Open Journal of
Clinical & Medical
Case Reports

Volume 2 (2016)
Issue 5

ISSN 2379-1039

# Successful Chemoradiotherapy for Neuroendocrine Tumor grade 3 arising from the Mandibular Gingiva: A Case Report and Literature Review

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## Abstract

Extrapulmonary small cell carcinoma is a kind of neuroendocrine tumor grade 3 (neuroendocrine carcinoma). This is a rare malignant neoplasm, and no definitive treatment has been recommended. A 68-year-old man had pain and swelling in his left mandibular gingiva. Computed tomography indicated the left mandibular gingival tumor with the mandibular bone invasion and the submandibular lymph node metastasis. Histological examinations of the tumor revealedthe tumor cells were morphologically similar to small cell carcinoma, and immunohistochemically negative for chromogranin A, synaptophysin, but positive for PGP9.5.He was diagnosed with neuroendocrine tumor grade3 (UICC-TNM cT4aN1M0 Stage IVa). Chemotherapy, consisting of cisplatin (80mg/m$^2$ day1, every 3 weeks) and etoposide (100mg/m$^2$ day1-3, every 3 weeks), and concurrent radiotherapy (total of 60Gy) were administered. After chemoradiotherapy he achieved a complete response(CR). The present case demonstrated that extrapulmonary neuroendocrine tumor of mandibular gingiva could be successfully treated by systemic chemoradiotherapy.

## Keywords

Extrapulmonary neuroendocrine tumor; Mandibular gingiva; Chemoradiotherapy; Cisplatin; Etoposide; Complete response;

## Introduction

Neuroendocrine tumor is defined as epithelial neoplasm with neuroendocrine differentiation [1]. Neuroendocrine tumor arises in most organs and has characteristics of the site of origin [1-5]. Since the first description of neuroendocrine tumor in 1930s [6], many studies about neuroendocrine tumor in each organ had been carried out and various different diagnostic criteria were proposed [2], however, they resulted in confusions [1]. Updated classification of neuroendocrine tumor was issued by the World Health Organization (WHO) in 2010 [2, 3, 7]. According to this, neuroendocrine tumor is classified based on its differentiation, which refers to the extent of cancerous, neoplastic, or resemble normal cells [8]. Well differentiated neuroendocrine tumor cells produce large amounts of secretory granules with diffuse expression of neuroendocrine markers [8]. In contrast, poorly differentiated neuroendocrine tumor cells show atypical, sheet-like, diffuse and irregular nuclei, less cytoplasmic secretory granules, and limited

biomarker expression [2, 9-11]. Well differentiated neuroendocrine tumor is classified to the low grade (grade1) and the intermediate grade (grade2) based on their biologic aggressiveness measuring the rate of proliferation [1, 8, 11]. Poorly differentiated neuroendocrine tumor is usually high grade (grade 3), and it is named neuroendocrine carcinoma [1, 2, 7, 11]. High grade (grade 3) neuroendocrine tumors include small cell carcinoma and large cell neuroendocrine carcinoma variants, and the small cell carcinoma mostly arises from lungs.

