Primary and Secondary Small Cell Neuroendocrine Carcinoma of the Larynx: A Review

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Abstract: Primary laryngeal small cell neuroendocrine carcinoma (SCNC) is an unusual malignancy accounting for <0.5% of laryngeal carcinomas. To date, approximately 200 cases of primary and 5 of secondary SCNC of the larynx have been reported. This tumor most often presents in the sixth and seventh decades in men who are heavy cigarette smokers. The lesion may be associated with different paraneoplastic syndromes (ectopic adrenocorticotropic hormone syndrome, Schwartz–Bartter syndrome or syndrome of inappropriate secretion of antidiuretic hormone, and Eaton–Lambert myasthenic syndrome) or with ectopic hormone production. The diagnosis is based essentially on the histologic appearance of the tumor, confirmed by immunocytochemical investigations. Concurrent chemoradiotherapy regimens offer potential for long-term survival. This tumor is biologically aggressive, and the extent of the disease is the most significant independent prognostic factor of survival. The survival rate is similar to that with pulmonary SCNC.

Keywords: small cell carcinoma; small cell neuroendocrine carcinoma; larynx; therapy; prognosis

Small cell neuroendocrine carcinoma (SCNC) is a highly aggressive malignancy, occurring most commonly in the lung,1 where it constitutes 25% of all malignancies. Many other terms have been used to refer to this tumor, including small cell carcinoma, which is preferred by pathologists.2 The tumor is composed of oval or spindle cells with evidence of neuroendocrine differentiation.

Extrapulmonary SCNCs are relatively uncommon neoplasms and are considered to account for 2.5% to 5% of all SCNCs.3 They have been reported in many areas of the body.1,2,4 The most common site of extrapulmonary SCNC is the esophagus,5,6 SCNC also arises primarily in the head and neck region,3,7–11 where it most commonly involves the larynx.12

The purpose of this article is to give the reader an overview about this unusual tumor of the larynx.

Terminology

Various terms have been used in the past to designate this tumor, with a list that includes small cell carcinoma, oat cell carcinoma, anaplastic cell carcinoma, anaplastic small cell carcinoma, small cell undifferentiated carcinoma, neuroendocrine carcinoma, neuroendocrine neoplasm, endocrine carcinoma, small cell endocrine carcinoma, poorly
differentiated neuroendocrine carcinoma, neuroendocrine carcinoma with exocrine differentiation, Kultschitzky cell carcinoma, neuroendocrine carcinoma of small cell type, apudoma, reserve cell carcinoma, small cell tumor, microcytoma, carcinoma with amine-precursor uptake decarboxylase cell differentiation, undifferentiated carcinoma, and small cell neuroendocrine carcinoma.

Many authors consider SCNC of the larynx to represent the least differentiated end of a spectrum of neuroendocrine carcinomas, with carcinoid tumor representing the well-differentiated end and atypical carcinoid tumor an intermediate-differentiated group.12–17

INCIDENCE

Primary SCNC of the larynx is an unusual malignancy accounting for <0.5% of laryngeal carcinomas in 1 large series.13 In 1991, Gnepp18 published a review on this subject and approximately 125 cases of SCNC of the larynx were recorded. In 1998, Ferlito et al14 determined that there were only 160 cases of primary SCNC of the larynx reported in the literature at that time. In 2006, Ferlito et al12 mentioned that approximately 180 cases of SCNC of the larynx had been reported in the literature and only a limited number have been added since then.19–23

The precise incidence of this neoplasm in the larynx is difficult to assess because many cases have been described as poorly differentiated squamous cell carcinoma, anaplastic carcinoma, basaloid squamous cell carcinoma, and solid variant of adenoid cystic carcinoma.24

SCNCs presenting initially in head and neck sites may be metastases from distant sites, which in several cases are the lungs. Metastases from pulmonary and extrapulmonary SCNC have been reported in the hard palate and infra-orbital region,25 tongue base,26 tonsils,27 bilateral parotid gland,28,29 submandibular gland,30 nose,31 lip,32 and gingiva.33 There are also 5 cases of laryngeal metastases from pulmonary (3 cases), tracheal (1 case), and prostatic SCNC (Table 1).34–39 The case of prostatic carcinoma metastasizing to the vocal cord was previously reported by Tețu et al.39

In 2006, Kaira et al19 reported a second primary SCNC of the larynx in a long-term survivor of SCNC of the lung. There are no similar reports in the literature involving the larynx.19

CLINICAL FEATURES

The neoplasm affects mainly men of 50 to 60 years of age (range, 23–91 years) who have been heavy cigarette smokers. The neoplasm may occur in any part of the larynx, although the supraglottis is the most commonly affected site.

