Case Report
Primary combined small cell carcinoma of larynx with lateralized histologic components and corresponding side-specific neck nodal metastasis: report of a unique case and review of literature

Gitika Aggarwal1, Lana Jackson2, Suash Sharma1

Departments of Pathology1 and Otolaryngology2, Medical College of Georgia, Augusta, GA 30912.

Received October 10, 2010; accepted November 25, 2010; Epub December 3, 2010; published January 1, 2011

Abstract: Combined small cell carcinoma (neuroendocrine) of the larynx has been rarely reported in the literature, and included in the current WHO classification. We hereby report an unusual case of combined carcinoma of the larynx; composed mainly of small cell neuroendocrine carcinoma nearly confined to the right side (mainly involving supraglottis extending to glottis) with synchronous minor in-situ and invasive squamous cell carcinoma component located on the left side of larynx (mainly glottis). Interestingly, this side-specific distribution of tumor was recapitulated in its metastatic nodal spread; so that right cervical lymph nodes showed only metastatic small cell carcinoma and left cervical lymph nodes only metastatic squamous cell carcinoma. To the best of our knowledge, the present case is the seventeenth reported case of a combined small cell carcinoma of larynx, second case in which individual tumor components were lateralized on either side of larynx, and the first case in which this side-specificity of tumor was reflected in its metastatic neck nodal spread. This report emphasizes the value of accurate pathologic diagnosis including diversity in differentiation and localization of laryngeal tumors, and underscores the need for thorough pathologic examination of bilateral laryngeal tumors. The pre-operative diagnostic yield of small cell carcinoma (pure or combined) can be enhanced by including deeper submucosal biopsies on laryngoscopy in all those cases in which the extent of disease on imaging is disproportionately larger than the apparent mucosal involvement on laryngoscopy. This approach can facilitate selection of neoadjuvant or palliative chemo-radiotherapy in large or unresectable tumors.

Keywords: larynx, combined small cell carcinoma, small cell carcinoma, squamous cell carcinoma, deeper biopsies, nodal metastatic carcinoma

Introduction
Small cell carcinoma neuroendocrine type (SCCNET) is an unusual neoplasm accounting for only 0.5% of all laryngeal carcinomas, and in western countries is often related to smoking and alcohol abuse [1,2]. When SCCNET is associated with a squamous or adenocarcinoma component, these tumors are referred to as combined or composite carcinomas [1,2]. The combined carcinomas are reportedly unusual, represent less than 10% of all the SCCNETs of larynx [2], and are summarized in Table 1. Most of these cases have been associated with a squamous cell carcinoma, either in-situ or invasive. The few reported cases have been mostly males in sixth and seventh decades of life, most commonly occurring in supraglottic region followed by glottis. However, the metastatic pattern of spread of combined carcinomas has not been described accurately with regards to its individual components. In this report, we describe an unusual case of combined carcinoma of larynx, in which the small cell and squamous cell carcinoma components were lateralized to either side of larynx, a pattern which was also reproduced in its metastatic neck nodal spread. The diagnostic, management and histogenetic implications are discussed.

Case presentation
A 59-year-old white male presented with a 5-month history of worsening hoarseness, pro-
Primary combined small cell carcinoma of larynx

Progressive otalgia and hemoptysis. He was also noted to have progressive dysphagia and aspiration with solids. There was no history of weight loss. His past medical history was significant for myocardial infarction and degenerative joint disease with back pain and arthritis. He quit alcohol consumption 20 years ago but had been smoking 3 packs per day of tobacco for 40 years. He had a positive family history of coronary artery disease and cerebrovascular disease but no history of any malignancy in the family. He underwent cervical spine surgery twice in the past and had a chest tube placement for spontaneous pneumothorax.

On laryngoscopic examination, a large fungating tumor mass was noted involving the right pyriform sinus and aryepiglottic fold, obliterating the ventricle. There was impaired mobility of the right true vocal cord, and the airway was noted to be marginal. The CT scan demonstrated a right transglottic mass invading the pre-epiglottic space, as well as with subglottic extension, and crossing midline to the left side. There were multiple metastatic neck nodes at the right 2B, 3 and 4 levels. However, no distant metastases were noted on the chest roentgenogram, abdominal sonogram, and bone scan.

