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Case report

Small Cell Neuroendocrine Tumor of the Larynx – A Small Case Series

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A B S T R A C T

Neuroendocrine tumors are the most common nonsquamous types of laryngeal neoplasms. They are classified as typical carcinoids, atypical carcinoids, small-cell neuroendocrine carcinomas, and paragangliomas. The aim of the paper is to present four patients with small-cell neuroendocrine tumor arising in larynx. There were one woman and three men whose ages were 47–77 years; all of them had metastases when first seen. The clinical presentation and management of such type of tumor are discussed. Small-cell neuroendocrine carcinomas are very aggressive neoplasms. Patients could benefit from surgery, but radiotherapy and chemotherapy remain the treatment of choice. Examination of a large series is required to define the most useful diagnostic methods and the most successful treatment modalities.

Key words: *laryngeal cancer, small cell carcinoma, neuroendocrine tumors*

Introduction

Laryngeal cancer is the most common head-and-neck cancer and accounts 2.4% of new cancer diagnoses annually in men[1]. Squamous cell carcinoma accounts for more than 90% of laryngeal cancers and it is the most common histologic finding. Neuroendocrine tumors are the most common nonsquamous types of neoplasms arising in larynx and represent <1% of all primary laryngeal tumors[2].

Gastrointestinal tract is the commonest site for the occurrence of neuroendocrine tumors (about 70% of cases) followed by the respiratory tract (about 25%). The first laryngeal neuroendocrine tumor (atypical carcinoid tumor) was reported in 1969 by Goldman et al.[3]. These tumors have a predilection for the supraglottis[4]. Most patients are males, 50 to 70 years of age at presentation and more than 70% of them have a history of smoking.

Neuroendocrine tumors of the larynx represent a heterogeneous group of neoplasms. The World Health Organization classified these tumors into 4 subtypes: typical carcinoid (well differentiated neuroendocrine carcinoma, grade I), atypical carcinoid tumor (moderately differentiated neuroendocrine carcinoma, grade II; large cell neuroendocrine carcinoma), small cell neuroendocrine carcinoma (poorly differentiated neuroendocrine carcinoma, grade III), and paragangliomas[5]. The most frequent type is the atypical carcinoid, while the typical carcinoid is a very rare tumor.

Small-cell neuroendocrine tumors of larynx are very rare. Histologically, they are divided into 3 types: oat cell, intermediate cell, and combined variants. Light microscopy is usually diagnostic but in some instances must be supported by immunohistochemistry which reveals positivity for either epithelial or neuroendocrine markers. This tumor is highly aggressive and should be considered disseminated at initial diagnosis. The treatment is by chemotherapy and radiotherapy. Surgery for this tumor should be reserved for cases of local relapse with no evidence of metastasis. The prognosis of these patients is the worst, with 5-year survival rates of 5%[6]. The survival rates are similar to those for small cell lung cancer and do not correlate with the tumor size.

In this paper we present the clinical and histopathological features of 4 cases of small-cell neuroendocrine

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tumors of the larynx. Two patients were diagnosed and treated at Clinical center of Serbia, Belgrade, a 2 of them at the Clinical center of Montenegro, Podgorica. We also review previously published papers on the diagnosis and treatment of these rare neoplasms.

Case Report 1

A 54-year-old male, tobacco smoker, presented with bilateral cervical lymphadenopathy, hoarse voice and difficulty breathing progressively getting worse for the last 2 years. An indirect laryngoscopy was performed which revealed a large supraglottic mass extending to the tongue base. A tracheostomy was placed and patient underwent laryngoscopy and biopsy. The histopathological evaluation revealed a poorly differentiated neuroendocrine carcinoma. Immunohistochemistry was diffusely positive for synaptophysin and chromogranin-A. Immunohistochemistry for cytokeratins (CK) 5/6 and p63 was negative. Immunohistochemistry for Ki-67 showed 50% of the cells to be positive. No distant metastases were identified by radiology. Pharyngolaryngectomy with bilateral neck dissections was performed. Metastatic carcinoma was present in 14 of 24 lymph nodes. The patient was disease free after 15 months of follow up.