Extrapulmonary small cell carcinoma is a rare neuroendocrine tumor grade3 arising from outside of the lungs, and accounts for 2.5-5.0% of all small cell carcinomas in the United States [15, 16]. Because of its low incidence, the standard treatment of extrapulmonary small cell carcinoma has not been established [17]. Since the characters of morphology, immunohistochemistry and ultrastructure of extrapulmonary small cell carcinoma are similar to those of small cell lung carcinoma [9], extrapulmonary small cell carcinoma is considered to potentially share common features with small cell lung carcinoma [18]. For this reason, extrapulmonary small cell carcinoma has been treated similarly to small cell lung carcinoma [6]. However, the current studies indicated that the primary site affects prognosis of extrapulmonary small cell carcinoma [15] and significant molecular differences exist between small cell lung carcinoma and extrapulmonary small cell carcinoma, which might cause distinct clinical courses. Whereas mean survival time of extrapulmonary small cell carcinoma patients with all stages and primary sites has been reported to be 20 months and a 5-year overall survival (OS) of them was as low as 8% despite multimodality treatment [19], treatment outcomes are significantly different depending on the primary sites. For example, gynecologic and head and neck tumors were associated with better overall survival [9, 15, 17, 20-21]. As the differences between small cell lung carcinoma and extrapulmonary small cell carcinoma emerge, moreover depending on their primary sites, it might not be enough to follow therapeutic strategies of small cell lung carcinoma, and adequate therapy to each case should be performed. We report here a rare case of extrapulmonary small cell carcinoma arising from the mandibular gingiva, which was achieved a complete response with chemoradiotherapy. The present report might be helpful for future development of therapies of extrapulmonary small cell carcinoma.

## Case Report

A 68-year-old male was admitted to the dental clinic because he had suffered from pain and swelling of his left mandibular gingiva from the middle of August 201x. Administration of antibiotics and dental extraction of foreteeth of the lower left jaw did not ameliorate his symptoms. He was referred to the department of dental surgery of our hospital in September 201x. His vital sign was within normal limits, and his Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) was 0. His father had history of cancer of the floor of mouth. Computed tomography(CT) and magnetic resonance imaging(MRI) revealed that the tumor, of which the major axis was 3.6 cm (Figure1-a), invaded the left mandibular bone (Figure1-b) and metastasized to the submandibular lymph node(Figure1-c). Fluorodexyglucose-positron emission tomography (FDG-PET) showed the primary tumor and a lymph node metastasis to be metabolically active, but no other metastatic lesion was identified. Histological examination of the biopsy specimen of the tumor revealed that small cell carcinoma cells proliferating in solid sheets and cords patterns with high nucleus to cytoplasm ratio (N/C ratio) and hyperchromatic nuclei (Figure 2-a). Immunohistochemically, these cancer cells were positive for AE1/AE3(Figure 2-b),

weakly positive for protein gene product 9.5 (PGP9.5) (Figure 2-c), and negative for chromogranin A, synaptophysin, CD56, and p63. He was finally diagnosed with extrapulmonary neuroendocrine tumor arising from the left mandibular gingiva, cT4aN1M0, clinical stage IVa, and was referred to our department in October 201x.

His general condition was well and organ functions were preserved. The laboratory results were as follows: white blood cells, 5250/μl; hemoglobin, 14.7g/dl; platelets, 192000/μl. Serum pro-gastrin-releasing peptide and neuron-specific-enolase levels were 43.7 pg/ml (normal; < 81.0 pg/ml) and 12.3 ng/ml (normal; <16.3 ng/ml), respectively. He had an indication for receiving concurrent chemoradiotherapy according to limited disease cases of small cell lung carcinoma. Since the tumor was growing to double in size in one month (Figure3-a,b), we started systemic chemotherapy with cisplatin (80mg/$m^2$ day1, every 3 weeks) and etoposide (100mg/$m^2$ day1-3, every 3 weeks) before initiation of radiotherapy. The tumor had reduced to half the size after the start of chemotherapy, but it increased again on the 28th day of the first cycle. From the second cycle, he was concurrently administered the radiotherapy of a total of 60Gy in 30 fractions. Although Common Terminology Criteria for Adverse Events(CTCAE) Version 4.0 grade 4 neutropenia and grade 3 febrile neutropenia developed during the treatment, they were immediately resolved by the administration of granulocyte colony-stimulating factor. CTCAE grade 3 mucositis, grade 2 anorexia, and grade 2 nausea were also seen, but no other severe adverse events were observed. After 4 cycles of chemotherapy and the concurrent radiotherapy the primary tumor disappeared (Fig.3-c) and a metastatic lymph node decreased in size (<10mm in the minor axis). The lesions were metabolically negative by FDG-PET (Fig.4-a,b). A complete response (CR) defined by Response Evaluation Criteria In Solid Tumors (RESIST) version 1.1 was achieved. The tumors have maintained CR without any therapies for15 months from the initial diagnosis.