He underwent a total laryngectomy with right hemithyroidectomy and bilateral modified neck dissection. The frozen sections on all the submitted margins were reported as negative for tumor.

Pathologic findings

On gross examination of the laryngectomy specimen, a 3.0 cm x 2.5 cm mass was palpable involving the right epiglottis and upper larynx. Serial sections revealed a large ill-defined 5.3 x 2.9 x 1.5 cm tumor mass located mainly in the right supraglottis and involving a portion of epiglottis. The tumor extended inferiorly to involve right glottis and true vocal cord. The tumor also appeared to cross midline as a plaque like lesion to involve left glottis and true vocal cord. The tumor had variable gross morphology ranging from ulcerated to nodular to plaque-like growth. The tumor infiltrated deeply to involve the thyroid cartilage. Cut surfaces of the submitted right hemithyroid were homogenous and tan-brown, without any gross involvement by the tumor.

Microscopic sections from the larynx revealed a combined tumor, composed predominantly of small cell neuroendocrine carcinoma lateralized to the right side and squamous cell carcinoma to the left side. Majority of the tumor (>90%) involved right supraglottis with slight contiguous extension to left supraglottis, and had a histologic appearance of small cell carcinoma (Figure 1A). In contrast, the smaller plaque like tumor (<10%) involving left glottis showed mainly invasive squamous cell carcinoma with a small focus of in-situ squamous cell carcinoma (Figures 2A and 2B). Small cell carcinoma was deeply invasive reaching up to thyroid cartilage,
whereas squamous cell carcinoma showed relatively superficial stromal invasion without thyroid cartilage involvement. The two tumor components mostly showed a collision phase with distinct boundaries, but with a focus of gradual transition in one of the examined sections (Figure 3). All the surgical margins were free of tumor, however the tumor closely approached (~0.1 mm) the right anterior soft tissue margin. Neck lymph nodes showed metastatic carcinoma bilaterally. In right neck, the metastatic tumor involved 7 out of 14 right level II and 4 out of 6 right level III neck lymph nodes, and represented small cell neuroendocrine carcinoma morphology exclusively (Figure 4A). Right level IIB (14) level IV (11) and superficial (3) lymph nodes were uninvolved. In left neck, only 1 out of 8 level IIB lymph nodes showed metastatic poorly differentiated squamous cell carcinoma (Figure 4B). Left level III (7), IV (4) and paratracheal (3) lymph nodes were all uninvolved. No metastatic small cell carcinoma was identified in the left neck nodes or soft tissue.

Immunohistochemical profile of diffuse synaptophysin positivity in small cell neuroendocrine carcinoma component (Figure 1B) and CK5/6 and p63 positivity in squamous cell carcinoma component in the laryngectomy sections, supported the histologic diagnosis. Immunostains for CK7, CK20 and chromogranin were negative. The discohesive poorly differentiated neoplastic cells in left neck level IIB lymph node showed immune-positivity for pankeratin, but were negative for pan-melanoma, CD45, CD30 and CD68, thereby confirming the histologic impression of metastatic squamous cell carcinoma.

Discussion

Primary laryngeal carcinomas constitute around 2% to 5% of all malignancies worldwide and approximately 12500 new cancer diagnoses in the United States every year [1]. Majority (95%) of the laryngeal carcinomas are primary squamous cell carcinomas. Neuroendocrine tumors of the larynx comprise only about 0.5% of all laryngeal tumors [2]. Pure small cell carcinoma of larynx was first described by Olofsson.
Primary combined small cell carcinoma of larynx

and van Nostrand in 1972 [3], and is a now a well recognized, uncommon entity. However, rarely small cell carcinomas have been reported as primary combined carcinomas of larynx with synchronous admixed squamous cell carcinoma [1,4].

Ferlito et al. [5] first used the term “Combined small cell carcinomas of larynx” to describe these morphologically distinct synchronous tumors showing divergent lineages of differentiation. Gnepp et al. [6] and Gianoli et al. [7] described the presence of mixed squamous cell and small cell anaplastic carcinoma in the larynx as “Composite tumor of larynx”. Mills et al in 1981 [8] studied ultrastructural characteristics in 2 cases of small cell carcinoma of larynx which revealed the presence of both squamous features (intracytoplasmic tonofilaments and desmosomes) as well as dense core granules in the tumor cells. One of their cases also had a biphasic light microscopy consisting of both small cell and squamous cell components.