Case Report 2

A 67-year-old man, a known smoker for more than 45 years, presented with dysphonia for over 4 months. Laryngoscopy showed an exophytic mass at the epiglottic base extending to the both true vocal cord. On examination he had a 2.0 cm left neck mass. Radiologic studies showed no evidence of metastatic disease. A biopsy of laryngeal mass was interpreted as poorly differentiated neuroendocrine carcinoma, grade III. Immunohistochemistry revealed expression of synaptophysin, neuron-specific enolase (NSE), chromogranin-A and CD56. Immunohistochemistry for CK 5/6, CK19, p63 and TTF1 (thyroid transcription factor-1) was negative. Subtotal laryngectomy and neck dissections were performed. On last follow-up 2 months after his operation, he had no evidence of disease.

Case Report 3

A 77-year-old man with a long smoking history underwent a direct microlaryngoscopy for dysphonia and dyspnoe over 3 months. The indirect laryngoscopy detected the anterior subglottic tumor. The patient underwent neck computerized tomography (CT) with contrast medium which showed the presence of a mass in the right subglottic area, obstructing the subglottic airway. CT scan revealed lymphadenopathy in the left supraclavicular fossa, and liver and lung metastases. The histological diagnosis was small cell neuroendocrine carcinoma-poorly differentiated (Figure 1). No immunohistochemical stains were performed on this initial biopsy. Urinary levels of chromogranin A (CgA) and 5-hydroxyindole acetic acid (5-HIAA) were increased (CgA: 23.38 mg/24h; normal value 2–15 mg/24h; 5-HIAA: 309.8 ng/mL; normal value 0–100 ng/mL). A tracheostomy was placed. The patient started treatment with long-acting release octreotide but he died 4 months after diagnosis. No post-mortem tumor workup was performed.

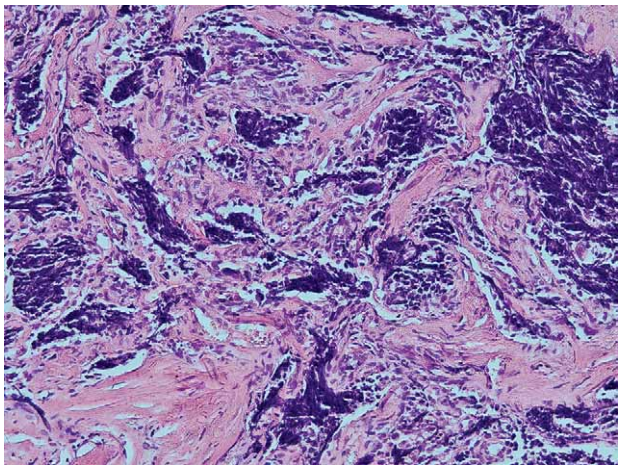

Fig. 1. Small cell neuroendocrine carcinoma of the larynx, showing the typical oat cells, nuclear molding and a high mitotic index (H&E, ×200).

Case Report 4

This 47-year-old woman, who was a smoker, presented with a left neck mass of 1 month duration with occasional dysphagia. On physical examination, she had 3 cm palpable left sided cervical lymphadenopathy (Figure 2). Laryngoscopy revealed a mass of the laryngeal aspect of the epiglottis and left false vocal cord. A laryngoscopic biopsy was performed and the neoplasm was diagnosed as a squamous cell carcinoma. The patient underwent a horizontal supraglottic laryngectomy and radical neck

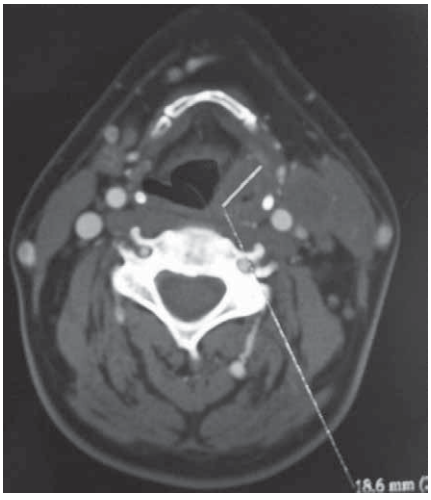

Fig. 2. Axial contrast-enhanced computed tomographic scan with laryngeal mass and left sided cervical lymphadenopathy.