## Discussion

This patient was histologically diagnosed with neuroendocrine tumor grade 3, especially extrapulmonary small cell carcinoma, based on the similar morphological feature of the tumor cells to small cell carcinoma. The tumor cells are immunohistochemically negative for chromogranin A, synaptophysin, CD56 and p63, but weakly positive for PGP9.5, which were not necessarily typical for neuroendocrine cell carcinoma. Chromogranin A and synaptophysin are known to be sometimes negative in case of poorly differentiated cell carcinoma [10]. We concluded the diagnosis by the cellular morphology and positive staining with AE1/AE3 and PGP9.5.

Dakhil et al proposed prognostic factors of extrapulmonary small cell carcinoma including stage of disease, ECOG-PS, site of primary disease, use of chemotherapy, and number of modalities of used therapy [20]. Especially the patients with extrapulmonary small cell carcinoma of breast, genitourinary, gynecology, and head and neck had a better prognosis [10, 17, 20, 22]. Dakhil et al reported head and neck limited disease extrapulmonary small cell carcinoma patients had a median survival of 17 months [9] and Hatoum et al reported that of 22 months [17]. In contrast, a median survival time of extrapulmonary small cell carcinoma of gastrointestinal organ was around 6 months in both reports [17, 20]. The present case, with limited disease, in head and neck area, treatments by chemoradiotherapy, and a favorable PS, was suggestive to be a better prognosis. It is fundamentally difficult to specify the actual factors of a favorable prognosis in each patient with head and neck extrapulmonary small cell carcinoma. The most important reason why the present tumor completely responded and did not progress was thought to be

the primary site. The patient was diagnosed soon after the initiation of his symptoms, and started chemotherapy. Moreover, he was administered a combination chemotherapy of cisplatin and etoposide without dose reduction and a radiotherapy of 60Gy. We could carefully perform these intensive therapies with close observation of the tumor. Additionally, the tumor site was advantageous for radiotherapy because of few organs next to the tumor.

Though this patient might have an indication for radical surgery, we chose chemoradiotherapy because it had a good effect on extrapulmonary small cell carcinoma and we took his physical appearance into consideration. Since the tumor regrew after chemotherapy alone, concurrent chemoradiotherapy was adequate in this case. However, the time to relapse tends to be usually short in poorly differentiated neuroendocrine head and neck carcinoma even if it has high initial response rates [23], and we should consider the surgical resection when the tumor recurred.

Prophylactic cranial irradiation should be considered as a part of the standard treatment of patients for small cell lung carcinoma patients in complete response [24]. However, in case of extrapulmonary small cell carcinoma, brain metastasis is rare and the therapeutic effect of Prophylactic cranial irradiation is not clear [25, 26]. Mason et al reported their retrospective study showing that brain metastasis was uncommon without Prophylactic cranial irradiation and routine use of Prophylactic cranial irradiation was not recommended [25]. Besides that, Dakhil and Hatoum did not employ Prophylactic cranial irradiation for their patients with extrapulmonary small cell carcinoma and no association was found with their prognosis [17, 20]. Considering above information, Prophylactic cranial irradiation was not performed for the present patient.

Based on the emerging data of extrapulmonary small cell carcinoma, therapeutic strategy for the disease has generally tended to follow that for small cell lung cancer. However, since extrapulmonary small cell carcinoma itself consists of a variety of different diseases, it might be insufficient to employ uniform therapeutic strategy. In accordance with the possible prognostic factors of extrapulmonary small cell carcinoma, more adequate modification of therapy would be performed in each case. We demonstrated an extrapulmonary small cell carcinoma arising from the mandibular gingiva could be successfully treated with chemoradiotherapy. We believe that the present information should be of important not only for treatment of head and neck extrapulmonary small cell carcinoma but also development of new strategies for extrapulmonary small cell carcinoma arising various primary sites.