Based on our review, a total of 16 cases of combined small cell carcinoma have been reported in the literature to date [1, 4-12]. Their main clinico-pathologic characteristics including the pattern of metastatic spread are summarized in Table 1. Majority of these patients were males, in sixth to seventh decade of life. Most common site of origin of the primary tumors appeared to be right hemilarynx involving suraglottic and glottic regions. Review of the metastatic patterns of such combined tumors reveals that most reported cases have had mixed cellular patterns in varying proportions in metastases at different sites.

To the best of our knowledge, the present case is the seventeenth reported case of a combined small cell carcinoma of larynx, second case in which individual tumor components were lateralized on either side of larynx [1,9], and the first case in which this side-specificity of tumor was reflected in its metastatic neck nodal spread (Table 1). Therefore, our case is unique in demonstrating a distinct pattern of metastatic involvement of regional lymph nodes that corresponded to the laterality of the histological components of primary tumor. Moreover, our case clearly showed that the tumor mass and extent of spread was recognized to be much greater on CT scan and on serial sectioning of laryngectomy specimen (transglottic, subglottic and crossing midline), than initially estimated on laryngoscopic examination or on external gross pathologic evaluation. This raises the point that pre-operative diagnostic yield of small cell carcinoma (pure or combined) can be enhanced by including deeper submucosal biopsies on laryngoscopy in all those cases in which the extent of disease on imaging is disproportionately larger than the apparent mucosal involvement on laryngoscopy.

The exact etio-pathogenesis of combined small cell carcinoma is uncertain. However, multiple

Figure 4. (A) Metastatic small cell carcinoma component involving lymph node (H&E x 200). (B) Metastatic squamous cell carcinoma component involving lymph node (H&E x 200).
Table 1. Review of clinicopathologic features of the reported cases of combined carcinoma of the larynx