Symptoms and signs are similar to those found with other laryngeal neoplasms and depend upon the region involved. Patients often present with complaints of hoarseness and a neck mass. About half of all patients with laryngeal SCNC have cervical lymph node metastases at presentation18 and the tumor should be considered as a disseminated disease at presentation.40 More than 90% of patients with laryngeal SCNC eventually develop metastatic disease.18 The most common sites of spread are cervical lymph nodes, liver, lung, bone, and bone marrow.41 The clinical absence of cervical and distant involvement does not exclude the presence of micrometastases, which become clinically evident after a few months.

Table 1. Laryngeal metastases resulting from SCNC reported in the world literature.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Primary site</th>
<th>Location of laryngeal metastasis</th>
<th>Symptoms</th>
<th>Other sites of metastases</th>
<th>Follow-up from initial diagnosis of malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolla et al34</td>
<td>1968</td>
<td>60</td>
<td>M</td>
<td>Lung</td>
<td>True and false vocal cords, anterior commissure</td>
<td>Hoarseness, dry cough</td>
<td></td>
<td>DOD, 6 mo</td>
</tr>
<tr>
<td>Kyriakos et al35</td>
<td>1978</td>
<td>57</td>
<td>M</td>
<td>Trachea</td>
<td>Below the true vocal cords</td>
<td>Dyspnea</td>
<td>Liver, esophagus, lymph nodes, pancreas</td>
<td>DOD, 29 mo</td>
</tr>
<tr>
<td>Radici et al36</td>
<td>1988</td>
<td>59</td>
<td>M</td>
<td>Lung</td>
<td>Vocal cord and ventricle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiaoni et al37</td>
<td>1989</td>
<td>53</td>
<td>F</td>
<td>Lung</td>
<td>False vocal cord</td>
<td>Dysphonia</td>
<td></td>
<td>Alive, 60 mo</td>
</tr>
<tr>
<td>Grignon et al38a</td>
<td>1990</td>
<td>71</td>
<td>M</td>
<td>Prostate</td>
<td>Vocal cord</td>
<td>Change in voice</td>
<td>Bones</td>
<td>DOD, 22 mo</td>
</tr>
</tbody>
</table>

Abbreviations: SCNC, small cell neuroendocrine carcinoma; DOD, dead of disease.

*This case has been also mentioned by Tețu et al.39
PARANEOPLASTIC SYNDROMES ASSOCIATED WITH LARYNGEAL SMALL CELL NEUROENDOCRINE CARCINOMA

