Primary small cell neuroendocrine carcinoma of the oral cavity: A case report and review of the literature

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Abstract. Small cell neuroendocrine carcinoma (SNEC) of the oral cavity is a rare and distinctive tumor with aggressive clinical behavior. Thus far, only a small number of cases have been reported and no definitive standard treatment strategy has been determined. The current study reports a case of oral SNEC arising in the lower gingiva in a 73-year-old male. Computed tomography displayed a relatively well-defined mass measuring 2.8x2x1.4 cm in size. The mass was located in the buccal side of the right mandibular posterior gingiva and exhibited no bony involvement. Histopathological examination revealed a proliferation of small cells with ovoid- to spindle-shaped nuclei, fine granular chromatin, inconspicuous nucleoli, scant cytoplasm and high mitotic activity. Immunohistochemically, the tumor cells were positive for cytokeratin AE1/AE3, chromogranin A, synaptophysin and neuron-specific enolase. Surgical resection and radical neck dissection were performed prior to the administration of adjuvant chemotherapy with a combination of cisplatin and etoposide. No evidence of local recurrence or metastasis was observed at 14 months post-surgery.

Introduction

Small cell neuroendocrine carcinoma (SNEC), which is the most common type of pulmonary neoplasm, is an aggressive malignancy with a tendency for regional and distant metastasis. Extrapulmonary SNECs represent 2.5-5% of all SNECs (1,2), of which head and neck cases comprise 10-16%. The larynx is the most commonly affected site of head and neck SNEC, followed by the salivary glands and the sinonasal region (1-3). SNEC of the head and neck exhibits a preference for males, with a peak incidence from the fifth to seventh decades of life, and occurs most frequently in men with a heavy smoking background (3-9). Patients typically present with painless masses and symptoms similar to other mucosal-based carcinomas at such sites. The tumors usually develop rapidly over several months, and cervical nodal metastases are very common (3,9). Paraneoplastic manifestations have been described in a few cases (3,6,9).

The diagnosis of SNEC is based on morphology and confirmation of origin by specific stains (10-12). In general, SNEC tumors are composed of sheets and nests of round to spindle-shaped cells with dense nuclei, fine granular nuclear chromatin, inconspicuous nucleoli and scant cytoplasm. In addition, cell necrosis and mitotic activity are commonly observed. The majority of SNEC tumor cells are immunoreactive for cytokeratins and epithelial membrane antigen, as well as the neuroendocrine markers, neuron-specific enolase, synaptophysin, chromogranin A, CD56 and CD57 (13-15). A thorough clinical evaluation of the patient is necessary to exclude the possibility of a metastatic SNEC (3,12). Although some differences may exist in the clinical behavior of tumors arising from different subsites, in general, SNEC of the head and neck have a tendency for aggressive local invasion and a strong propensity for both regional and distant metastasis (3,16). Treatment may include surgical resection, radiotherapy, chemotherapy, or some combination of these modalities (3,16). The overall prognosis of head and neck SNEC is poor (3,9,16).

Primary SNEC of the oral cavity is a rare neoplasm with only five cases reported in the English-language literature to date (4-8). This paucity of data means that a definitive therapeutic strategy has yet to be determined. The present study reports a rare case of SNEC of the gingiva and reviews the clinicopathological characteristics of this uncommon tumor type.

Case report

A 73-year-old male was referred to the Department of Pathology at the School and Hospital of Stomatology of Wuhan University for the evaluation of a swelling of the lower gingiva that had gradually increased in size over the preceding 12 months. The patient reported a >50-year history of smoking

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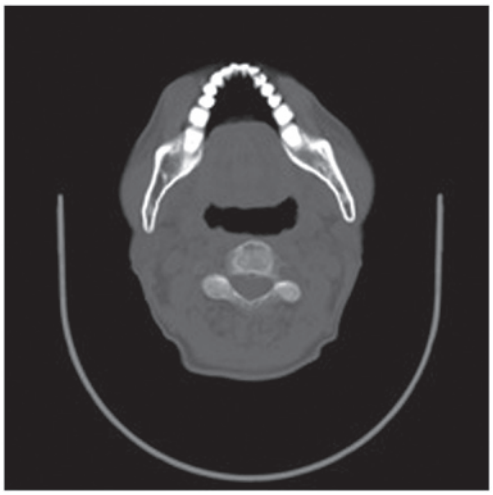

Figure 1. Computed tomography image demonstrating a soft-tissue mass measuring 2.8x2x1.4 cm in size, located in the buccal side of the right mandibular posterior gingiva.

