A	N/A	N/A	N/A	Sinonasal carcinoma rT2N2aM0 stg. IVA	SCNEC	Etoposide and cisplatin chemotherapy (planned for three cycles/4 weeks)

N/A, not available, -, negative staining; +, positive staining; SCNE, small cell neuroendocrine carcinoma

3.2 Discussion

Neuroendocrine carcinoma is a neuroendocrine carcinoma that secretes neuropeptides into the bloodstream [5]. Primary NEC of the head and neck are highly uncommon. According to the American Cancer Society, the head and neck NEC caused by metastatic cancer affects 1-8 percent of one percent of all oral malignancies and one percent of all jaw carcinomas are found in the mouth [4].

Because of the variations in therapy between NEC and the far more common squamous cell carcinoma, it is crucial to distinguish between the two. Due to the rarity of NEC, it has not been easy to classify its clinical and histopathologic tendencies [5]. One method to classify NECs is by counting their mitotic count and Ki67 index. The more poorly differentiated the tumor is, the greater their mitotic count / Ki67 index. For example, high-grade or G3 NECs will have a mitotic count $> 20 \times 10$ HPFs, and the Ki-67 level $> 20\%$. The cutoff value in determining a tumor's metastatic ability is Ki-67 level $> 20\%$. [8].

Atypical carcinoid, typical carcinoid, small cell carcinoma of the neuroendocrine type, small cell carcinoma of the neuroendocrine type, and mixed small cell carcinoma of the neuroendocrine type with non-small cell carcinoma are the four forms of NECs [9]. This classification does include a separate category for large cell neuroendocrine carcinoma [6].

2012 saw the addition of ranges for the Ki-67-labeling index and mitotic count to the WHO criteria and classification system for neuroendocrine carcinomas of the head and neck region. It has also been argued that LCNEC should be considered a different disease identity and that it should be classified separately from AC under the WHO categorization system and criteria [10].

Neuroendocrine carcinomas are split into two groups: those with largely epithelial differentiation (group I) and those with predominantly neural differentiation (group II, neuroendocrine carcinomas) (group III, neuroendocrine carcinomas) [4]. Wick classified the three NEC subtypes as grade I, grade II, and grade III NEC, respectively. is another option.⁵ When referring to neuroendocrine carcinomas in the

literature, the terms carcinoid, atypical carcinoid, and SmCC have been replaced by the terms WDNEC, MDNEC, and PDNEC. Furthermore, as previously indicated, the latter can be divided into two types: small-cell and large-cell forms of bacteria [4]. SmCC is a term used to describe a restricted number of reports. It is most commonly detected in the lungs; however, it has also been observed to occur in several extrapulmonary areas, accounting for only 4 percent of all SmCC [10].

2017 WHO book "Tumors of the Head and Neck" is updated with a new histologic classification classified into three types: well-differentiated, moderately differentiated, and poorly differentiated. The latter is further subdivided into LCNEC. It is important to note that LCNEC, which was previously associated with atypical carcinoid/moderately differentiated neuroendocrine carcinoma, grade III in the WHO 2005 edition, has now been reclassified as poorly differentiated NEC, grade III, with distinct morphology and in worse prognosis [11].

WDNEC are exceedingly rare ahead and neck lesions defined by local aggressiveness and reduced capability for metastasis. They manifest clinically as submucosal nodules, most frequently in the larynx [4]. WDNECs are structurally and microscopically identical to carcinoids, which are a condition that exists in the liver, appendix, and small bowel, among other locations [5]. There are 43 instances of a head and neck WDNEC, with the majority involving the supraglottic larynx, according to into Ferlito et al [5].

MDNEC is the most common non-squamous cell laryngeal malignancy, with the majority occurring in the supraglottis. Males aged 40-60 years old are more affected, with a ratio of male-to-female is 3:1. Compared to WDNEC, the history of tobacco use is frequently discovered in MDNEC patients. When examined clinically, nodules with or without ulceration are observed. The clinical course is aggressive, and numerous metastatic sites have been discovered as a result. Almost half of MDNEC patients acquire localized metastases, and 65 percent develop distant illnesses as a result of their disease. Among the symptoms include pain that seems like neuralgia and excessive secretion [4].

MDNEC forms nests and cables in the same way that the well-differentiated version does, but it is less organized. Increased mitotic activity, nuclear irregularity, pleomorphism, and localized necrosis are all features of the immoderately differentiated NEC.

Surgery is the most successful and well-differentiated treatment for NEC [5].

PDNEC is similar to MDNEC. Patients are typically in their older age and have a history of smoking. Usually, patients have nodal metastasis and paraneoplastic syndromes. It is usual for cancer to spread to lymph nodes in the surrounding area. a spread of cancer to distal organs such as the lung, liver, and skeleton [4].

According to Gnepp et al., 90 percent of individuals with poorly differentiated NEC of the larynx will develop metastases at some time, with metastasis most commonly occurring inside the cervical lymph nodes, lungs, liver, and bones are all affected. The most common subtype of NEC in the salivary glands is poorly differentiated NEC, which accounts for 2% of malignant parotid gland tumors and 3.5% of minor salivary gland neoplasms. Laryngeal carcinomas have a better prognosis than salivary island poorly differentiated NECs, with 2 and 5-year survival rates of 70% and 46%. They rarely cause cervical lymphadenopathy. Traditionally, radiotherapy and/or chemotherapy were used to treat poorly differentiated NEC [5].