## Figures

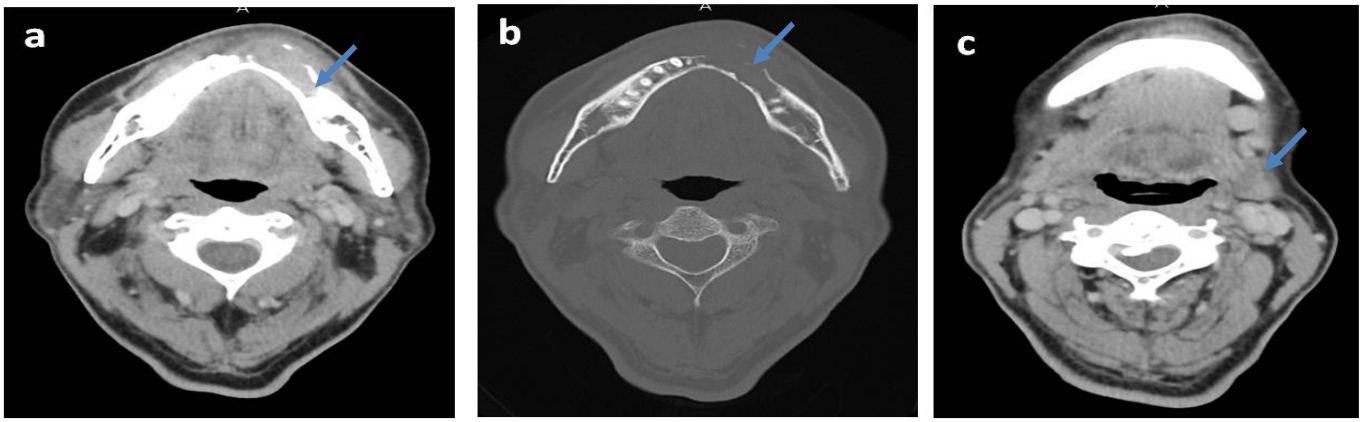



**Figure 1:** Contrast-enhanced computed tomography (CT) on 09-Oct-201x before the initial treatment. Axial CT (a, b) shows the tumor with an invasion of the left mandibular bone (arrows). Axial CT (c) shows the metastasis to the submandibular lymph node(arrow).

