CASE REPORT
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A Rare Laryngeal Tumor: Poorly Differentiated Primary Small Cell Neuroendocrine Carcinoma

Arie Frank Arensman[1], Laura Pingnet[1], Martin Lammens[1,2], Simon Nicolay[1,3], Olivier M. Vanderveken[1,4]

[1]University of Antwerp Faculty of Medicine and Health Sciences, Antwerp, Belgium
[2]Department of Pathology, Antwerp University Hospital, Edegem, Belgium
[3]Department of Radiology, Antwerp University Hospital, Edegem, Belgium
[4]Department of Otorhinolaryngology and Head and Neck Surgery, Antwerp University Hospital, Edegem, Belgium

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ABSTRACT

Laryngeal small-cell neuroendocrine carcinoma is a rare and aggressive type of tumor. Due to the poor degree of differentiation, laryngeal small cell neuroendocrine carcinoma has particularly aggressive biological behavior with a tendency to early and widespread dissemination resulting in a poor prognosis. Based on presenting symptoms and imaging appearance, no differentiation is possible between laryngeal small cell neuroendocrine carcinoma and other laryngeal malignancies. Laryngeal small-cell neuroendocrine carcinoma is distinguished from other types of malignancies with histological examination complemented by immunohistochemistry. Due to its rareness, an evidence-based approach is lacking. The treatment principles are deducted from treatment protocols of small cell lung cancer and individual clinician's experience. The suggested preferred treatment of laryngeal small cell neuroendocrine carcinoma is a combination of chemotherapeutic agents. The prognosis is poor with a reported 5-year disease-specific survival of 18%-30%. Systemic dissemination at initial presentation is the only variable associated with a worse prognosis and treatment modality does not affect prognosis.

Keywords: Laryngeal neoplasms, small cell carcinoma, neuroendocrine carcinoma, chemoradiotherapy

Introduction

Merely 0.3% of laryngeal malignancies are of a non-squamous cell cancer (SCC) origin. Neuroendocrine carcinoma (NEC) arises predominantly in the gastrointestinal or respiratory tract, and a laryngeal NEC is a rare phenomenon. The classification of NEC is based on the degree of differentiation: well-, moderately, and poorly differentiated NEC. The latter consists of small-cell NEC and large-cell NEC. In this case report, the case of a 61-year-old man with a poorly differentiated subglottic laryngeal small cell neuroendocrine carcinoma (L-SCNEC) is described, according to the CARE guidelines.[1] Verbal informed consent was obtained from the patient who agreed to take part in the study.

Case Presentation

In March 2020, a 61-year-old man presented to the emergency department with a 2.5 months' history of hoarseness accompanied by increasing inspiratory stridor. He presented hemodynamically stable but slightly hypoxic with an oxygen saturation of 95%. Additionally, the patient experienced complaints of fatigue, dysphagia, throat pain, back pain, and an unintended weight loss of 6 kg over the past 5 months. The patient is an active smoker, with a 70-pack-year history. Fiberendoscopy displayed an immobile left vocal cord completely enclosed by a mass that extended from the subglottic larynx (Figure 1).

A full-body computed tomography scan (Figure 2) revealed a large mass centered at the subglottic larynx, extending from the supraglottic larynx to the proximal trachea, with tracheal stenosis to a minimum of 6 mm. The thyroid and proximal esophagus were also invaded. Additionally, multiple lesions suspected of hematogenous metastases were seen in the lungs, the liver, the right adrenal gland, and the bone.

A tumor was visualized with direct laryngoscopy and biopsy samples were collected. Histological examination indicated an L-SCNEC (Figure 3). Immunohistochemistry with Thyroid