LCNEC of the head and neck is distinguished by (a) a light microscopic pattern that indicates NE origin; (b) Large polygonal cells with a low nuclear-to-cytoplasmic ratio (N/C), coarse nuclear chromatin, and a high prevalence of nucleoli are seen in this population; (c) Mitotic rate exceeding 10 mitoses/2 mm² or 10 high-power fields per second, as well as frequent necrosis; and (d) NE characteristics can be detected via immunohistochemistry or electron microscopy (EM).⁶ On the surface of the tumor cells, neurosecretory granules that are membrane-bound and electron-dense are observed. The presence of synaptophysin, chromogranin, cytokeratin AE1/AE3, neuron-specific enolase, and other proteins in the NEC may indicate the presence of NEC [5].

SmCCs are characterized by little round, oval, or spindle cells with feature variations of neuroendocrine. In addition, several scientists have classified some carcinomas as having an "intermediate" cell type, comprised of somewhat bigger cells with characteristics and behavior that are distinct from those of SmCC. Despite the fact that the majority of SmCCs in the head and neck areas do not produce hormones in a practical sense, some tumors have been discovered to contain peptide hormones. Carotinin, bombesin, neuron-specific enolase, serotonin, and carcinoembryonic antigens are

examples of neurotransmitters (CEAs). The iCK20 staining method is frequently used to differentiate Merkel cell carcinoma (which stains positive) from SmCC (typically stains negative) [7].

Inflammation and the release of cytokines are two main events in the development, migration, and progression of tumors. Stress is also a known contributing factor in cancer development through hormonal and immunological processes. Stress will activate the hypothalamic-pituitary-adrenal (HPA) axis to increase cortisol, norepinephrine (NE), and epinephrine (E) levels. All these stress hormones and imbalances of neuroendocrine factors will produce tumor growth factors and contribute to the carcinogenesis process, whether directly or indirectly [12].

Another pathology to carcinogenesis considered is via cancer stem-cell and clonal evolutionary processes. Head and neck malignancy especially have a small group of cells named cancer 'stem' cells (CSC) near blood vessels, as tumor progenitor cells, causing tumor self-renewal, and multipotency [13].

A complete medical history, as well as a thorough physical examination, are required in order to diagnose NEC. The symptoms include neck mass and dysphagia; specifically, the most common is a globus sensation. Other symptoms are weight loss, dyspnea, hoarseness, and throat pain [2]. With laryngeal lesions, it is possible to have respiratory discomfort. Pain or a palpable mass indicates involvement of the salivary glands [8]. Numb chin syndrome is supposed to raise the probability of malignancy [4].

Image-guided procedures such as periapical/panoramic x-rays, ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI) as well as fluorodeoxyglucose-positron emission tomography (FDG-PET) are used for diagnosing, staging, and monitoring therapeutic responses. Because it is both fast and detailed, multi-slice CT is an ideal choice because it can yield multiplanar reformatted pictures. With its higher soft-tissue resolution, MRI is an excellent tool for detecting head and neck masses as well as the cerebral dissemination of tumors.⁸ Additional testing such as FNABs (fine needle aspiration biopsies) is frequently required. It has a 95% specificity and 64% sensitivity [4].

NEC is differentiated from other lesions using a panel of biomarkers that includes epithelial markers (high and low molecular weight CK, carcinoembryonic

antigen, and epithelial membrane antigen), neuroendocrine markers (synaptophysin, NSE, chromogranin, and S100), and neuroendocrine polypeptides (bombesin and calcitonin), among others. HMB-45 and S100 are both used for detecting melanoma, but S100 is preferred because HMB-45 can also be positive in NEC. NEC can be distinguished from paraganglioma because paraganglioma is not calcitonin positive. Specifically, MDNEC is calcitonin positive. Another calcitonin positive lesion is medullary thyroid carcinoma; a clinicopathologic correlation is needed to diagnose accurately. The marker used to distinguish MCC from SmCC is CK20 and TTF-1. PDNEC and MDNEC can have the appearance of poorly differentiated squamous cell carcinoma with positive CK; the way to determine both is MDNEC will be neuroendocrine marker negative. Finally, CD56, a neural cell adhesion molecule, becomes the SmCC marker of decision [5].

The surgical modality is suboptimal for the aggressive oropharyngeal NEC because it only targets local diseases. When treating NEC, especially the small cell variant, systemic chemotherapy should be a part of the treatment plan in every patient [3]. However, in patients with deglutition problems, commonly found in patients with advanced hypopharyngeal tumors, there is a higher risk of incomplete chemoradiotherapy [8].

Prognosis will be determined by the overall disease stage, particularly the N-stage status and distant metastases; and ectopic hormone production [14]. Neck metastases and Stage IV disease are associated with poor outcomes. According to the research, extensive/recurrent extrapulmonary PD NEC patients treated with cisplatin/etoposide-based ChT can expect a median progression-free survival of 4–9 months and a median overall survival of 10–19 months [12].

In terms of the types of NECs, oropharyngeal is a more aggressive type than SCC, also with a worse prognosis. It is more likely to develop early regional lymphatic and systemic metastases. In one study, the median survival time for small cell NEC of the tonsil was found to be 18 months [3]. As expected, the most common predictor of death is distant metastases [12].

A link between oropharyngeal NEC and high-risk human papillomavirus is becoming more apparent, according to new research (HPV) [3]. The presence of HPV in these cases showed better outcomes. This improved prognosis is not present in oropharyngeal NETs. However, due to the rarity of cases that being reported, it is challenging to figure any significant

associations with HPV infection [13]. The importance of EBV infection in NECs is even less than that of HPV [12].

4. CONCLUSION

Head and neck neuroendocrine carcinomas have distinct characteristics and histopathological entities. Therefore, a positive immunohistochemistry assay was significant findings to inaugurate the diagnosis.

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