Small cell neuroendocrine carcinoma of the larynx: a clinical case and literature review

Clinical Case

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Abstract

Neuroendocrine carcinomas (NEC) are rare and heterogeneous tumours in the Head and Neck (HN), especially in the larynx, representing less than 1% of primary tumours.
They are classified into different grades according to cellular differentiation. Treatment is multidisciplinary and includes chemotherapy, surgery, and radiotherapy.
We describe the case of a 73-year-old patient with progressive dysphonia and laryngeal lesion. Histological biopsy of the lesion confirmed small cell neuroendocrine carcinoma (SNEC).
The patient was staged as T3N0M0 and underwent concurrent chemotherapy and radiotherapy. Due to acute airway obstruction, she underwent CO2 laser surgery.
Following treatment with radiotherapy (total dose of 70Gy) and chemotherapy with carboplatin and etoposide, the patient was in good overall condition with no treatment-related complaints.
Treatment of SNEC generally involves a multidisciplinary approach; however, the recurrence rate is high, highlighting the need for rigorous monitoring for early intervention, as well as long-term follow-up to assess treatment efficacy and patient survival.
In conclusion, this case represents a rare entity, diagnosed in an early stage in which a radical treatment was possible thanks to a multidisciplinar approach, with no major intercurrence, and with no evidence of relapse until the present moment.

Keywords: Small Cell Neuroendocrine Carcinoma; Larynx Carcinoma; Chemoradiotherapy

Introduction

Neuroendocrine carcinomas (NECs) of the larynx are rare subtypes of head and neck (HN) tumors, accounting for less than 1% of all primary laryngeal neoplasms. They are the second most common histological subtype of laryngeal tumors after squamous cell carcinoma. The most common location

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of NECs in the HN is the larynx. Laryngeal NECs are more common in the supraglottic region (57.9%), and most patients (66.7%) are diagnosed in stage IV[1,7].

These tumors originate from pluripotent cells and, according to the 2017 World Health Organization (WHO) classification, are subdivided into three grades: grade 1, well-differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated, which includes the small cell neuroendocrine carcinoma (SCNEC) subtype (the most frequent) and large cell NEC subtype (the least frequent)[1,2].

NECs are more common in men than in women, with a male: female ratio of 3:1[4,12]. They are typically diagnosed between the fifth and seventh decades of life and often associated with a history of smoking[12].

Clinically, these tumors are characterized by nonspecific symptoms such as dysphonia, dysphagia, and odynophagia, which result from the tumor's mass effect. They rarely present as paraneoplastic syndromes due to hormonal overproduction by the tumor[4].

Different tumor subtypes may have overlapping histological and immunohistochemical characteristics, which makes staging and diagnosis challenging. The pathological assessment of NECs follows the TNM Staging System[18], and the recommended tests include contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the HN, thoracic CT, and possibly positron emission tomography (PET).

Treatment includes a combination of surgery, chemotherapy, and radiotherapy[5]. Surgical removal is the main therapeutic strategy for well-differentiated tumors. It usually involves a subtotal or total laryngectomy, depending on the size of the tumor, with no need for lymphadenectomy, given that these tumors rarely metastasize to the lymph nodes. Radiotherapy and chemotherapy are ineffective for this tumor subtype[5]. Surgery combined with lymph node dissection at levels IIA and III is recommended for moderately-differentiated supraglottic and glottic tumors. Neoadjuvant, adjuvant, or even radical radiotherapy and chemotherapy have been shown to be effective in some patients[7,13]. Surgery reportedly has no impact on the local control of the disease in patients diagnosed with SCNEC or large cell NEC; therefore, it is not the recommended treatment. SCNEC is treated with radical radiotherapy with concomitant or adjuvant chemotherapy[5]. Radical radiotherapy treatment regimens for supraglottic laryngeal tumors may vary, usually ranging between 66–70 Gy administered in daily doses of 2 Gy for high-risk areas. For low-risk areas, the dose can vary between 45–50 Gy (2 Gy/day) or 54–63 Gy (1.6–1.8 Gy/day). When radiotherapy is administered concomitantly with chemotherapy, the total dose for high-risk areas is 70 Gy, administered in daily doses of 44–50 (2 Gy/day) or 54–63 Gy (1.6–1.8 Gy) [17].