Corresponding author: Arie Frank Arensman, e-mail: FrankArensman@gmail.com
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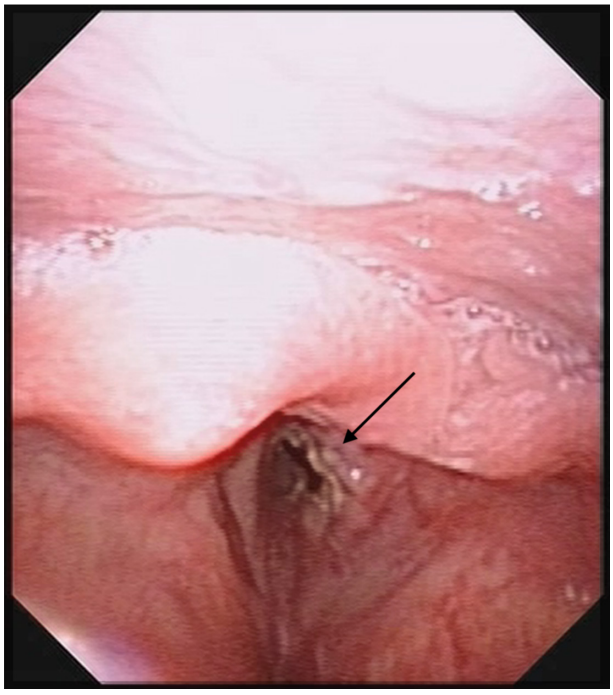

Figure 1. Fiberendoscopy images of a laryngeal mass with complete enclosure of the left vocal cord and subglottic extension.

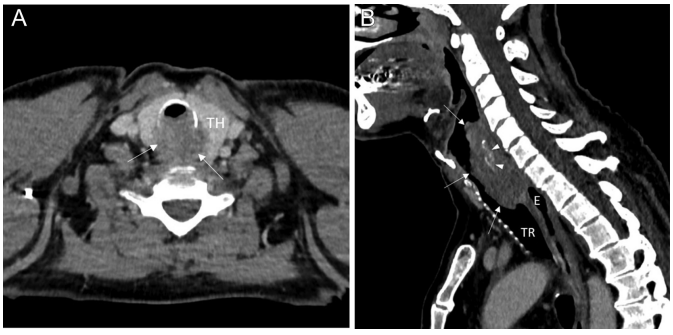

Figure 2. Axial and sagittal reconstructions of a contrast-enhanced computed tomography scan show a large hypodense mass (arrows) extending from the supraglottic larynx to the proximal trachea (TR). There is erosion of the cricoid cartilage (arrowheads) and invasion of the left lobe of the thyroid (TH) and the proximal esophagus (E).

Main Points

- Consider a laryngeal small cell neuroendocrine carcinoma (L-SCNEC) when observing a laryngeal malignancy, due to a bleaker prognosis in comparison with the more common squamous cell cancer.
- Laryngeal small cell neuroendocrine carcinoma has a dismal prognosis with a 5-year disease-specific survival of approximately 20%.
- The optimal treatment of L-SCNEC is disputed, but results favor a combination of chemotherapy agents including cisplatinum and radiotherapy.
- The role of surgery in L-SCNEC is limited to local control in early-stage disease or rescue therapy in case of local relapse.
- Active case documentation of extrapulmonary small cell neuroendocrine tumors is essential to facilitate the evidence-based therapeutic approach.

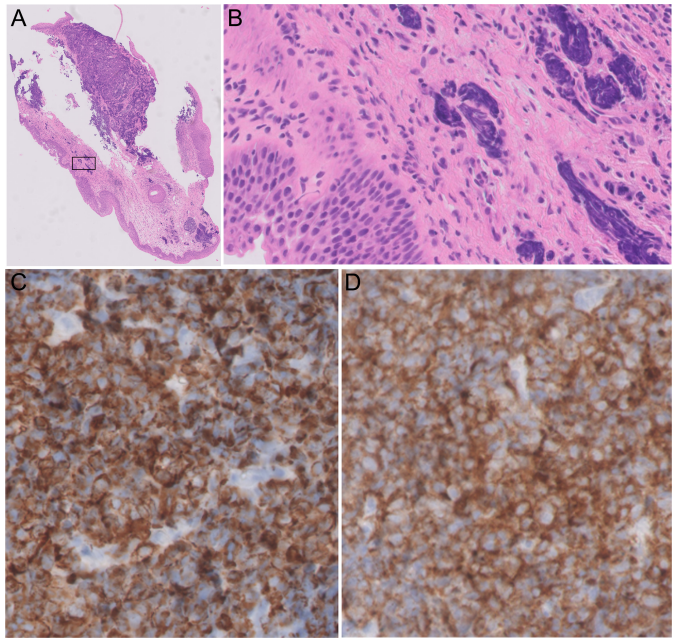

Figure 3. (A) Photomicrograph of tracheal biopsy with large tumoral mass and smaller extensions that are more superficial (Box in A, Magnification in B). (B) The tumor is composed of small cells with a hyperchromatic nucleus, there is much crush artifact. The tumor cells are immunohistochemically positive for both keratine (C) and synaptophysin (D). (A and B, hematoxylin–eosin (HE); C, cytokeratin; D, synaptophysin; original magnification A: 20×, B, C, and D: 200×.

