Small Cell Neuroendocrine Carcinoma of the Larynx: A Case Report and Literature Review

Larenks Küçük Hücreli Nöroendokrin Karsinomu: Olgu Sunumu ve Literatür Araştırması

Abstract
A small cell neuroendocrine neoplasm of the larynx is a very rare and aggressive type of malignancy. Neuroendocrine carcinomas are most frequently seen in the lungs. The larynx is the most frequently involved site in the head and neck.

Primary small cell neuroendocrine carcinoma of the larynx constitutes less than 0.5% of all laryngeal cancers. This paper reports a case of a 41-year-old male patient who presented with a poorly differentiated neuroendocrine carcinoma of the supraglottic larynx.

Keywords
Neuroendocrine Tumors; Larynx; Carcinoma

Özet
Larenksin küçük hücreli nöroendokrin karsinomu çok nadir görülür ve agresif seyri tümörlerdir. Nöroendokrin karsinomlar en sık olarak akciğerde görülürler. Baş boyun bölgesinde ise en sık olarak larenksde görülürler. Primer larenks küçük hücreli nöroendokrin karsinomu tüm laringeal neoplazmların %0.5’inden azını tespit eder.

Az diferansiye larenks nöroendokrin karsinom tanısı konulup kemoterapi tedavisi uygulanan 41 yaşında erkek hasta literatür eşliğinde sunulmuştur.

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Nöroendokrin Tümör; Larenks; Karsinom

DOI: 10.4328/JCAM.4785
Received: 14.08.2016
Accepted: 31.08.2016
Printed: 01.06.2016

Journal of Clinical and Analytical Medicine
Introduction
Squamous cell carcinomas constitute more than 90% of all laryngeal cancers. Non-squamous cell cancers account for 5% and are composed of salivary gland tumors, sarcomas, and neuroendocrine tumors.

Neuroendocrine cancers can affect all organs including the larynx, with a prevalence of 1%. They are subdivided into four subgroups: well differentiated (carcinoid), moderately differentiated (atypical carcinoid), poorly differentiated (small cell) neuroendocrine carcinomas, and paragangliomas. Small cell neuroendocrine carcinoma is the most aggressive form; to date, 180 cases have been reported in the literature [1,2].

Small cell neuroendocrine carcinoma is most frequently seen in the lungs. The larynx is the most frequently involved site in the head and neck. Primary small cell neuroendocrine carcinoma (SCNC) of the larynx constitutes less than 0.5% of all laryngeal cancers. Primary laryngeal neuroendocrine carcinomas metastasize frequently. Cervical lymph nodes are the most frequently involved sites. Chemoradiotherapy is the first choice of treatment, as surgery has been shown to be unsuccessful [2].

Case Report
A 41-year-old male applied with complaints of neck swelling and hoarseness which had been present for two months. His endoscopic laryngeal examination revealed a bluish-purple exophytic and ulcerative mass at the laryngeal side of the epiglottis, starting 1 cm inferior to the tip of the epiglottis, invading the left false cord. The distance between the tumor and the anterior commissure was 3 mm (Figure 1). During the neck examination, a 3x3 cm, smooth-surfaced and semi-mobile mass was palpated at the left upper-middle jugular region. Computerized tomography (CT) of the neck revealed a lobulated, irregular soft tissue mass that involved laryngeal surface of the epiglottis, preepiglottic space, left paraglottic space, vallecula and left aryepiglottic fold. In addition, there was a 37x28 mm mass lesion located between thyroid cartilage and sternocleidomastoid muscle with a hypodense central part (Figure 2). A direct laryngoscopy and biopsy was performed.

The result of histopathologic examination was “poorly differentiated neuroendocrine carcinoma (small cell).” Fine needle aspiration biopsy of the neck mass also revealed “metastasis of neuroendocrine carcinoma.” The patient consulted with medical oncology and radiation oncology departments and it was decided to administer chemotherapy and radiotherapy first, and later consider surgery. The patient was administered 6 cycles of 130 mg cisplatin and 200 mg etoposide with concomitant neck radiotherapy (6500 cGy). The patient had cardiac and respiratory arrest six months after chemoradiotherapy. He was resuscitated after endotracheal intubation and admitted to the intensive care unit. The patient, intubated and connected to the respiratory support volume equipment, stayed in the intensive care unit for 30 days. He started to breathe spontaneously after 30 days and he was extubated. He was discharged from the intensive care unit but died ten days thereafter.

