

Primary Neuroendocrine Carcinoma Combined with Squamous Cell Carcinoma of the Soft Palate: A Case Report and Review of Literature

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Abstract

Background: Neuroendocrine carcinomas (NECs) are rare neoplasms that widely occur in various organs. They are heterogeneous and vary from low to high grade malignant. NEC presenting with a squamous cell carcinoma (SCC) component is referred to as a composite tumor. Thus far, few cases of this composite tumor in the oral cavity have been reported in the literature; thus, the histogenesis remains unclear. **Case Presentation:** We encountered a rare case of a primary NEC combined with SCC, occurring at the soft palate in a 59-year-old man. A resected specimen of the tumor was composed of two components: NEC and SCC. The NEC area contained small round to oval atypical cells arranged in nests with a glandular-like-pattern, hyperchromatic molded nuclei, a high nuclear-to-cytoplasmic ratio, and a scant eosinophilic cytoplasm. The SCC area was composed of non-keratotic, dysplastic oval to spindle-shaped squamous cells with indistinct cell borders and large nuclei that were hyperchromatic and pleomorphic. Immunohistochemically, the tumor cells of the NEC component were positive for chromogranin A, synaptophysin, CD56, and p16, whereas those of the SCC component were positive for 34βE12, p63, and p16. **Conclusion:** In consideration of the morphological and immunohistochemical results, the final diagnosis was a primary NEC combined with SCC of the soft palate.

Keywords

Oral Cavity, Neuroendocrine Carcinoma, Squamous Cell Carcinoma, Combined Tumor

1. Introduction

Neuroendocrine carcinomas (NECs) are classified as a subgroup of neuroectodermal neoplasms with epithelial differentiation, which are heterogeneous and vary from low to high grade malignant. They can widely occur in different organs, particularly the lungs and larynx [1]. According to the World Health Organization (2017), NECs of the larynx are classified as well, moderately, and poorly differentiated types [2]. Two subtypes of poorly differentiated NECs are recognized as small cell and large cell NEC [2]. Most NECs of the head and neck region occur in the larynx and salivary glands. The oral cavity is an unfrequent location of primary NECs [1] [3] [4]. Interestingly, an NEC combined with a squamous cell carcinoma (SCC) component is referred to as a composite tumor [5]. To the best of our knowledge, there have only been three cases of NEC combined with SCC in the oral cavity reported to date [6] [7] [8]. Although some cases of NEC and SCC overlap have been reported, the possible role of neuroendocrine differentiation in head and neck SCC remains unclear [7]. In this report, we describe a rare case of a primary NEC combined with SCC of the soft palate, and discuss the etiology as well as the histopathological and immunohistochemical features of the tumor.

2. Case Presentation

A 59-year-old Japanese man, with a history of smoking, presented to our hospital with a chief complaint of a painful mass of the right side of the soft palate that first appeared 2 months beforehand. An intraoral examination revealed an irregular reddish mass, measuring approximately 5 × 4 cm (**Figure 1**). An incisional biopsy was performed, which resulted in a diagnosis of cT2N0M0 SCC. Hence, tumorectomy of the soft palate to the mesopharynx was performed along with neck dissection and flap reconstruction using the forearm skin. There was no evidence of disease at 30 months after surgery.

3. Pathological Findings

Microscopically, the resected specimen consisted of two components (**Figure 2(A)** and **Figure 2(B)**). One of the components was composed of solid nests,



Figure 1. Intraoral photograph showing a tumor in the right soft palate.