Primary SCNC of the larynx may be associated with paraneoplastic syndromes, akin to small cell cancer of the lung, and this may be the reason for presentation. In 1979, Trotoux et al. described a case of SCNC of the subglottic region associated with syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (or Schwartz–Bartter syndrome). The patient was seen with initial headache, confusion and temporospatial disorientation, hyperreflexia, hyponatremia, hypochloremia, serum hyposmolarity, reduced hematocrit, negative free-water clearance, and high plasma levels of antidiuretic hormone. The diagnosis of the subglottic tumor was only reached 3 months later. In 1984, Medina et al. reported a case of primary SCNC of the larynx associated with clinical and electromyographic evidence of the myasthenic syndrome. In 1985, Bishop et al. reported a case of laryngeal SCNC associated with ectopic adrenocorticotropic hormone (ACTH) syndrome. The cell cytoplasm was immunoreactive for ACTH, gastrin-releasing polypeptide, neuron-specific enolase, β-endorphin, calcitonin, and keratin, by indirect immunoperoxidase techniques. In 1989, Takeuchi et al. reported a case of SCNC of the larynx in a 53-year-old man. The tumor was associated with SIADH, and hyponatremia persisted until the patient’s death, despite the administration of salt. Postmortem revealed no central nervous system lesions or lung diseases. In 1995, Myers and Kessimian described a patient with SCNC of the larynx who had clinical complications of SIADH. The diagnosis of this endocrine syndrome was confirmed by the finding of serum hyponatremia and hypo-osmolarity, urine hypo-osmolarity, and an increased urinary sodium concentration. Careful patient evaluation identified only the laryngeal neoplasm as the cause of SIADH and excluded any other potential causes (pulmonary neoplastic or nonneoplastic diseases, central nervous system lesions, drugs). All 5 patients with laryngeal SCNC associated with paraneoplastic syndromes died (Table 2). Ectopic hormone production without clinical syndromes associated with laryngeal SCNC has been reported in 6 other patients (Table 3). The paraneoplastic syndromes have not been described in association with combined SCNC. The combined SCNC is a neoplasm in which there is a definite component of SCNC with squamous cell carcinoma and/or adenocarcinoma.

PATHOLOGY

Macroscopically, the tumor often presents as ulcerated submucosal nodular or polypoid mass and it may vary in size from 0.5 to 3–4 cm. The

### Table 2. Reported cases of laryngeal SCNC with paraneoplastic syndromes.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Paraneoplastic syndrome</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trotoux et al.</td>
<td>1979</td>
<td>61</td>
<td>M</td>
<td>SIADH</td>
<td>DOD, 7.7 mo</td>
</tr>
<tr>
<td>Medina et al.</td>
<td>1984</td>
<td>64</td>
<td>F</td>
<td>Eaton-Lambert</td>
<td>DOD, 11 mo</td>
</tr>
<tr>
<td>Bishop et al.</td>
<td>1985</td>
<td>60</td>
<td>F</td>
<td>ACTH</td>
<td>DOD, 0.5 mo</td>
</tr>
<tr>
<td>Takeuchi et al.</td>
<td>1989</td>
<td>53</td>
<td>M</td>
<td>SIADH</td>
<td>DOD, 15 mo</td>
</tr>
<tr>
<td>Myers and Kessimian</td>
<td>1995</td>
<td>58</td>
<td>M</td>
<td>SIADH</td>
<td>DOD, 2 mo</td>
</tr>
</tbody>
</table>

Abbreviations: SCNC, small cell neuroendocrine carcinoma; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; DOD, dead of disease; ACTH, adrenocorticotropic hormone.

### Table 3. Reported cases of laryngeal SCNC with ectopic hormone production.

| Authors                  | Year | Age | Sex | Hormones               | Method    | Follow-up  |
|--------------------------|------|-----|-----|------------------------|-----------|
| Gould et al.             | 1981 | 59  | M   | Calcitonin             | IHC       | DOD, 18 mo |
|                         |      | 61  | F   | Calcitonin, somatostatin, ACTH | IHC       | NED, 8 mo  |
| Weidauer et al.          | 1985 | 42  |     | Serotonin              | IHC       | Alive, 16 mo |
| Woodruff et al.          | 1985 | 51  | M   | Serotonin              | IHC       | DOD, 15 mo  |
| Springall et al.         | 1986 | 53  |     | Bombesin               | IHC       |            |
| Googe et al.             | 1988 | 77  | F   | Serotonin              | IHC       | NED, 7 mo  |