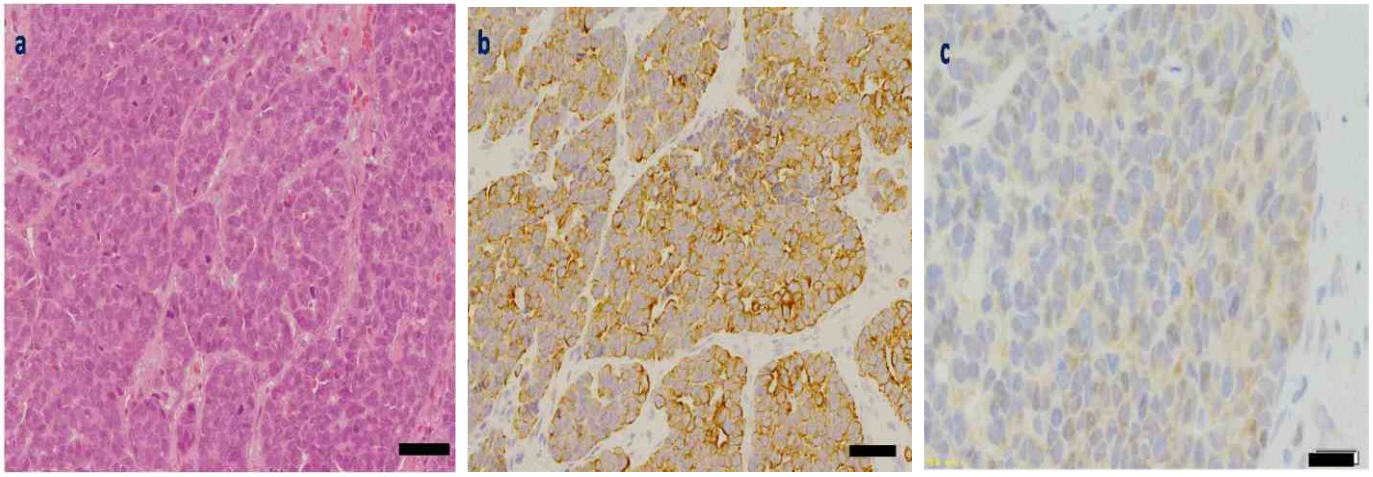



**Figure 2:** Histopathological examination of the biopsy specimen of the tumor: Hematoxylin and eosin(HE) staining shows proliferating carcinoma cells in solid sheets and cords patterns, and they have high nucleus to cytoplasm ratio (N/C ratio) and hyperchromatic nuclei.

Bar: 50 μm (a). AE1/AE3 is positive and the cells have the perinuclear staining pattern which is characteristic of neuroendocrine tumors. Bar: 20 μm (b). Immunohistochemistry reveals Protein Gene Product 9.5(PGP9.5) is weakly positive. Bar:20 μm(c).

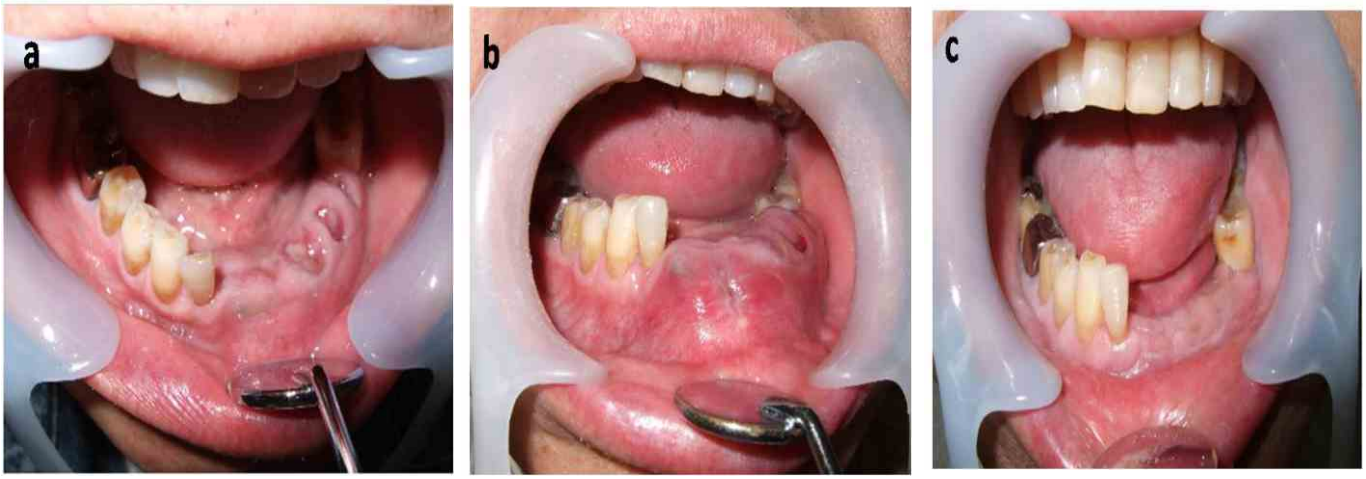
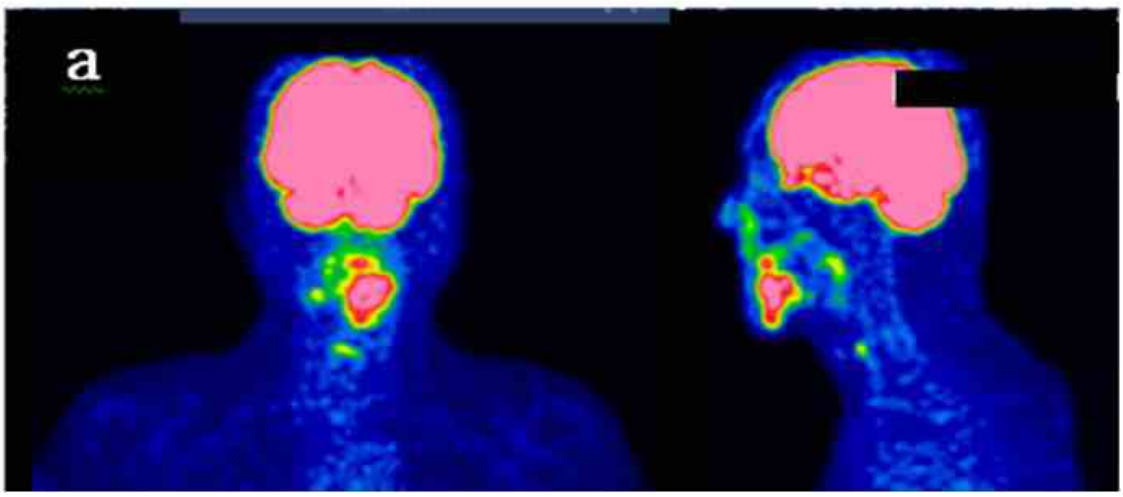