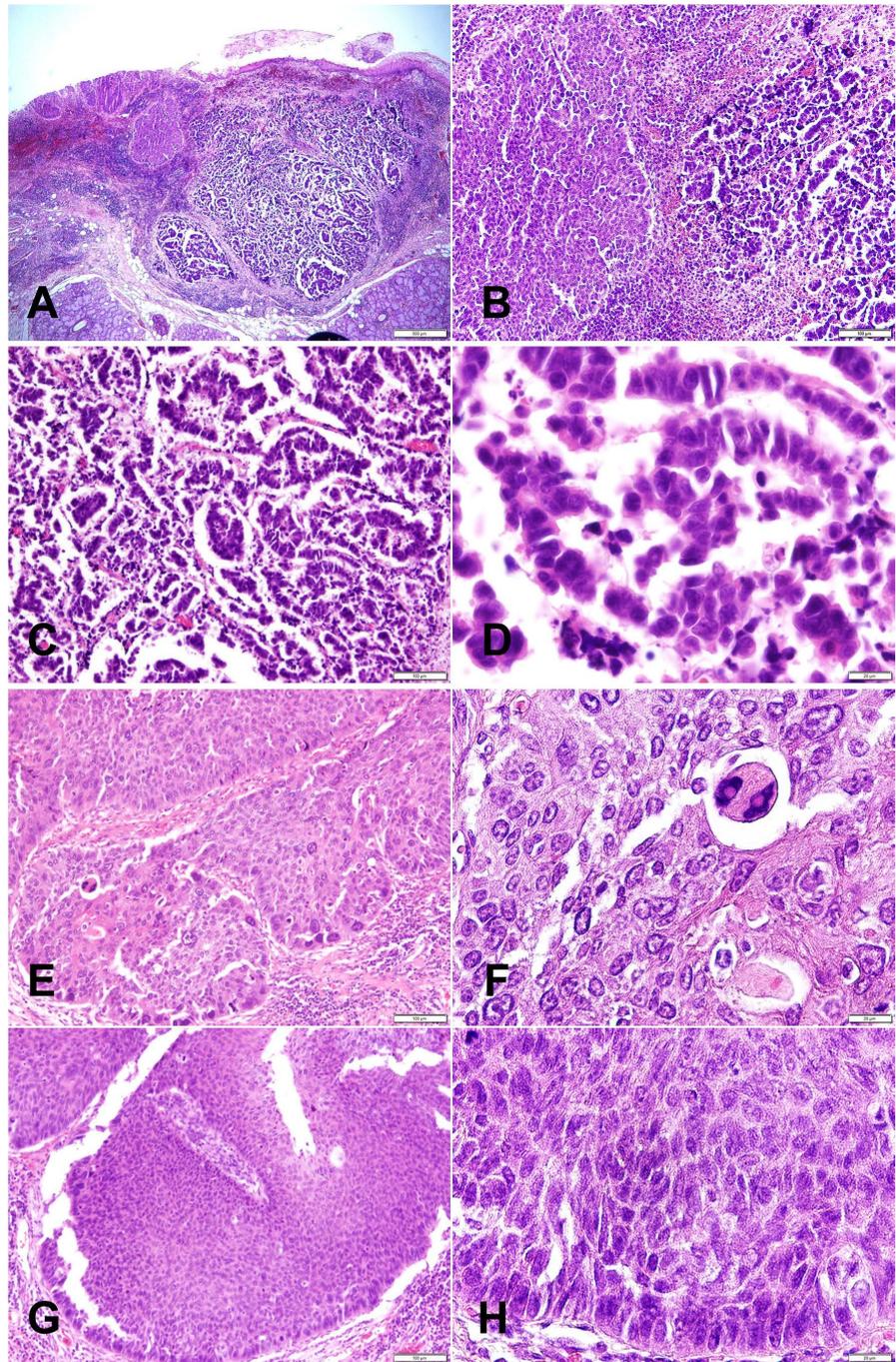


Figure 2. Microscopic findings (A), (B) The tumor consisted of two components of squamous cell differentiation with a few basaloid nests part (left) and nests of atypical small cells (right) (H&E; 20× and 100×). (C) Tumor showing solid nests, cords, and glandular-like patterns with dispersed high mitotic activities (H&E; 100×) (D) Higher magnification photomicrograph of (C), showing small round to oval atypical cells and hyperchromatic molded nuclei with inconspicuous nucleoli (H&E; 400×). (E) Tumor showing non-keratotic, dysplastic oval to spindle-shaped squamous cells with indistinct cell borders (H&E; 100×). (F) Higher magnification photomicrograph of (E), showing that the nuclei of the tumor cells were large, hyperchromatic, and pleomorphic (H&E; 400×). (G), (H) Tumor nests composed of closely packed basaloid cells. Nuclear palisading was observed at the periphery of the nests (H&E; 100× and 400×).