Discussion
Epithelial tumors with neuroendocrine differentiation can occur in any organ of the body. Laryngeal neuroendocrine carcinomas constitute less than 1% of all laryngeal neoplasms. To date, 436 laryngeal neuroendocrine carcinomas (LNC) have been reported in the literature [3].

Laryngeal neuroendocrine carcinomas are also divided into three subgroups according to their degree of differentiation: differentiated LNC (carcinoid), moderately differentiated LNC (atypical carcinoid) and poorly differentiated LNC (small cell) [4,5].

Small cell neuroendocrine carcinoma (SCNC) is an extremely aggressive tumor and is most frequently seen in the lungs. Its most common extrapulmonary site is the esophagus. It is most frequently seen in the larynx in the head and neck region. It has been given a number of names in the literature: small cell carcinoma, oat cell carcinoma, anaplastic cell carcinoma, anaplastic small cell carcinoma, endocrine carcinoma, poorly differentiated neuroendocrine carcinoma, neuroendocrine carcinoma with exocrine differentiation, Kultschitzky cell carcinoma, apudoma.
reserve cell carcinoma, microcytoma, and small cell neuroendocrine carcinoma [2].

Primary small cell neuroendocrine carcinomas constitute less than 0.5% of all laryngeal cancers. Ferlito et al. [6] reported a total of 180 cases in their literature review in 2006.

Laryngeal SCNC is more frequently seen in males in their 6th-7th decades and patients usually have a history of smoking. While tumors can appear anywhere in the larynx, the supraglottis was involved in most of the published cases. Patients usually apply with hoarseness and a neck mass. Approximately half of the published cases reported neck metastasis [2]. In accordance with the literature, our patient was a 41-year-old male whose complaints were hoarseness and a neck mass, and whose tumor was supraglottic.

More than 90% of laryngeal SCNC metastasize, most frequently to cervical lymph nodes, the liver, lungs, bones, and bone marrow. SCNC that metastasized to the central nervous system have also been reported in the literature [2,7].

The tumor may present macroscopically as a polypoid mass or ulcerated submucosal nodules and its size may range between 0.5 and 4 cm. Necrosis and nuclear hyperchromasia are prominent in small cell neuroendocrine carcinomas. There is a typical crush artefact. The tumor strongly stains with cytokeratin, epithelial membrane antigen, chromogranin, synaptophysin, and somatostatin. There is no necrosis in atypical carcinoid [8]. There were tumor nests in the lamina propria in our case (Figure 3). In addition, the tumor cells were round with prominent nuclei and there was necrosis in patches with frequent mitotic figures (Figure 4). The tumor cells stained strongly with chromogranin A (Figure 5). The tumor was negative for synaptophysin and CK 5/6.

Radiological imaging does not give us information about the nature of the tumor, but it may help us to determine the extension of the tumor. The most helpful imaging modality is CT. In radiology, necrosis or cavitation is seen less frequently in small cell carcinomas when compared to squamous cell carcinomas [9]. In our patient, necrosis was seen at the center of the laryngeal mass and in the lymphadenopathy located at the upper-middle cervical region (Figure 2).

Review of the reported cases indicates that radical surgical procedures (total laryngectomy and radical neck dissection) have been unsuccessful in laryngeal SCNC. Thus, radical surgical procedures must be avoided and concomitant chemoradiotherapy must be considered. Ferlito et al. [2] reported more than 5-year survival in 3 of their 14 patients who had chemoradiotherapy.

Barker et al. [10] reported that head and neck non-sinosal neuroendocrine carcinomas responded well to etoposide and cisplatin at a high rate. In line with the literature, we did not plan surgery at first, and instead considered chemoradiotherapy. We administered 3 cycles of a cisplatin and etoposide combination with concomitant 6500 cGy radiotherapy.

Laryngeal SCNC are the most aggressive laryngeal tumors. Mean survival is 9.8 months (range 1-26 months). Death is usually due to widespread metastases. We did not determine any metastasis in our patient other than cervical metastasis and progression of the lesion.

Conclusion

Neuroendocrine carcinomas are rare tumors of the larynx; the small cell variant is a subgroup with an exceedingly poor prognosis. Immunohistochemical staining has an important role in the diagnosis. The treatment options for these tumors are different than for squamous cell carcinoma, the most frequently seen tumor of the larynx. Chemoradiotherapy is the treatment of choice.
Competing interests
The authors declare that they have no competing interests.

References

How to cite this article: