Case Report

Primary Small Cell Carcinoma of the Hypopharynx: A Report of Two Cases and Review of Nine Additional Cases

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Objective. Two patients with primary small cell carcinoma (SmCC) of the hypopharynx, an extremely rare site for the occurrence of SmCC, are reported and nine additional well-documented cases are reviewed. Methods. Case report and review of the literature concerning primary SmCC of the hypopharynx. Results. On the final analysis, we reviewed eleven cases of primary SmCC of the hypopharynx. The tumors contained mixed elements of SmCC and squamous cell carcinoma (SCC) in six (55%) of eleven patients. Out of eleven patients, two patients had distant metastasis at the initial presentation. Even though nine patients presented with locoregional disease, development of distant metastasis after treatment was seen in five patients (56%), whereas there was no report of treatment failure on the primary site. To achieve more than two-year survival, patients should have received more than 4 cycles of chemotherapy. Conclusion. We report two cases of primary SmCC of the hypopharynx with a review of the literature. In more than half of the cases, combined carcinomas with SCC are seen. Because this tumor has a strong propensity for distant metastasis even in patients with clinically localized tumor, new powerful systemic agents should be explored.

1. Introduction

Small cell carcinoma (SmCC) is a common pulmonary neoplasm, which comprises approximately 10% of all pulmonary carcinomas in Japan [1]. It is increasingly recognized that SmCC may also arise in extrapulmonary sites throughout the body, commonly in the esophagus, large bowels, the bladder, the uterine cervix, and the larynx [2]. Similar to small cell lung carcinoma (SCLC), extrapulmonary SmCC (EPSmCC) is aggressive with rapid local progression and early regional and distant spread [2]. The incidence of EPSmCC is much lower than for SCLC accounting for only 6% of SmCCs [3, 4]. Most available literature on this condition exists in the form of case reports and retrospective series. The role of local and systemic therapies for EPSmCC is still not clearly defined [3, 4].

The first case of EPSmCC arising in the head and neck was a primary tumor in the larynx reported by Olofsson and Van Nostrand in 1972 [5]. Since then, it has been reported to occur in multiple sites of the head and neck throughout the upper aerodigestive tract, including the larynx, paranasal sinuses, and salivary glands [6]. However, in the head and neck, the hypopharynx is an unusual site for this tumor. Owing to the paucity of cases of primary SmCC of the hypopharynx, little information is available concerning their diagnosis and management. We report two cases of SmCC arising from the hypopharynx that occurred in a 75-year-old man and a 73-year-old man, along with a review of the available literature on primary SmCC of the hypopharynx.

2. Case Reports

2.1. Case 1. A 75-year-old man with 30 pack-years smoking history consulted his regular otolaryngologist because of a 3-month history of dysphagia. Laryngoscopy revealed a large tumor in the right pyriform sinus (Figure 1). A biopsy of the tumor showed features of neuroendocrine tumor suggesting SmCC and additional component of squamous cell carcinoma (SCC) (Figure 2). Fludeoxyglucose F 18 positron emission tomography (18F-FDG-PET) analysis disclosed multiple
positive accumulations in vertebral bones besides the right pyriform sinus and bilateral neck lymph nodes. As a result, his tumor was the primary hypopharyngeal SmCC and classified as cT2N2cM1 (7th edition of the UICC and AJCC staging system). Chemotherapy was applied with 4 cycles of etoposide and cisplatin as a standard regimen usually intended for treatment of aggressive SCLC. The patient partially responded to the treatment but finally succumbed to the progression of the cancer six months after the treatment.