**Figure 3:** Pictures of the primary tumor in the left mandible at initial visit on 07-Oct-201x (a), at the day before the first cycle of VP-16/CDDP(EP) on 04-Nov-201x (b) and at the day of 3 weeks after the treatment finished on 10-Mar-201x+1 (c).



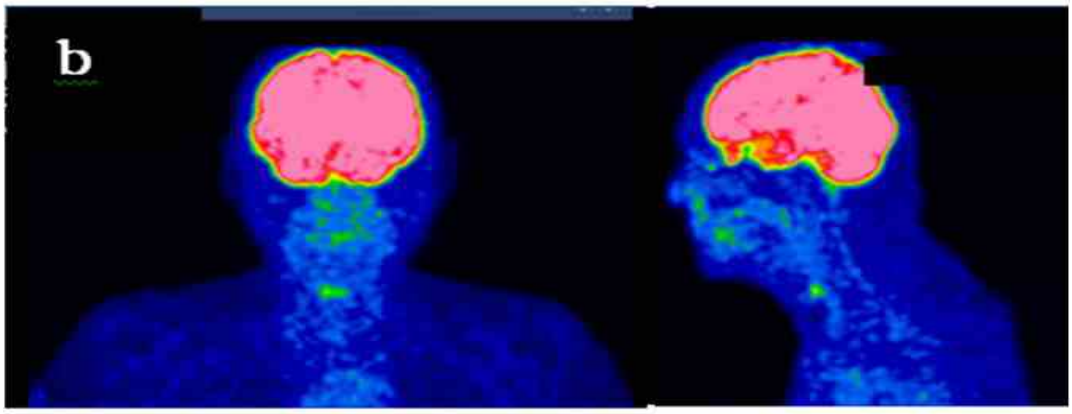



**Figure 4:** Fluorodeoxyglucose-positronemission tomography (FDG-PET) scan. The lesions were metabolically positive on 14-Oct-201x (a), but negative on 23-Mar-201x+1 (b).

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**Manuscript Information:** Received: December 13, 2015; Accepted: March 15, 2016; Published: March 16, 2016

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**Citation:** Inoue S, Shibata Y, Shirakawa T, Noda Y, Natsuda S, Goto T et al. Successful chemoradiotherapy for neuroendocrine tumor grade3 arising from the mandibular gingiva: a case report and literature review. Open J Clin Med Case Rep. 2016; 1089



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