<table>
<thead>
<tr>
<th>Source</th>
<th>Age/sex</th>
<th>Site</th>
<th>Histologic pattern of primary tumor</th>
<th>Positive lymph nodes</th>
<th>Distant metastasis</th>
<th>Metastatic histologic phenotype</th>
<th>Therapy</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eusebi et al, 1978</td>
<td>63/M</td>
<td>Rt.supraglottis and glottis</td>
<td>HL: SmCC and SCC</td>
<td>+</td>
<td>-</td>
<td>SmCC (LN)</td>
<td>HL + RND</td>
<td>DOD at 24 mths.</td>
</tr>
<tr>
<td>Mills et al, 1983</td>
<td>49/M</td>
<td>Rt. supraglottis and glottis</td>
<td>TLP: kSCC (60%) and SmCC (40%)</td>
<td>+</td>
<td>-</td>
<td>SmCC (1 LN, Rt. thyroid)</td>
<td>TLP+ RND+ Rt. thyroid lobectomy, XRT</td>
<td>NED, at 6 mths.</td>
</tr>
<tr>
<td>Ferlito et al, 1985</td>
<td>50/M</td>
<td>Lt. hemilarynx</td>
<td>TLP: SCC and SmCC</td>
<td>+</td>
<td>NA</td>
<td>SmCC</td>
<td>TLP+ LRND, XRT</td>
<td>DOD at 14 mths.</td>
</tr>
<tr>
<td>Ferlito et al, 1985</td>
<td>54/M</td>
<td>Glottis and sub-glottis</td>
<td>TL: SCC and SmCC</td>
<td>-</td>
<td>-</td>
<td></td>
<td>TL+RND, XRT</td>
<td>NED at 42 mths.</td>
</tr>
<tr>
<td>Ferlito et al, 1985</td>
<td>47/M</td>
<td>Rt.supraglottis and glottis</td>
<td>TL: SCC and SmCC</td>
<td>+</td>
<td>+</td>
<td>Lung, bone, and brain</td>
<td>Chemo, XRT</td>
<td>DOD at 48 mths.</td>
</tr>
<tr>
<td>Ferlito et al, 1985</td>
<td>45/M</td>
<td>Rt.supraglottis and glottis</td>
<td>TL: SCC and SmCC</td>
<td>+</td>
<td>-</td>
<td></td>
<td>Chemo, XRT</td>
<td>DOD at 21 mths. (of SCC of oral cavity)</td>
</tr>
<tr>
<td>Ferlito et al, 1985</td>
<td>56/M</td>
<td>Epiglottis</td>
<td>TL: SCC and SmCC</td>
<td>-</td>
<td>-</td>
<td></td>
<td>Chemo, XRT</td>
<td>NED at 77 mths.</td>
</tr>
<tr>
<td>Gnepp et al, 1983</td>
<td>57/M</td>
<td>Rt. glottis</td>
<td>TLP: SCC and SmCC</td>
<td>+</td>
<td>+</td>
<td>Bone</td>
<td>TLP+ RRND, XRT</td>
<td>DOD at 3.5 mths.</td>
</tr>
<tr>
<td>Cosby and Babin, 1988</td>
<td>56/M</td>
<td>Lt. supraglottis</td>
<td>Bx: PD SCC</td>
<td>+</td>
<td>-</td>
<td>SmCC (LN)</td>
<td>TL+ LRND, Chemo</td>
<td>Lost to follow up during Chemo</td>
</tr>
<tr>
<td>Gianoli et al, 1992</td>
<td>83/M</td>
<td>Rt. supraglottis</td>
<td>Bx: WD k SCC</td>
<td>-</td>
<td>-</td>
<td></td>
<td>TL+ MND</td>
<td>NED at 8 mths.</td>
</tr>
<tr>
<td>Jaiswal and Hoang, 2004</td>
<td>41/M</td>
<td>Lt glottis, Rt hemilarynx</td>
<td>Bx Lt. vocal cord: SCC in situ</td>
<td>NA</td>
<td>-</td>
<td></td>
<td>Chemo, XRT</td>
<td>NED at 8 mths.</td>
</tr>
<tr>
<td>Barbeaux et al, 2006</td>
<td>61/M</td>
<td>Rt. glottis</td>
<td>Bx: Mixed SCC and SmCC</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>-Chemo, XRT; TL+ RND - Chemo</td>
<td>AWRR at 44 mths.</td>
</tr>
<tr>
<td>Barbeaux et al, 2006</td>
<td>54/F</td>
<td>Lt. subglottis</td>
<td>Bx: Mixed SCC and predominant SmCC</td>
<td>-</td>
<td>+</td>
<td>bone, lung, peritoneum, LN</td>
<td>XRT, Chemo</td>
<td>AWD at 36 mths.</td>
</tr>
<tr>
<td>Our case</td>
<td>59/M</td>
<td>Rt.supraglottis, epiglottis and glottis, Lt.glottis</td>
<td>Bx: Mixed SCC and SmCC</td>
<td>+</td>
<td></td>
<td></td>
<td>TL+ BMND + Rt. thyroid lobectomy</td>
<td>Lost to follow up During XRT.</td>
</tr>
</tbody>
</table>

Abbreviations: Rt.: Right; Lt.: Left; LN: lymph node; SMUC: Small cell carcinoma; SCC: Squamous cell carcinoma; WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated; k: keratinizing; Bx: Biopsy; SL: Supralaryngectomy; TL: Total Laryngectomy; HL: Hemilaryngectomy; TLP: Total laryngopharyngectomy; RND: Radical neck dissection; RRND: Right radical neck dissection; LRND: Left radical neck dissection; MND: Modified neck dissection; BMND: Bilateral modified neck dissection; XRT: Radiotherapy; Chemo: Chemotherapy; NED: No evidence of disease; AWD: Alive with disease; AWRR: Alive with recurrent relapses; DOD: Died of disease; mths.: months; NA: not available; M: Male; F: Female.
hypotheses have been proposed to explain combined or mixed tumors. These include pluripotent precursor stem cell origin with subsequent divergent differentiation into Kulchitsky cells, squamous cells, and/or glandular cells [5]. Other theories include neoplastic stem cell differentiating into two or more morphologically and structurally different neoplastic cells. This concept has been proved experimentally [13]. Based on these theories, it appears that combined carcinomas likely arise from neoplastic transformation of a differentiated precursor or a neoplastic stem cell with divergent differentiation potential. Moreover, foci of transition between the two morphotypes, and in-situ squamous component in this case suggest that combined tumors may represent examples of extreme tumor heterogeneity or dedifferentiation.