2.2. Case 2. A 73-year-old man, with no history of smoking, presented with a two-month history of progressive dysphagia. Fiberscopic examination revealed a large mass arising from the hypopharynx with normal vocal cord movement (Figure 3). A biopsy of the tumor revealed that the tumor had features of neuroendocrine tumor suggesting pure SmCC. Magnetic resonance imaging (MRI) studies with intravenous contrast revealed that the tumor occupying the right pyriform sinus extended to the cervical esophagus with the right cervical lymph node metastases (Figure 4). 18F-FDG-PET analysis indicated a positive accumulation in the hypopharynx and the right neck and no evidence of pulmonary primary or distant metastases. On the basis of these clinical findings, the final diagnosis was made to be primary SmCC of the hypopharynx classified as cT3N2bM0 (7th edition of the UICC and AJCC staging system). As the tumor completely obstructed the hypopharynx, he was not able to eat liquid food or even receive a nasogastric tube placement. Because he had been suffering from malnutrition and being at risk for aspiration, he was considered as a high-risk candidate for chemotherapy or chemoradiotherapy. As he desired to resume eating as soon as possible at the sacrifice of his larynx, total pharyngolaryngectomy with jejunal autotransplant reconstruction was performed. On gross examination of the total pharyngolaryngectomy specimen, 5.5 cm × 2.6 cm × 4.0 cm mass located mainly in the right pyriform sinus was identified. The tumor extended inferiorly to involve the cervical esophagus. Histopathological examination showed the tumor was composed of two separate patterns which were SmCC lateralized to the pharyngeal side and SCC to the esophageal side. SCC deeply infiltrated beyond the underlying muscle layer, whereas SmCC showed relatively superficial stromal invasion without the muscle involvement. Both tumor components showed clear boundaries, but a focus of gradual transition was seen. In right neck, the metastatic tumor involved 2 out of 11 level II nodes, 2 out of 9 level III nodes, 1 out of 8 level IV nodes, and 1 out of 11 level VI nodes. Microscopic sections of the metastatic nodes also revealed combined SmCC and SCC. No metastatic lymph node was identified in the left neck. Immunohistochemical staining panel showed a diffuse positive reaction to synaptophysin and chromogranin A in SmCC component in both primary and metastatic sites. The cells from this component also showed positive reactions to CD56 and thyroid transcription factor 1 (TTF-1). The cells from the SCC component showed positive reactions to p63 and p40, while synaptophysin, chromogranin A, CD56, and TTF-1 were negative. The staining patterns of immunohistochemical study allow confirmation of combined small cell neuroendocrine differentiation and SCC in this tumor (Figure 5). After surgery, the patients received 4 cycles of systemic chemotherapy with carboplatin and etoposide at 4-week interval. Although the surgical margins were microscopically tumor-free, postoperative local radiation at a dose of 60 Gy and prophylactic brain irradiation at a dose of 25 Gy in 10 fractions were administered. At the 8-month follow-up, multiple pulmonary recurrence developed and the patient received salvage chemotherapy with 7-ethyl-10-[[4-(1-piperidino)-1-piperidine] carbonyloxyacamptothecin (CPT-II). However, Grade 3 CPT-II-related diarrhea at the first cycle resulted in the discontinuation of the therapy. Nevertheless, the patient was alive with disease for 26 months after the initial treatment.

3. Systematic Review of the Literature

We used the PubMed database for articles published up to May 2016 using the following relevant keywords: hypopharynx and (“small cell carcinoma” or “oat cell carcinoma” or “neuroendocrine carcinoma”), mixed with a hand search of reference sections of relevant papers, we found thirteen cases [7–18] of the primary hypopharyngeal origin since the first case was described in 1980 [7]. However, four cases [13–15, 17] were excluded from this study because they had no firm histopathological diagnosis for SmCC. On the final analysis, we reviewed nine well-documented cases of primary SmCC of the hypopharynx combined with the data from our patient. For each patient, information was collected on age at diagnosis, sex, smoking history, staging, presenting symptom, disease extent, subsites of the hypopharynx, histology, treatment modalities, and prognostic outcome (Table 1). On the basis of the analysis, out of 11 patients with SmCC of the hypopharynx, 7 patients had disseminated disease throughout the course.

