

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

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ABSTRACT

Small cell neuroendocrine carcinomas are a rare entity of laryngeal cancers, they represent 1% of all invasive laryngeal cancers. These are rare tumors with a poor prognosis. Treatment options are often extrapolated from small cell lung cancer and limited retrospective studies. The preferred treatment is a multimodal approach combining radiotherapy and systemic treatment. We report the case of a patient treated for a small laryngeal cell neuroendocrine carcinoma at the radiotherapy department of the Hassan II University Hospital Center in FES.

KEYWORDS: Neuroendocrine carcinoma; Larynx; Treatment

INTRODUCTION

Laryngeal neuroendocrine tumors are rare. They constitute a group of heterogeneous tumors. According to the 2017 WHO proposed classification, small cell-type (SCNEC) is a poorly differentiated neuroendocrine carcinomas which have been mainly described in pulmonary tumor pathology. In fact, the primary extrapulmonary localization represents less than 5%, which explains the rarity of publications relating to similar cases. Small cell carcinoma is known to be radio and chemo-sensitive, but with frequent locoregional and metastatic recurrence and a low 5-year survival rate. We report the case of a patient treated for a small laryngeal cell neuroendocrine carcinoma at the radiotherapy department of the Hassan II University Hospital Center in FES.

CASE PRESENTATION

A 56-year-old male with a long history of smoking (30 pack-year) was admitted in Hassan II university Hospital (FES, MOROCCO). The patient complained of neck tumor progressing in size over 1 year and a progressive hoarseness. one month before coming to the hospital, the patient noticed a difficulty in swallowing

of solid food, and loss of appetite and weight. Physical examination revealed enlarged cervical lymph node on the left side of the neck painless without inflammatory signs. Direct laryngoscopy showed a tumor of the left Glottis and supraglottis larynx, invading the left vocal cord, the left ventricular band, the vallecula, the anterior commissure and the left piriform sinus. Multiple punch biopsies were taken from the mass. Pathological examination of the biopsy showed a small cell undifferentiated carcinoma. The immunohistochemistry showed that the tumor cells were positive for cytokeratin, and synaptophysin on the other hand, there was no expression of TTF1, no expression of chromogranin, and rare cells expressing p40. These results confirm the diagnosis of a small cell neuroendocrine carcinoma of the larynx.

Cervical computed tomography (CT) showed an expansive mass involving the Glottis and supraglottis larynx, (Figure 1) the left pharyngo-epiglottic fold the homolateral vallecula, the epiglottis, the anterior commissure and vocal cords, the ary-epiglottic fold. Infiltration of the HTE lodge, the piriform sinus and the parapharyngeal space.

Quick Response Code:



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Received: November 15, 2021

Published: November 30, 2021

How to cite this article: Zenab A, Amina B, Wissal H, Fatima ZF, Moustapha EM, Najib B, Touria B. Small Cell Neuroendocrine Carcinoma of the Larynx: Case Report and Literature Review. 2021- 3(6) OAJBS.ID.000353. DOI: [10.38125/OAJBS.000353](https://doi.org/10.38125/OAJBS.000353)

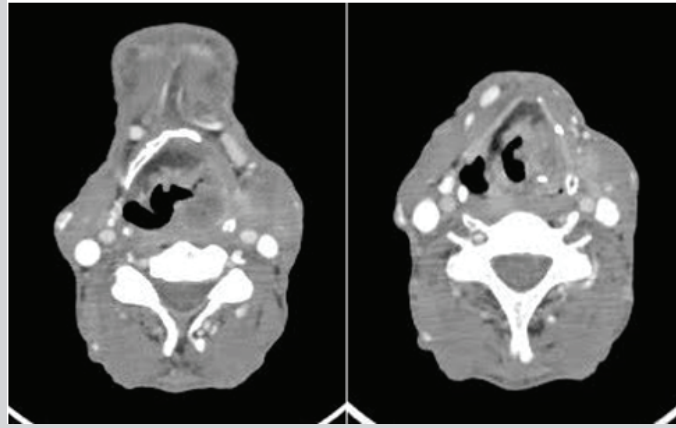


Figure 1: Contrast enhanced CT scan showing an expansive mass involving the Glottis and supraglottis larynx.

It remains distant from the oropharynx, and the subglottic larynx. Enlarged neck lymph nodes on the left II and III region (Figure 2). Thoraco abdomino pelvic CT did not show any distant

metastasis. The tumor was classified T3N1M0 according to the 8th edition of the AJCC TNM system.

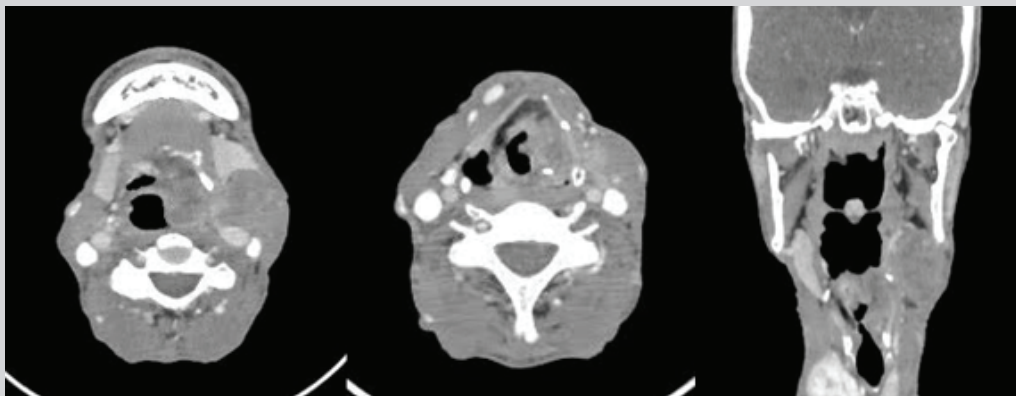


Figure 2: Contrast enhanced CT scan showing an enlarged neck lymph nodes on the left II and III region.