(~1.5 packs per day) and alcohol consumption. Furthermore, a physical examination disclosed a non-tender mass on the buccal gingiva, extending from the right lower first premolar to the right lower second molar. The mass was hard and elastic on palpation, and the overlying mucosa exhibited mild hyperemia. In addition, panoramic radiography revealed no bony involvement. Computed tomography displayed a relatively well-defined mass, measuring 2.8x2x1.4 cm in size, located in the buccal side of the right mandibular posterior gingiva (Fig. 1). Imaging features and clinical examination revealed no significant lymphadenopathy, and laboratory findings, including a complete blood count, blood biochemistry and urine analysis, were within normal limits. An additional computed tomography image of the patient's chest and abdomen, and a bone scan, revealed no abnormalities. Thus, a clinical diagnosis of epulis was determined. An incisional biopsy was performed under local anesthesia. Histological examination of the biopsy identified a malignant neoplasm consisting of small cells with ovoid- to spindle-shaped nuclei, fine granular chromatin, inconspicuous nucleoli and scant cytoplasm (Fig. 2A). The tumor cells were arranged in solid nests, sheets and cords, with frequently occurring brisk mitotic figures and areas of necrosis (Fig. 2B). Immunohistochemically, the tumor cells were positive for cytokeratin AE1/AE3, chromogranin A (Fig. 3A), synaptophysin (Fig. 3B) and neuron-specific enolase. By contrast, the cells were negative for S-100, vimentin, smooth muscle actin, human melanoma black-45, leucocyte common antigen, cluster of differentiation (CD)99, CD56, thyroid transcription factor-1 and cytokeratin 20. The Ki-67 labeling index was 70%. In consideration of these findings, the patient was diagnosed with primary SNEC of the gingiva.

Subsequently, the patient underwent a wide resection of the gingival tumor with a partial mandibulectomy and radical neck dissection under general anesthesia. No tumor was identified in any of the resected regional lymph nodes and the post-operative course was uneventful. The patient received six cycles of adjuvant chemotherapy with cisplatin (80 mg/m^2) and etoposide (100 mg/m^2), administered on days 1-3 of a 21-day cycle, which was well-tolerated. At 14 months post-surgery,

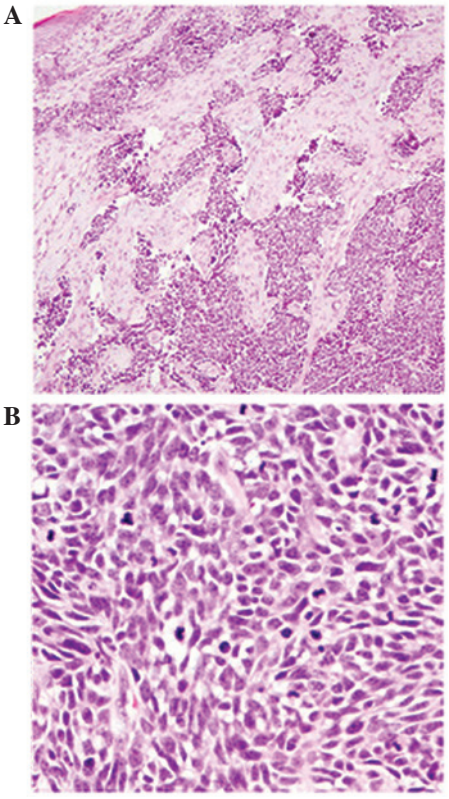

Figure 2. (A) Histological examination demonstrating the infiltrated tumor under the oral epithelium, with cells growing in nests and cords (hematoxylin and eosin stain; magnification, x100). (B) High-power histological examination revealing ovoid- to spindle-shaped nuclei, fine granular chromatin, inconspicuous nucleoli, scant cytoplasm and high mitotic activity in the tumor cells (hematoxylin and eosin stain; magnification, x400).

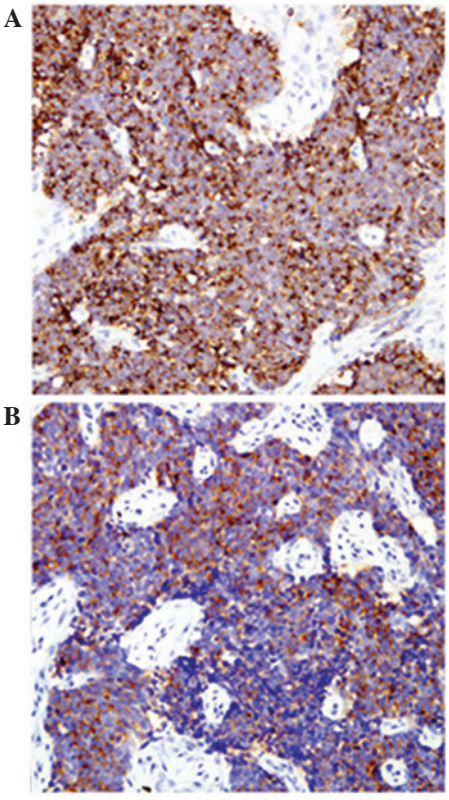

Figure 3. Immunohistochemical staining of the tumor cells revealing positive staining for (A) chromogranin A and (B) synaptophysin (magnification, x200).

the patient remained clinically well with no evidence of local recurrence or metastasis, which was confirmed by computed tomography imaging of the head, neck and chest, and a bone scan.

The present study was approved by the Ethics Committee of the School and Hospital of Stomatology (Wuhan University, Wuhan, China) and written informed consent was obtained from the patient.