transcription factor-1 (TTF-1) antibodies was positive, reinforcing the diagnosis of an extrapulmonary primary L-SCNEC. Fluorodeoxyglucose positron emission tomography/computed tomography confirmed a malignant process in the subglottic region with involvement of the proximal esophagus and suspicious bilateral lymph nodes in the neck. Additionally, multiple metastases were identified in the lungs, right adrenal gland, liver, and vertebrae C6-T1 (Figure 4). Further evaluation by cerebral magnetic resonance imaging ruled out brain metastases.

A stage IV L-SCNEC was diagnosed. It was not possible to differentiate a primary L-SCNEC from a large metastatic mass originating from a primary small cell lung cancer (SCLC). However, the latter seemed less likely due to the large volume of the laryngeal mass and the metastatic aspect of the lung lesions on chemotherapy (CT). This ambiguity did not affect the treatment regimen, which is similar for both malignancies. Considering the late-stage presentation with systemic dissemination and the aggressive character of L-SCNEC, curative treatment was not intended.

Palliative treatment was initiated consisting of CT with carboplatin–etoposide and concurrent consolidation radiotherapy (RT) with partial response after 4 cycles of carboplatin–etoposide. Progressive disease was detected at 5 months and consequently, second-line treatment with topotecan was initiated. Disease progression continued and off-label administration of third-line temozolomide was initiated based on molecular studies. Despite an observed partial response after 2 cycles, fulminant disease progression was observed 8 months into treatment. Best supportive care was offered and the patient passed away 10 months after the initial diagnosis.

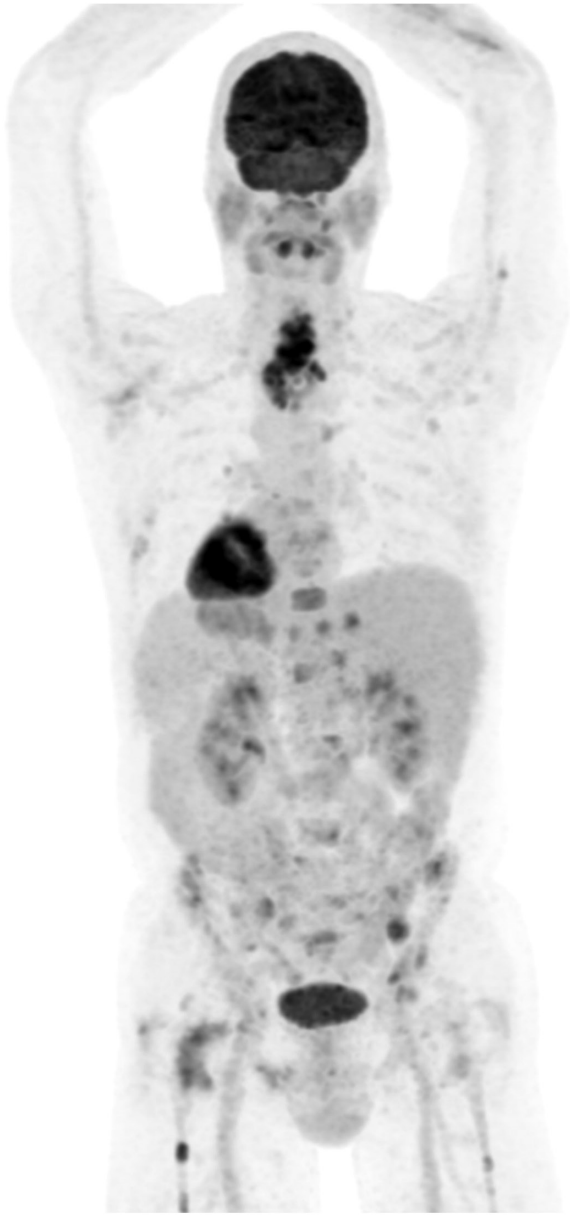

Figure 4. Maximum intensity projection (MIP) reconstruction of a fluorodeoxyglucose positron emission tomography/computed tomography scan showing a large tumoral process at the level of the larynx and proximal trachea, multiple suspicious lymph nodes in the neck and the mediastinum, as well as diffuse metastases in bone and bone marrow, liver, lung, and right adrenal gland.