Chemotherapy regimens described in previously published studies include agents such as cyclophosphamide, doxorubicin, vincristine, methotrexate, and lamustine[5]. More recent studies used cisplatin, with or without etoposide[14-16] . Although there are no clear recommendations on the chemotherapy regimen to be used concomitantly with radiotherapy for the treatment of SCNEC of the larynx, the recommended regimen for small cell lung carcinoma[19] and sinonasal small cell carcinoma[17] is a combination of cisplatin and etoposide.

As these are rare tumors, a detailed description of the treatment used is essential for understanding the clinical-pathological behavior and thus determining the best therapeutic approach. In this context, we present a clinical case of SCNEC of the larynx, followed by a literature review to contextualize and substantiate the topic.

Results | Case report

A 73-year-old woman with a history of asthma, pulmonary emphysema, 52 pack-years of smoking, and grade 3b/4 chronic kidney disease complained of dysphonia that had progressed over several years and worsened in the previous week. Initial nasopharyngolaryngoscopy (NPL) revealed

a vegetating lesion approximately 1 cm in diameter located on the right arytenoid/aryepiglottic fold, with an apparent extension to the ipsilateral ventricular band. The pyriform sinuses were clear bilaterally. The vocal folds were difficult to visualize due to the size of the lesion, but their mobility appeared to be preserved. Cervical palpation revealed no adenopathy or palpable swelling. A cervical-thoracic CT scan showed a pseudonodular neoplasm, approximately 1.5x1 cm in size, in the right aryepiglottic fold (Figure 1), with apparent invasion of the pre-epiglottic fat but no invasion of the thyroid cartilage or evidence of cervical, mediastinal, or hilar lymphadenopathy (Figure 1).

The patient underwent suspension laryngoscopy for biopsy and staging of the lesion. Histological examination revealed SCNEC (Figure 2) with positive immunoreactivity for synaptophysin, chromogranin, and CKAE1/AE3, p16, and a proliferative index (Ki67) of 70–80% (Figure 3). Staging tests (cerebral MRI and cervical-thoracic CT) excluded distant metastasis.

The tumor stage was determined as SCNEC, cT3 N0 M0. The multidisciplinary group

Figure 1
Axial (a and b), sagittal (c), and coronal (c) computed tomography (CT) sections of the neck showing a moderately-enhanced lesion in the supraglottic region measuring approximately 1.5 × 1 cm