cords, and glandular-like structures with dispersed high mitotic activities (**Figure 2(C)**), in addition to small round to oval atypical cells with hyperchromatic molded nuclei, high nuclear-to-cytoplasmic ratios, inconspicuous nucleoli, and scant eosinophilic cytoplasm, as well as oval-shaped cells with abundant cytoplasm (**Figure 2(D)**). The histologic differential diagnosis of the first component included poorly differentiated SCC, basaloid SCC (BSCC), adenosquamous carcinoma, and NEC. The other component consisted of two phenotypic morphologies. The major area was non-keratotic consisting of dysplastic oval to spindle-shaped squamous cells with indistinct cell borders (**Figure 2(E)**) and large nuclei that were hyperchromatic and pleomorphic (**Figure 2(F)**). A few nests were composed of small and crowded basaloid cells. Nuclear palisading was observed at the periphery of the nests (**Figure 2(G)** and **Figure 2(H)**). There was no metastasis to the neck lymph nodes.

The two components clearly showed different immunostaining patterns. Nest of atypical small cells were positive for neuroendocrine markers chromogranin A (**Figure 3(A)**), synaptophysin (**Figure 3(B)**), CD56 (**Figure 3(C)**), and p16 (**Figure 3(D)**), but negative for 34 β E12 and p63. Areas of differentiated squamous cells and a few basaloid nests were positive for 34 β E12 (**Figure 3(E)**), p63 (**Figure 3(F)**), and p16 (**Figure 3(G)**), but negative for all neuroendocrine markers. Both tumor components were negative for carcinoembryonic antigen (CEA). The immunohistochemical analysis results of the tumor components are summarized in **Table 1**. Based on these histological and immunohistochemical features, the final diagnosis was primary NEC combined with SCC of the soft palate.

4. Discussion

NECs constitute a heterogeneous group of neoplasms with a wide range of tissue origins, histomorphological features, and clinical symptoms [4]. In addition, Mahomed *et al.* attempted to classify oral NECs into typical carcinoid, atypical carcinoid, small cell, and large cell types [9]. Epidemiologically, laryngeal NECs usually occur twice as common in males than in females and have been reported in patients in the sixth to seventh decade of life [10]. Most patients are heavy tobacco users [10]. Most NECs in the head and neck region occur in the larynx and salivary glands. The oral cavity is a rare site for primary NECs, which have been reported in only 15 cases to date [3] [4] [6] [7] [8] [11]-[19]. The clinicopathological features of the reported cases of primary neuroendocrine tumor of the oral cavity are summarized in **Table 2**. The sites of primary NECs in the oral cavity were the gingiva, tongue, retromolar region, uvula, floor of the mouth, mandible, and buccal mucosa. The prognosis of oral NECs varies from no evidence of disease at follow-up, to local recurrence and distant metastasis [3]. Some researchers have reported composite tumors of NEC and SCC in various locations, including the lungs and larynx [5] [20]. To the best of our knowledge, there have only been three cases of NEC combined with SCC in the oral cavity