Discussion

Neuroendocrine carcinomas constitute a heterogeneous group of neoplasms that have a wide range of histomorphological features and clinical behaviors. According to the 2005 World Health Organization classification of head and neck tumors, neuroendocrine carcinomas may be subclassified into typical carcinoid, atypical carcinoid and SNEC, corresponding to well-, moderately- and poorly-differentiated neuroendocrine carcinoma, respectively (9). However, in the past 10 years, novel data has supported the recognition of large cell neuroendocrine carcinoma as a distinctive type of high-grade carcinoma in the head and neck (10,11). Neuroendocrine carcinomas of the oral cavity, such as large cell neuroendocrine carcinoma, were not incorporated into the 2005 classification of neuroendocrine neoplasms of the head and neck due to their rarity. In 2007, Mahomed (12) proposed to classify oral neuroendocrine carcinomas into typical carcinoid, atypical carcinoid, SNEC (including Merkel cell type and pulmonary type) and large cell neuroendocrine carcinoma. The true origin of oral neuroendocrine carcinomas remains unclear. As neuroendocrine cells are typically found in the oral squamous epithelium, various studies have proposed that these cells are the origin of oral neuroendocrine carcinoma; however, others consider that they derive from pluripotent cells within the squamous epithelium and the minor salivary gland (12-14).

Primary SNEC of the oral cavity is a rare disease entity, with only six cases (including the present case) reported in the English-language literature thus far (4-8). All six cases occurred in men, with a mean age of 68 years (range, 59-76 years). Three cases arose in the tongue, two in the gingiva and one in the cheek. The majority of patients were reported to have a history of heavy tobacco smoking. Furthermore, cervical lymph node metastases were reported in four cases, including three presenting at the time of the initial diagnosis, and distant metastases were reported in three cases. Of the four patients with available follow-up data, two succumbed to the disease 10 and 30 months after diagnosis, one was alive with disease 16 months after the initial manifestation, and one was alive with no evidence of disease 14 years after surgery.

The diagnosis of SNEC depends on the pathology and immunohistochemistry of the tumor. The histological characteristics are those of classic small cell carcinoma, consisting of tightly packed cells with little cytoplasm, angulated hyperchromatic nuclei with fine granular chromatin, inconspicuous nucleoli and nuclear molding. Necrosis is typically extensive and the mitotic count is high (11,12,15). Immunohistochemically, the tumors are positive for neuroendocrine markers, in particular synaptophysin and chromogranin A, and are broadly positive for low molecular weight cytokeratins (15). The differential diagnosis for SNEC of the oral cavity includes typical and atypical carcinoids, large cell neuroendocrine carcinoma, Merkel cell carcinoma, malignant melanoma, malignant lymphoma, and metastatic SNEC. Furthermore, a high mitotic index and extensive necrosis distinguish SNEC from typical and atypical carcinoids. In contrast to SNEC, the neoplastic cells in large cell neuroendocrine carcinoma frequently contain a relatively large and/or polygonal cytoplasm, and typically have vesicular chromatin and prominent nucleoli. In addition, cytokeratin 20 positivity is a specific marker for Merkel cell carcinoma and thus, is valuable for discriminating it from SNEC. In the present case, diagnoses of malignant melanoma and malignant lymphoma were dismissed due to negative results for HMB-45, S-100 and leucocyte common antigen expression. Similarly, the possibility that the current tumor was a metastatic SNEC was dismissed, as extensive clinical investigation failed to detect a primary tumor site.

Due to the paucity of reported cases of oral SNEC, there is a definitive lack of standard protocol for the management of this type of tumor. As SNEC is an aggressive malignancy with high rates of local recurrence and metastatic spread, multimodal therapy, including radical surgery, chemotherapy and radiotherapy, is required. However, numerous patients exhibit disseminated disease at the time of diagnosis, thus, undergoing radical surgery is not feasible. In these cases, therapeutic radiotherapy and chemotherapy are advocated (16). The chemotherapeutic regimen for small cell carcinoma of pulmonary origin, which typically includes cisplatin and etoposide, has been used for the treatment of extrapulmonary lesions (2,3,16). The current case was considered to be operable as the patient presented with a single localized gingival lesion. Therefore, surgical treatment was initially performed, followed by the administration of cisplatin and etoposide adjuvant chemotherapy. The patient was free of disease at 14 months post-surgery. However, regular long-term follow-up is required to detect any local or distant recurrence.

In conclusion, the current study presents a rare case of SNEC of the oral cavity. Although intraoral occurrences are rare, clinicians should be aware of this possibility, particularly in elderly men with a history of heavy smoking. The correct diagnosis was formed through the combination of morphological and immunohistochemical evaluations. In addition, a thorough clinical evaluation of the patient was necessary to exclude a diagnosis of a metastatic tumor. Due to the paucity of studies, the standard treatment protocol for patients with oral SNEC remains uncertain; however, surgery combined with adjuvant chemotherapy may be an optimal management strategy for patients with localized lesions.

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