After discussing the case in a multidisciplinary consultation meeting, a concomitant radio chemotherapy was indicated. The technique used was IMRT (intensity modulated radiotherapy), the radiation dose was 70GY (2.0Gy/fraction; daily Monday-Friday in 7wk). Concomitant chemotherapy combined cisplatin 80mg / m² on D1 and etoposide 100mg / m² from D1 to D3, at a rate of one course every 3 weeks. 6 months after the end of treatment the patient remains in a good loco-regional control.

DISCUSSION

Neuroendocrine tumors can occur in any part of the body, but they are mostly reported in Gastrointestinal tract and bronchial system. In 1969 Goldman et al reported laryngeal neuroendocrine tumor as separate entity, and after that more than 700 cases have been described in the literature [1]. Neuroendocrine tumors of the larynx constitute a heterogeneous group of tumors. According to the 2017 WHO proposed classification, the poorly differentiated neuroendocrine carcinomas (NECs) comprise the poorly differentiated neuroendocrine carcinomas of a small cell-type (SCNEC) and a large cell-type. The other two tumors of epithelial origin are the well differentiated neuroendocrine carcinoma and the moderately differentiated neuroendocrine carcinoma [2].

Neuroendocrine carcinomas represent approximately 1% of malignant laryngeal tumors. but it is the second most common laryngeal malignancy. The majority of patients with small cell

carcinoma are males between the ages of 60 and 70, and as with pulmonary localization, this tumor appears to be closely related to tobacco [1].

These tumors can affect all levels of the larynx, but more frequently the supraglottis [3]. In our case the patient is 56 years old, chronic smoker, with a tumor of the Glottis and supraglottis larynx.

A clinical presentation of poorly differentiated laryngeal NECs is similar to the case of a conventional squamous cell carcinoma growing in the corresponding part of the larynx [1]. Patients present with nonspecific symptoms, including hoarseness and or breathing problems. About half of patients present with cervical lymph node metastasis, and Many have distant metastases. Rarely paraneoplastic syndromes are reported [4,5]. The diagnostic investigation should include a direct laryngoscopy with a biopsy and pathological examination which will confirm the diagnosis.

SCNEC grows in nests, sheets, and trabeculae of cells, with occasional nuclear palisading or rosette-like structures [6]. It is highly infiltrative, with frequent perineural and lymphovascular invasion. The tumor is composed of small to medium sized cells with hyperchromatic nuclei, finely granular chromatin, and indistinct nucleoli with scant cytoplasm. Nuclear moulding, prominent crush artefact, necrosis, apoptosis, and DNA coating of vessel walls (the Azzopardi phenomenon) are classic features, accompanied by a high

mitotic rate (> 10 mitoses per 2 mm² or 10 high-power fields). Both SCNEC and LCNEC are positive for cytokeratin's (in particular low-molecular-weight cytokeratin's) by immunohistochemistry, and SCNEC may exhibit a perinuclear or dot-like pattern. According to the 2017 WHO classification of Head and Neck Tumors, at least one positive neuroendocrine marker (synaptophysin, chromogranin or CD56) is required for the diagnosis of SCNEC. TTF1 immun-expression is variable. SmCC and LCNEC are negative or only weakly positive for p63 and are consistently negative for CK5/6 [2].

Before retaining the primary character of a small cell carcinoma of the larynx, bronchoscopy and a pulmonary CT scan are required. SCNEC are very aggressive and almost 50% of patients have cervical lymph node metastases at diagnosis. Between 60% to 90% of patients develop distant metastases. The most common sites of metastasis are lung, liver, bone [7]. Small cell neuroendocrine neoplasm of the larynx has an extremely poor prognosis, with five-year survival rates of 5% [8]. Generally, cervical and distant metastases are seen at the time of diagnosis. surgery alone does not improve local tumor control [9,10], and chemotherapy and radiotherapy are the mainstays of treatment.

The combination of primary radiation therapy and chemotherapy resulted in median patient survival of 55 months, representing significantly longer survival than with any other treatment regimen [11]. In view of the rarity of the disease and the absence of randomized trials, evidence has mainly been extrapolated from small cell lung cancer. Combination chemotherapy with cisplatin, carboplatin and etoposide is commonly used to treat small cell lung cancer [1]. Other systemic options currently under intensive research in small cell lung cancer, including checkpoint inhibitors administered in different combinations with RT and/or ChT, will probably in the future also find a place in the management of laryngeal poorly differentiated NECs [12,13].

Resistance to chemotherapy represents an important indicator of poor prognosis. The recurrence is usually generalized, and the results of any therapy are poor. Nevertheless, palliative chemotherapy may be warranted even under these circumstances, as some improvement in the quality and length of life may be achieved. As the chemotherapeutic agents commonly employed do not penetrate the blood-brain barrier, prophylactic cranial irradiation has been suggested as part of the management of this cancer [14]. However, Ferlito and Rinaldo have pointed out that central nervous system metastasis occurs in only 7.7% of patients with laryngeal small cell neuroendocrine carcinoma, and this occurs usually as a preterminal event. Therefore, such elective treatment is not indicated [15].

CONCLUSION

Small cell neuroendocrine carcinoma is rarely diagnosed in the supraglottic larynx, but it should be recognized because of

its biologic potential for rapid growth, early dissemination, and responsiveness to chemotherapy. radiotherapy and chemotherapy remain the treatment of choice.

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