dissection on the left side. Based on the surgical sample a diagnosis of small cell neuroendocrine carcinoma- grade III was made, and confirmed after revision of the sample. Immunohistochemistry for cytokeratins (CK) 5/6 was positive and for neuron-specific enolase (NSE) was negative. Metastatic carcinoma was present in one of 14 lymph nodes (largest 2.8 cm). One month later the patient developed cervical lymphadenopathy on the right side and neck dissection was performed. She was treated with postoperative chemotherapy and radiation, completing the full course. However, she died 10 months after diagnosis.

Discussion

Neuroendocrine tumor of larynx is an extremely rare disease classified as typical carcinoids, atypical carcinoids, small-cell neuroendocrine carcinomas, and paragangliomas.

Extrapulmonary small cell carcinoma is relatively rare disease and account for 2.5 to 5% of all small-cell neuroendocrine carcinomas[7]. The larynx is one of the most common extrapulmonary sites but this an unusual neoplasms account for only 0.5% of all laryngeal carcinomas[8]. Small cell carcinoma of larynx was first described by Olofsson and van Nostrand in 1972[9]. In 2008, Ferlito and Rinaldo reported that there were approximately 200 cases of primary and 5 of secondary small-cell neuroendocrine carcinomas of the larynx published in the literature at that time[10].

Small-cell neuroendocrine carcinomas is also reffered to as small cell carcinoma, oat cell carcinoma, anaplastic cell carcinoma, anaplastic small cell carcinoma, small cell undifferentiated carcinoma, poorly differentiated neuroendocrine carcinoma, neuroendocrine carcinoma, etc.

The pathological diagnosis is based on histological, ultrastructural and immunohistochemical criteria. Histologically, small-cell neuroendocrine carcinomas are classified as oat-cell, intermediate-cell, or combined-cell types. The oat cell carcinoma is composed of small cells with hyperchromatic nuclei and sparse cytoplasm. Cell necrosis and mitotic activity are frequent. In the intermediate cell type the cells are slightly larger with a more abundant cytoplasm. A mixture of small cell neuroendocrine carcinoma with another tumor, usually squamous cell carcinoma or adenocarcinoma is the combined type. Based on Aggarwal et al. review, a total of 17 cases of combined small cell carcinoma have been reported in the literature to date[11].

Immunohistochemistry is a valid adjuvant in the light evaluation of the morphological criteria of these neoplasms. Small cell neuroendocrine carcinoma may be immunoreactive with cytokeratins, EMA, CEA, and with general neuroendocrine markers, including chromogranin, neuron-specific enolase, CD56, CD57, synapthophysin, neuropeptides, including calcitonin, somatostatin, adrenocorticotropic hormone, bombesin, and serotonin. Also, small cell neuroendocrine carcinoma may be positive for thyroid transcription factor-1 (TTF-1).

Small-cell neuroendocrine carcinomas usually arise submucosally. Laryngeal small cell carcinoma can occur in any region of the larynx but the most frequent site of disease is the supraglottic region, in particular aryepiglottic fold, arytenoid, epiglottis. The most common symptoms are hoarseness, dysphagia, pharyngodynia, hemoptysis and dyspnea and differ according to the site and the extent of disease. Subglottic small cell carcinoma is extremely rare presented with dyspnea, hoarseness, and dysphagia. In our series one of four cases presented with subglottic tumor and other three patients with supraglottic localisation.

Small-cell neuroendocrine carcinomas are very aggressive neoplasms. About half of all patients present with cervical lymph node metastases[12]. More than 90% of patients with this tumor develop metastatic disease[8]. They are characterized by diffuse early metastasis. The most frequent sites of metastatic spread are the cervical lymph nodes, bone, skin, liver and lung. Small cell neuroendocrine carcinoma of the larynx should be regarded as a systemic disease[13].