Abbreviations: SCNC, small cell neuroendocrine carcinoma; IHC, immunohistochemistry; DOD, dead of disease; NED, no evidence of disease; ACTH, adrenocorticotropic hormone.
lesion is formed by small cells of varied shape with scanty cytoplasm and relatively large, hyperchromatic, oval, round, or spindle-shaped nuclei with delicate chromatin and inconspicuous nucleoli (Figure 1). Necrosis and nuclear molding are prominent. Typical crush artifact is present. Mitoses are numerous and vascular, perineural and skeletal muscle invasion are commonly seen. Rosette (which is a type of formation or structure in which the cells have a circular radiate arrangement resembling a rose formation) is rare (Figure 2). The stroma is scanty and rarely mucoid. Scattered neoplastic multinucleated giant cells may be present. Occasionally, the cells appear to cluster around alveolar-like spaces containing diastase periodic acid-Schiff (PAS)-positive material. Stains for argyrophilia and argentaffinity are usually negative. Morphologically, immunohistochemically, and ultrastructurally, laryngeal SCNC is identical to its pulmonary counterpart. The combined SCNC in unusual neoplasm represents <10% of all SCNCs of the larynx. A laryngeal tumor showing squamous, glandular, neuroendocrine and exocrine, as well as chondrosarcomatous and rhabdomyosarcomatous differentiation has also been reported.

Several studies have focused on the immunohistochemical characterization of the SCNC of the larynx in order to obtain more information on the nature of this neoplasm. The tumor may express positivity for cytokeratin, epithelial membrane antigen, carcinoembryonic antigen, Ber-EP4, chromogranin, synaptophysin, Leu 7 (CD57), neuron-specific enolase, protein gene product 9.5, calcitonin, somatostatin, neurofilaments, ACTH, C-flanking peptide of human probombesin (CFB), bombesin, serotonin, neurotensin, gastrin-releasing polypeptide, β-endorphin, calcitonin gene-related peptide, and neural cell adhesion molecule. Cytokeratin stains are usually positive and may show the punctate perinuclear positivity typical of lung small cell carcinoma. Positivity for thyroid transcription factor 1 may be present. Although electron microscopy does not enjoy the same popularity it once did, ultrastructurally most tumors contain only sparse neurosecretory granules, confirming their neuroendocrine nature.

HISTOGENESIS

The histogenesis of SCNC has remained obscure. It is thought to originate from endocrine cells or argyrophilic Kultschitzky cells normally found in animal and human laryngeal mucosa. The coexistence of divergent differentiation (squamous, glandular, exocrine, neuroendocrine, chondrosarcomatous, and rhabdomyosarcomatous) supports the hypothesis that this neuroendocrine neoplasm arises from a common primitive and pluripotential stem cell rather than from a specific neuroendocrine precursor.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis presents no major difficulty and is based essentially on the histologic appearance of the lesion, confirmed by immunocytochemical investigations. The tumor needs to be differentiated from small cell squamous carcinoma (or “pseudo” oat cell carcinoma), atypical carcinoid tumor, basaloid squamous cell carcinoma, lymphoma. Immunohistochemistry is useful in distinguishing SCNC from small cell squamous carcinoma. Atypical carcinoid tumor does not show the
degree of necrosis or mitotic and apoptotic activity of SCNC. SCNCs of the lung and extrapulmonary SCNCs express K homology domain containing protein, but carcinoid tumors (typical and atypical) do not.\textsuperscript{58,59} Basaloid squamous cell carcinoma shows the basaloid and squamous components. The presence of overlying squamous dysplasia is strongly supportive of basaloid squamous cell carcinoma. The presence of spindle-shaped cells, rosettes, and glandular structures in SCNC and the usually high mitotic index may assist in the differential diagnosis with respect to malignant lymphoma. Leukocyte common antigen is present in lymphomas but is absent in SCNC. Occasionally, lung SCNC may metastasize to the larynx; therefore, a primary SCNC of the lung should be ruled out before assuming that the laryngeal tumor is a primary neoplasm. A metastasis from a primary SCNC of the lung must be excluded by a normal plane radiograph and CT of the chest and a normal sputum cytology or negative bronchoscopy.\textsuperscript{60}

**PRETREATMENT EVALUATION**

After the diagnosis is established with a biopsy and confirmed by immunohistochemical investigations, the patient should undergo a full metastatic evaluation because the lesion could be a metastasis from an SCNC of the lung or extrapulmonary SCNC (such as trachea, prostate). A proper diagnosis is important in order to choose optimal treatment.