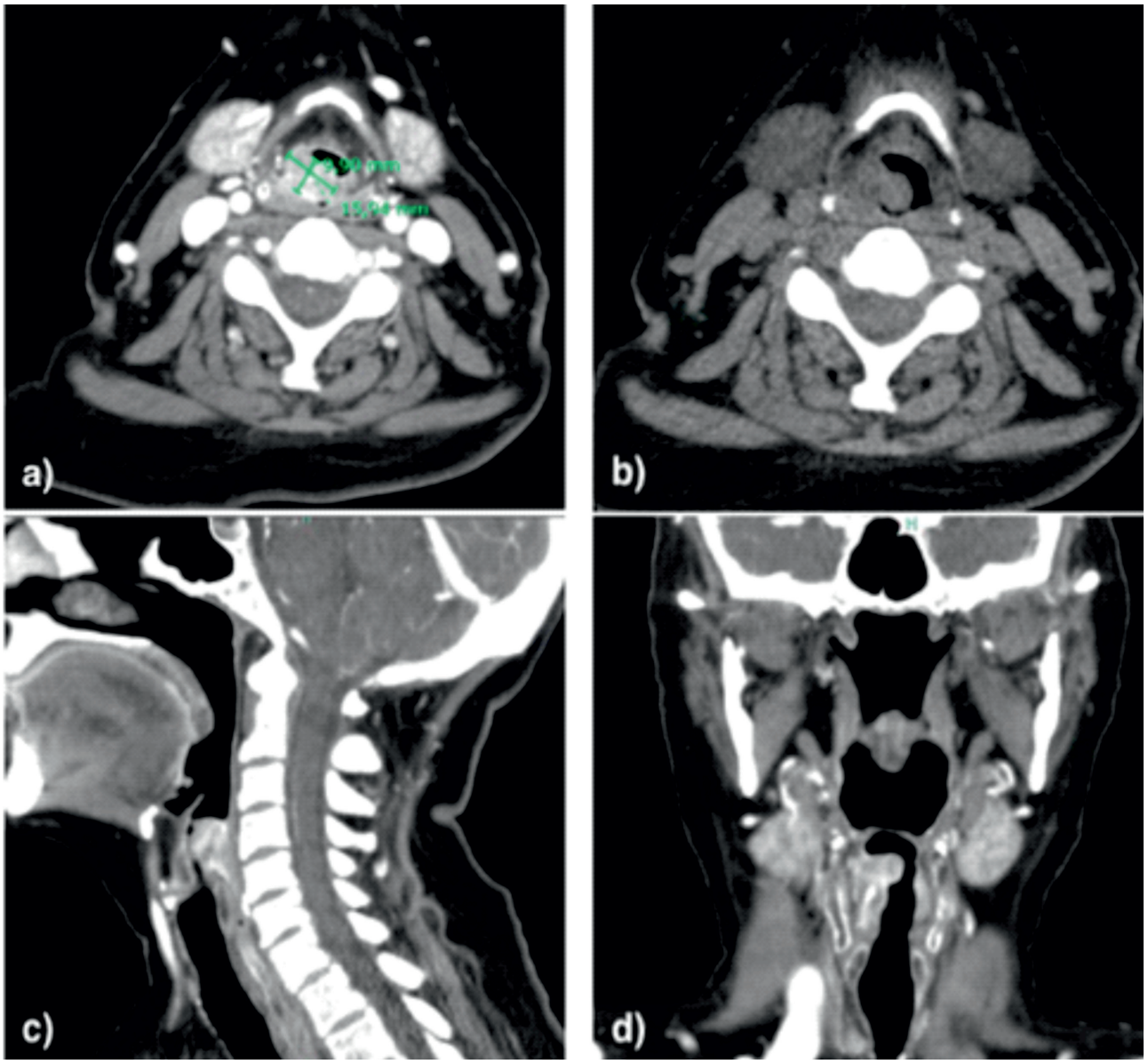
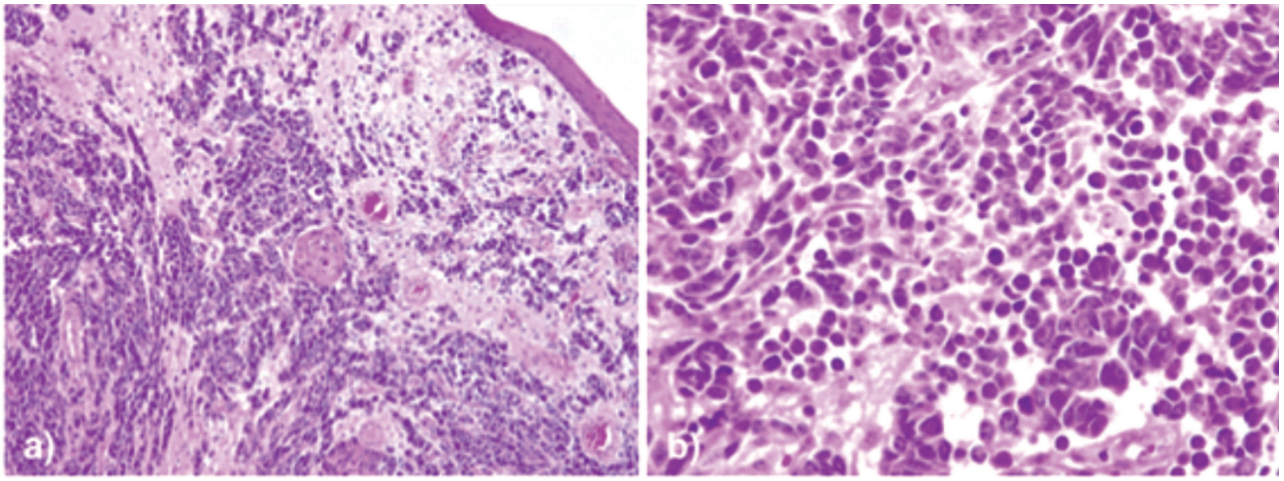


Figure 2
a) Hematoxylin & eosin ×10, b) Hematoxylin & eosin ×40. Laryngeal mucosa with the neoplasm consists of small ovoid cell nests, with scarce cytoplasm, hyperchromatic nuclei with salt and pepper chromatin, and barely evident nucleolus. Additionally, nuclear molding and occasional mitotic figures indicate small cell neuroendocrine carcinoma (SCNEC).