4. Discussion

EPSmCC is a distinct rare entity accounting for 6% of all SmCCs [3, 4] and approximately 7 to 11% of cases involve the head and neck [3, 4]. SmCCs of the larynx are well...
Figure 2: Histopathological and immunohistochemical features of the combined SmCC and SCC of the hypopharynx. (a) This tumor consists of a mixture of SmCC (center, arrow) and SCC (peripheral) (hematoxylin-eosin, original magnification 400x). (b) The p63 reactivity is seen in the nuclei of the cells of SCC but is not seen in SmCC component. (c) The CD56 reactivity in SmCC component is seen but is not seen in SCC component. (d) Chromogranin A shows positive cytoplasmic staining in SmCC component.

Figure 3: Fiberscopic view of the hypopharynx filled with a large soft tissue mass with necrotic appearance (arrow).

investigated as to their clinical features because the larynx is the most common affected site in the head and neck and to date, there were over 160 reported cases [6]. On the contrary, the hypopharynx is an extremely rare site for the occurrence of SmCC as shown in this study. The present study showed that the clinical features of SmCCs were almost indistinguishable from SCC in this site, because presenting symptoms and clinical appearance are similar to SCC. The majority of those patients were males and presented after the age of 60 years with dysphagia and cervical mass. EPsmCC was reported as having a weak association with tobacco use [6]. All the tumors involved the pyriform sinus, where there is an area of predilection for SCCs. Therefore, a definitive diagnosis of SmCC should be made histopathologically. When specific structures of SmCC are histologically found in a tumor, particularly from an unusual location, such as the hypopharynx, routine immunohistochemical staining contributes to appropriate diagnosis and continuous early treatment as seen in the present report.

Interestingly, EPsmCC is associated with other histologic tumors like a SCC or an adenocarcinoma, referred to as combined carcinomas, because it might derive from a pluripotent stem cell that develops neuroendocrine features or a neoplastic stem cell with divergent differentiation potential [19]. The combined carcinomas are reportedly unusual representing less than 10% of SmCC of the larynx [20]. However, the present study showed that more than half of the patients with SmCC of the hypopharynx had tumors which contained mixed elements of SmCCs and SCCs. In
Figure 4: Preoperative cross-sectional MRI of the neck. (a) An enhanced sagittal image shows the tumor extending to the cervical esophagus (arrow). (b) An enhanced coronal image shows the large tumor completely occupying the hypopharyngeal space (black arrow). Note multiple lymph node metastases in the right neck (white arrows).