Neuroendocrine tumor of the larynx are rarely associated with clinically evident hormonal activity probably due to the reduced or absent secretion or release of hormonal substances. Different paraneoplastic syndromes, including Schwartz-Bartter syndrome due to inappropriate secretion of antidiuretic hormone[14–16], myasthenic syndrome of Eaton-Lambert[17] and ectopic adrenocorticotropic hormone syndrome[18] have been reported in cases of small cell neuroendocrine carcinoma of the larynx.

There is no specific treatment for neuroendocrine tumors of the larynx. Our patients were presented to the board for head and neck malignancies but also to the board for endocrine tumors. The therapeutic approach vary according to disease stage and these tumors are mostly treated as squamous cell carcinomas. Baugh et al. evaluated the various therapeutic modalities that have been used to treat this cancer[19]. They found that the combination of primary radiation therapy and adjuvant chemotherapy resulted in significantly longer survival than with any other treatment regimen. Important indicator of poor prognosis is resistance to chemotherapy. Surgical management of small cell neuroendocrine carcinoma of the larynx is not so effective[20]. Most authors generally agreed that surgery alone or in combination with radiotherapy does not cure local tumor. Therefore, radical surgical procedure is not recommended as the initial treatment of choice. Surgery for this tumor should be reserved for cases of local relapse with no evidence of metastasis[10,21].

The prognosis of small cell neuroendocrine carcinoma of the larynx is very poor and is similar to those for small cell lung cancer[22]. Gnepp et al. reported a mean survival time of 9.8 months (range, 1–26 months) of patients with small cell carcinoma of the larynx[23]. The 2- and 5-year survival rates are 16% and 5%, respectively[12]. Soga et al. found a 5-year survival rate of 7.7%[24]. These survival rates did not correlate with the size of tumor[12].

Conclusions

Laryngeal cancer is the most common head-and-neck cancer. Neuroendocrine tumors are the most common nonsquamous types of neoplasms arising in larynx. Neuroendocrine tumor of larynx is an extremely rare disease classified as typical carcinoids, atypical carcinoids, small-cell neuroendocrine carcinomas, and paragangliomas. Small-cell neuroendocrine carcinomas are classified as oat-cell, intermediate-cell, or combined-cell types. Small-cell neuroendocrine carcinomas usually arise submucosally in supraglottic region. Small-cell neuroendocrine carcinomas are very aggressive neoplasms characterized by diffuse early metastasis. There is no specific treatment for neuroendocrine tumors of the larynx. Patients could benefit from surgery, but radiotherapy and chemotherapy remain the treatment of choice. Small-cell neuroendocrine carcinoma is the most lethal tumor of the larynx with a five-year survival of 5%. Examination of a large series is required to provide clear diagnostic categories and to define the best treatment modalities.

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SITNOSTANIČNI NEUROENDOKRINI TUMORI GRKLJANA – MALA SERIJA SLUČAJEVA

SAŽETAK

Neuroendokrini tumori su najčešći neskvamocelularni tumori grkljana. Dijele se na: tipične karcinoide, atipične karcinoide, sitnostanične neuroendokrine tumore i paragangliome.Cilj ovog rada je da prezentiramo četiri pacijenta, jednu ženu i tri muškarca, sa sitnostaničnim neuroendokrinim tumorom grkljana. Pacijenti su bili uzrasta od 47–77 godina i svi su imali razvijene metastaze pri prvom pregledu. U radu je diskutirano kliničko ispoljavanje, dijagnostički i terapijski pristup pacijentima sa ovim agresivnim tipom tumora. Mada kirurgija ima određeno mjesto u liječenju, radioterapija i kemoterapija pretstavljaju terapiju izbora. Analiza većeg broja slučajeva je potrebna kako bi se utvrdili najkorisniji dijagnostički testovi i najefikasniji način liječenja.