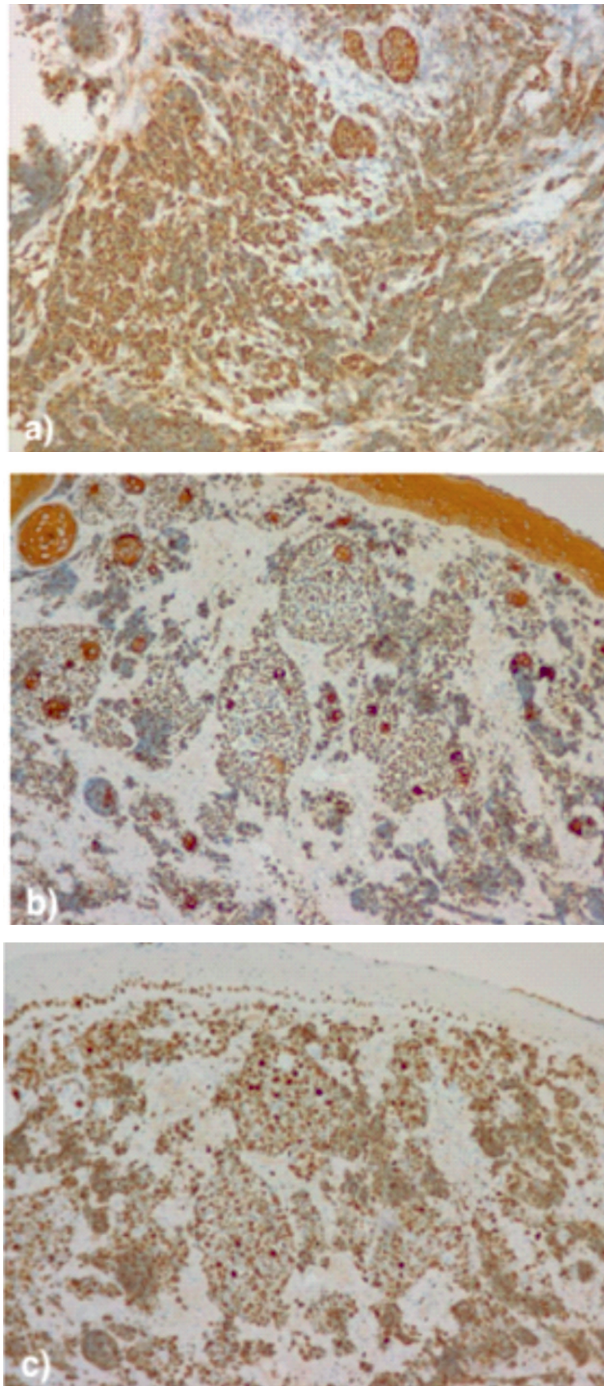


decided to treat the patient with concomitant chemotherapy and radiotherapy. Before starting the proposed treatment, the patient was admitted to the Emergency Department due to acute dyspnea and inspiratory stridor, which worsened when she lied down on her back. NPL showed that the neoplasm had increased in size, and exhibited a tilting movement toward the laryngeal inlet during inspiration. Focal fold visualization was limited, but their mobility seemed to be preserved. Therapeutic options, including surgical tracheostomy, were discussed with the patient. We decided to perform a suspension laryngoscopy for tumor debulking using CO_2 LASER, in the emergency room. The lesion was completely excised, along with a part of the aryepiglottic fold and right ventricular band, with exposure of the ipsilateral paraglottic space. Subsequent anatomopathological analysis confirmed surgical success (pT3 N0 R0). Subsequently, the patient started radiotherapy with a total dose of 70 Gy to the larynx, delivered in 35 daily fractions of 2 Gy per day, using the Volumetric Modulated Arc Therapy (VMAT)/Image-Guided Radiation Therapy (IGRT) technique (6 MV energy), according to computerized dosimetry planning. She also underwent concomitant chemotherapy with carboplatin (area under the curve [AUC] 5, day 1) and etoposide (100 mg/m^2 day 1, 2, and 3) every 21 days. At the end of the second cycle of chemotherapy, the radiotherapy was suspended for five days due to febrile neutropenia, which required hospitalization. Three months after the end of the treatment, the patient remains in good general condition and has no treatment-related complaints.