Discussion

The vast majority (99.7%) of laryngeal malignancies are identified as SCC on histopathological examination and merely a small portion (0.3%) is classified as another tumor entity, including small cell neuroendocrine carcinoma (SCNEC).[2] In a systematic review of the literature, only 230 cases of L-SCNEC were retrieved.[3] The majority (41%) of laryngeal NECs are identified as SCNEC.[4]

The most common presenting complaints of L-SCNEC are a palpable neck mass and hoarseness.[3-5] The average age at presentation is approximately 50-60 years old and a male preponderance of 3:1 is observed.[5] Most patients have a history of considerable tobacco use. When suspecting a laryngeal malignancy, national guidelines regarding the workup of head and neck cancer should be adhered to.[6] Imaging studies help to stage the disease, but the final diagnosis relies upon suggestive histologic architecture combined with the presence of at least 1 neuroendocrine marker according to the TNM classification and AJCC staging system.[3,7,8] Two-thirds of patients present with stage IV disease due to early systemic metastases and eventually 90% of patients develop distant metastases.[3,4]

Owning to its rarity, an evidence-based protocol concerning the management of L-SCNEC is non-existent. Treatment regimens of L-SCNEC are designed conforming to the treatment principles of SCLC and integrated with data extracted from the meta-analyses of case series and small retrospective studies.[9] Various modalities have been proposed including surgical resection, CT, and RT. A 1978 review suggested a combined surgical and RT approach, but a multimodal approach with combined chemotherapy and radiotherapy (CRT) is the most accepted treatment modality nowadays.[3,4] Some authors argue local control of early-stage L-SCNEC can be achieved with surgery, but RT of the primary tumor site is preferred.[10] This is in concordance with previous studies reporting more tumor relapses post-laryngectomy in poorly differentiated tumors.[11] The role of surgery in L-SCNEC is reduced to rescue therapy in case of local relapse.[10] The first-line CT regimen includes cisplatinum and etoposide.[3,4,12] Newer CT agents such as topotecan are reserved for second-line therapy. The additional benefit of RT could not be established in more recent studies as they demonstrated treatment modality, CT versus CRT, and did not significantly impact survival.[3,12,13] However, CRT is the mainstay treatment in approximately a third of patients.[3,4] Recommendations regarding prophylactic cranial irradiation (PCI) are not uniform. In contrast to SCLC, brain metastases are rarer in L-SCNEC and combined with the significant side effects of PCI, routine use of PCI cannot be recommended.[3,12,14]

Despite the application of multimodal therapy, the overall prognosis of L-SCNEC is poor with a 5-year disease-specific survival (DSS) ranging from 17.6% to 30.8%, depending on presenting tumor stage and therapy regimen.[3,4,8,15] Late-stage L-SCNEC prognosis is even worse with a 2-year DSS of 42.3% for stage III/IVa/IVb and 14.2% for stage IVc.[13] Response to treatment is frequently observed but is often only partial and temporary.[12] Presence of systemic disease is usually followed by death within 2 years.[5] These discouraging prognostics are distressing compared to the 40.2% overall 5-year DSS of SCC.[15]

The L-SCNEC is an uncommon malignancy with an aggressive disease course and a dismal prognosis. Therefore, ENT specialists should be aware of the possibility of L-SCNEC. The therapeutic approach of L-SCNEC is deduced from data of better-documented SCLC. Multimodal CRT treatment is preferred and generally, surgery should be discouraged due to early dissemination. A combination-chemotherapy regimen consisting of a platinum compound and etoposide is regarded as the first-line treatment and this has not changed over the past 50 years. Notwithstanding the logistic challenges, the medical community should be encouraged to document L-SCNEC

cases, actively participate in clinical trials and initiate international multicenter research to explore therapeutic options, and facilitate evidence-based medicine to improve survival.

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