A systemic work-up should include: panendoscopy of the upper aerodigestive tract, chest X-ray, radiographic imaging with CT and/or MRI of the head and neck, chest, brain, upper abdomen, bronchoscopy and evaluation of the sputum and/or bronchial washing, positron emission tomography scanning, and laboratory investigations (in particular, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, albumin, sodium). A bone marrow aspiration and biopsy may be performed. However, Pierce et al\textsuperscript{61} reported that the incidence of bone marrow metastasis was approximately 6% for patients with SCNC of the larynx.

**TREATMENT**

Radical surgical procedures (total laryngectomy and radical neck dissection) have failed in the majority of reported cases. Total laryngectomy will result in voice loss, and will control only the primary tumor. This is not justifiable if treatment is possible with modalities that preserve the voice and improve the clinical course. Therefore, radical surgical procedures should be avoided.\textsuperscript{40}

Concurrent chemoradiotherapy is the treatment of choice. Commonly used agents include cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, methotrexate, and lamostine. Three of 14 patients with laryngeal SCNC reported by Ferlito et al\textsuperscript{62} were noted to be free of disease >5 years following treatment with a multidrug chemotherapy regimen and radiotherapy. But long-term survival was restricted to patients with stage I (2 cases) and stage II (1 case) disease. Barker et al\textsuperscript{63} reported a high response rate to use of cisplatin/etoposide for nonsinonasal neuroendocrine carcinomas of the head and neck. The use of cisplatin is associated with a risk of ototoxicity. Chemotherapy with irinotecan hydrochloride (CPT-11) and cisplatin might be effective to improve median survival of patients with SCNC of the larynx.\textsuperscript{64}

Prophylactic cranial irradiation is not indicated in consideration that only 7.7% of laryngeal SCNC metastasize to the central nervous system\textsuperscript{65} and only as a preterminal event. Brain metastases were observed in a higher number of patients with SCNC of the lung compared with extrapulmonary SCNCs.\textsuperscript{66}

**PROGNOSIS**

Laryngeal SCNC is the most lethal aggressive tumor of the larynx. Although some patients have enjoyed a prolonged survival and even cure, laryngeal SCNC unfortunately has a generally dismal prognosis. In a review by Gnepp et al,\textsuperscript{41} 73% of patients with laryngeal SCNC died of disease with widespread metastases, with a mean survival time of 9.8 months (range, 1–26 months). The 2- and 5-year survival rates are 16% and 5%, respectively.\textsuperscript{18} In 2004, Soga et al\textsuperscript{67} reported a 5-year survival rate of 7.7%. The survival figures are similar to those for pulmonary SCNC.\textsuperscript{68–70} As in the lung,\textsuperscript{71} this tumor in the larynx is a frustrating lesion.\textsuperscript{24} Extent of the disease is a significant prognostic factor for survival.\textsuperscript{62} The prognosis of combined SCNC of the larynx is similar to that of a pure SCNC.

**CONCLUSIONS**

A few major conclusions can be drawn from our review. First, the larynx is considered the most common site of extrapulmonary SCNC of the head and neck, and approximately 200 cases of this
tumor have been reported in the literature. Only 5 cases of secondary SCNC to the larynx have been described. Second, the pathologist must be aware of this entity, because SCNC of the larynx has generally a dismal prognosis regardless the size of the primary tumor. The prognosis of combined SCNC of the lung, only 7.7% of regimens offers potential for long-term survival. Fifth, the use of concurrent chemoradiotherapy has been associated with ectopic hormone production and treatment. In other cases, this tumor has been observed in association with laryngeal SCNC, and all patients died. The evolution of hormonal syndromes is valuable for diagnosis and treatment. In other cases, this tumor has been associated with ectopic hormone production. Fifth, the use of concurrent chemoradiotherapy regimens offers potential for long-term survival. In contrast to SCNC of the lung, only 7.7% of laryngeal SCNCs metastasize to the central nervous system and only as a preterminal event. Therefore, prophylactic cranial irradiation is not indicated. Sixth, SCNC of the larynx is an aggressive neoplasm, often disseminated at presentation. The extent of the disease is the most significant independent prognostic factor for survival. The survival rate is similar to that of pulmonary SCNC.

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