Discussion

SCNEC is a rare and heterogeneous tumor, with distinct characteristics from squamous cell carcinoma. The larynx is the most frequently affected organ by HN tumors. These tumors can appear in any region of the larynx, with the supraglottic region being the most frequently reported location[1,3,5]. Their prognosis has little relation with the stage at diagnosis, unlike squamous cell carcinoma[3]. The main predictive factors for the prognosis and behavior of SCNEC are the histological characteristics of the tumor. In this report, we have described the case of a 73-year-old woman diagnosed with SCNEC of the larynx. This case is unusual not only due to the rarity of this histological type, but also due to its occurrence in a woman, which is much rarer than in men, as well as the apparent absence of metastasis at diagnosis, which

Figure 3
a) CK AE1/AE3 ×10; b) Chromogranin ×10; c) KI67 ×10. Immunohistochemical study of small cell neuroendocrine carcinoma (SCNEC). The lesion was positive for neuroendocrine markers and cytokeratin, with a proliferative index (KI67) of 70–80%.



is also uncommon in this group of patients. Treatment of SCNEC of the larynx may include a combination of chemotherapy, surgery, and radiotherapy[11]. A combination of different therapies is considered more effective. Given the rarity of SCNEC of the larynx, the treatment strategy is similar to that of small cell lung cancer, typically consisting of a combination of radiotherapy and chemotherapy[3,5,8,9]. Radical radiotherapy has been shown to be effective for local control of the disease, although it has no impact on overall survival. Combined adjuvant chemotherapy may increase survival, resulting in an overall survival of 55 months, which makes this the preferred therapeutic approach[3,5].

There is no consensus on the optimal chemotherapy regimen. In this case, after referring to the regimens in the latest case reports and reviews, we decided to use etoposide with carboplatin[14-16]. The combination of cisplatin and etoposide also follows international recommendations for the treatment of small cell lung carcinoma[19] and sinonasal carcinoma[17]. In this case, due to a history of grade 3b/4 chronic kidney disease, cisplatin was replaced with carboplatin.

Considering the anatomopathological and immunohistochemical characteristics of the case described here, as well as the evidence published in the literature, the multidisciplinary HN oncology group decided to administer concomitant chemo- and radiotherapy to this patient, and the attending oncologist chose to use carboplatin and etoposide.

The chemoradiotherapy treatment regimen was well tolerated by the patient, who experienced only mild acute toxicity, which confirms the feasibility and effectiveness of this therapeutic approach. Three months after the end of the treatment, the patient remains clinically stable, with no treatment-related complaints.

Even with a combination of radiotherapy and chemotherapy, the relapse rate for SCNEC of the larynx is very high[9]. Survival beyond 5 years after the initial diagnosis is rare, and overall survival is similar to that of small cell lung carcinoma[8]. Poorly-differentiated (grade 3) small or large cell tumors have the worst prognosis, as they are the most lethal of all subtypes of NECs of the larynx[8]. These tumors

develops metastases in 90% of cases, leading some authors to suggest that SCNEC should be treated as a systemic disease *ad initium*, similar to small cell lung carcinoma [5].

The literature review reinforced the scarcity of data and complexity of managing these cases, emphasizing the importance of detailed clinicopathological description of SCNEC to better understand the clinical progression and response to therapy. Finally, some studies have suggested a high relapse rate for SCNEC of the larynx, highlighting the need for close monitoring to facilitate early intervention, as well as long-term follow-up to evaluate the treatment effectiveness and patient survival. The clinical case described here had a short follow-up period. However, the patient is currently in good general condition and has no complaints so far.

Conclusion

SCNEC of the larynx is a rare and heterogeneous condition with diagnostic and therapeutic challenges. Despite the advances in treatment, the management of SCNEC remains complex, highlighting the importance of detailed clinical case descriptions and close long-term follow-up of such cases. Such comprehensive documentation is crucial for a better understanding of the clinical progression and treatment responses in patients with this condition.

Conflict of Interests

The authors declare that they have no conflict of interest regarding this article.

Data Confidentiality

The authors declare that they followed the protocols of their work in publishing patient data.

Human and animal protection

The authors declare that the procedures followed are in accordance with the regulations established by the directors of the Commission for Clinical Research and Ethics and in accordance with the Declaration of Helsinki of the World Medical Association.

Privacy policy, informed consent and Ethics committee authorization

All the processed data were based in published reports that fulfilled privacy policy and ethical considerations.

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Scientific data availability

There are no publicly available datasets related to this work.

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