Figure 5: Histopathological and immunohistochemical features of the combined SmCC and SCC of the hypopharynx. (a) SmCC component coexisting with SCC component accompanying keratinization (arrow) (hematoxylin-eosin, original magnification 200x). (b) The CD56 reactivity in SmCC component is seen but is not seen in SCC component. (c) The p63 reactivity is seen in the nuclei of the cells of SCC but is not seen in SmCC component. (d) Synaptophysin shows positive cytoplasmic staining in SmCC component.
| Number | Author            | Year | Age/sex | Smoking | Stage (TNM)          | Main symptom                          | Site             | Extent of lesion at presentation | Histology | Locoregional TX | Adjuvant systemic TX | PCI | Metastases (observed throughout the course) | Follow-up                           |
|--------|-------------------|------|---------|---------|----------------------|---------------------------------------|------------------|----------------------------------|------------|------------------|----------------------|-----|-------------------------------------------------|-------------------------------------|
| (1)    | Ferlito and Polidoro | 1980 | 57/M    | +       | T1N2bM0              | Neck mass                             | PS               | Locoregional                     | Combined with SCC | Radical S + RT | None                | −    | Cervical nodes, bone, soft tissue             | Died of cancer 3.5 months after diagnosis |
| (2)    | Mills et al.      | 1983 | 49/M    | +       | NA                  | Neck mass, dysphagia, weight loss     | PS               | Locoregional                     | Combined with SCC | Radical S + RT | None                | −    | Cervical nodes                                         | Alive free of cancer 6 months after treatment |
| (3)    | Baugh et al.      | 1985 | 63/F    | −       | T4a, more than N2c, M0 | Dyphagia, cervical mass               | PS               | Locoregional                     | Pure SmCC         | Incomplete S | Many times (more than four) | −    | Cervical nodes                                         | Alive free of cancer 55 months after diagnosis |
| (4)    | Baugh et al.      | 1985 | 35/M    | −       | T3N2aM0              | Dysphagia, weight loss                | Base of tonsil to PS | Locoregional                     | Pure SmCC         | RT               | none                | −    | Cervical node                                         | Alive free of cancer 21 months after diagnosis |
| (5)    | Gaba et al.       | 2005 | 65/M    | ex+     | T4aN1M0              | Dysphagia, weight loss                | PS               | Locoregional                     | Pure SmCC         | Incomplete S + CRT | Many times (more than four) | −    | Cervical node                                         | Alive free of cancer more than 24 months after diagnosis |
| (6)    | Sano et al.       | 2005 | 67/F    | +       | NA                  | Neck mass                             | PS               | Locoregional                     | Pure SmCC         | RT               | Less than four                     | −    | Cervical node, lung                                 | Died of cancer 13 months after diagnosis |
| (7)    | Uwa et al.        | 2013 | 73/M    | +       | T4aN2bM0             | Neck mass                             | PS               | Locoregional                     | Combined with SCC | Radical S       | None                | −    | Cervical and mediastinum nodes, liver, lung       | Died of cancer 9 months after treatment |
| (8)    | Bayram et al.     | 2015 | 50/M    | +       | T4aN2bM1 (lung)      | Severe respiratory distress           | PS               | Locoregional-distant             | Pure SmCC         | Incomplete RT       | Less than four                     | −    | Cervical and lung                                | Alive free of cancer 15 months after treatment |
| (9)    | Misawa et al.     | 2016 | 74/M    | +       | T2N0M0               | Throat pain, hoarseness               | PS               | Local                            | Combined with SCC | CRT             | None                | −    | Bone                                              | Died of cancer 7 months after treatment |
| (10)   | Nakahira et al.   | 75/M | +       | T2N2cM1 (bone)      | Dysphagia                            | Locoregional-distant                  | PS               | Combined with SCC                | None                | Many times (more than four) | −    | Bone, liver                                        | Died of cancer 6 months after treatment |
| (11)   | Nakahira et al.   | 73/M | −       | T3N2bM0             | Dysphagia                            | Locoregional                          | PS               | Combined with SCC                | Radical S + RT    | Many times (more than four) | +    | Cervical nodes, lung                               | Alive with cancer 26 months after treatment |

TX: therapy, PCI: prophylactic cranial irradiation, NA: not available, PS: pyriform sinus, S: surgery, RT: radiation therapy, and CRT: concurrent chemoradiotherapy.
lesions who received more than 4 cycles of chemotherapy after chemotherapy. In contrast, patients with locoregional (maximum 4–6 cycles as a standard) might lead to a failure of repetition of chemotherapy than recommended cycles composed of carboplatin and etoposide. Less frequency patients, 3 patients did not receive any chemotherapy and became disseminated status early after treatment. Out of 5 had clinically localized disease at diagnosis, 5 of 9 patients of limited stage. In the present study, although 9 patients lung carcinoma; http://www.nccn.org) recommend management guidelines for small cell lung carcinoma (National chemotherapy [22]. The latest evidence-based clinical management of SCLC. Although rare, some patients with EPSmCC will develop brain metastasis. To clarify the role of PCI for EPSmCCs, a prospective multicenter research using an exhaustive gene expression analysis might be needed to find biological differences between patients with brain metastasis and those with long-term remission.

5. Conclusion

We report two cases of primary SmCC of the hypopharynx with review of the literature. Combined carcinomas with SCC are usually seen. Because primary SmCCs of the hypopharynx have a strong propensity for distant metastasis even in patients with clinically localized tumor, treatment with radical surgery alone may control the primary tumor but offer less chance for cure. Improvement of survival might be achieved by the emergence of new powerful systemic agents.

Conflicts of Interest

The authors declare that there are no actual or potential conflicts of interest in relation to this article.

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