In spite of the rarity of these tumors, the biological behavior of combined small cell carcinomas (neuroendocrine type) of the larynx appears to be comparable to that of the pure laryngeal small cell carcinoma, neuroendocrine type. The dominant prognostic impact of small cell carcinoma component in combined tumors is likely due to its rapid growth, increased bulk and aggressive metastatic potential. The apparent clinical course of all the 16 reported cases of laryngeal combined carcinomas was fatal with early lymph nodal and distant spread in 9 cases. Although occasional patients survived up to 3 years following pathologic diagnosis, majority of these patients died within 2 years [3,5,8]. The deeply invasive nature of small cell carcinoma in this case and in reported cases suggests that deep biopsies at the sites of dominant disease on imaging may be needed to establish correct pre-operative diagnosis and allow proper selection of neoadjuvant or palliative chemo-radiotherapy in large or unresectable tumors.

Precise and detailed examination of laryngectomy specimens is very important for the appropriate treatment as well as prognosis, and one of the most important component is reporting the pattern of metastatic spread. Squamous cell carcinomas of larynx may spread directly to contiguous structures, or via lymphatic and blood vessels to lymph nodes and more distant sites. On the other hand, small cell carcinoma is an aggressive tumor with early regional and distant metastases. Almost half of patients present with positive cervical lymph nodes and about 60-90% develop distant metastases [2]. The tumor spread in vast majority of cases is by the direct extension, lymphatics and by blood stream in more advanced cases.

Pressman et al. in 1981 [14] demonstrated that larynx must be considered a highly compartmentalized organ in which right and the left halves except their mucosal surfaces, are physiologically and anatomically separated from each other. Lymphatic drainage from all levels, of larynx is mainly to ipsilateral cervical lymph nodes, except subglottic area which has a bilateral lymphatic distribution. Their basic study on anatomy of larynx concluded that direct, contiguous spread of laryngeal cancer from one side to the other is via interlacing superficial or mucosal lymphatics that spread over the entire mucosal surface without limitation. On the other hand, cancer spread to the ipsilateral lymph-nodes is limited by the fact that submucosal or deep lymphatics form an independent network on each side without any crossover beyond the midline. Based on this study, the side-specific pattern of metastatic neck nodal spread of the tumor in our case can be explained by the independent spread of deeply invasive tumor of both histologic types separately in either hemilarynx along submucosal or deep lymphatics. This finding raises the consideration that primarily supraglottic or transglottic carcinomas such as our case should be substaged based on involvement of one or both sides similar to the current AJCC substaging of T1 glottic carcinomas into T1a and T1b based on involvement of one or both vocal cords.

Conclusion

Herein we report the seventeenth case of a combined small cell carcinoma of larynx, second case in which individual tumor components were lateralized on either side of larynx [1,9], and the first case in which this side-specificity of tumor was reflected in its metastatic neck nodal spread. The predominance of the biologically aggressive component in the combined tumor may impact overall survival. Pathologists need to examine adequate sections from either side of laryngectomy specimens. This is particularly relevant to establishing the correct diagnosis of the uncommon combined carcinomas of larynx. The gradual transition between the two morphotypes, and in-situ squamous component in this
case suggest that combined tumors may represent examples of extreme tumor heterogeneity or dedifferentiation. Consideration may be given to substage supraglottic or transglottic carcinomas based on tumor laterality akin to T1 glottic carcinomas in AJCC system. Finally, the preoperative diagnostic yield of small cell carcinoma (pure or combined) can be enhanced by including deeper submucosal biopsies on laryngoscopy in all those cases in which the extent of disease on imaging is disproportionately larger than the apparent mucosal involvement on laryngoscopy. This approach can facilitate selection of neoadjuvant or palliative chemoradiotherapy in large or unresectable tumors.

Please address correspondence to: Suash Sharma, MD, Department of Pathology (Anatomic Pathology), Medical College of Georgia, Augusta, GA 30912. Tel: 706-721-9362, E mail: susharma@mcg.edu

References