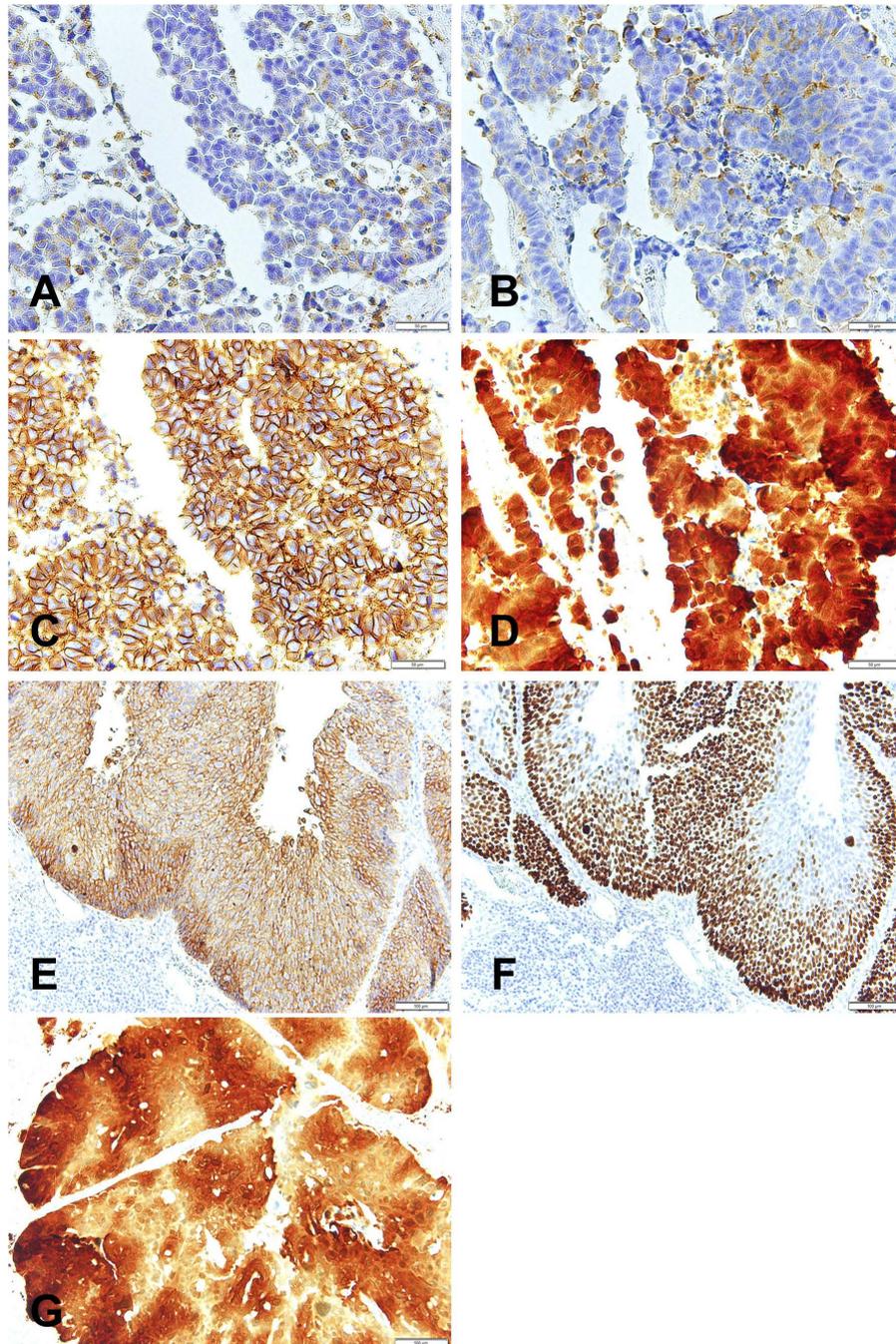


Figure 3. Immunohistochemical staining. Nests of atypical small cells were positive for (A) chromogranin A; (B) synaptophysin, (C) CD56; and (D) p16. Tumor cells of the squamous cell component and a few basaloid nests were positive for (E) 34βE12; (F) p63 and (G)p16.

reported to date, which were located at the floor of the mouth and gingiva [6] [7] [8].

The true origin and histogenesis of oral NECs are not clearly understood. Some researchers have proposed that NECs originate from neuroendocrine cells located at the basal layer of the oral squamous epithelium [9] [18] [21]. Another

Table 1. Summary of the immunohistochemical analysis results of the tumor components.

Marker	Atypical small cells	Squamous component and a few basaloid nests
34 β E12	-	+
p63	-	+
chromogranin A	+	-
synaptophysin	+	-
CD56	+	-
CEA	-	-
p16	+	+

hypothesis is that NECs are derived from primitive and pluripotent indifferent cells of either the squamous epithelium or minor salivary gland [18] [21]. NEC and SCC might arise from pluripotent cells that differentiated along two distinct pathways, or NEC could have differentiated secondarily from cells arising from a SCC [22].

The differential diagnosis of basaloid-like carcinomas of the head and neck included BSCC, high-grade NEC, and poorly differentiated SCC. Differential diagnosis between these carcinoma types can be difficult by simple hematoxylin and eosin staining, especially when dealing with small biopsy specimens. Immunohistochemical staining provides more specific tissue antigen and tissue origin results. High molecular weight cytokeratins, such as 34 β E12 and cytokeratin-5/6, can efficiently distinguish NECs from SCCs and BSCCs. Staining of SCCs and BSCCs is strongly positive for 34 β E12, while NECs are negative [6] [23]. p63 is also useful to identify basal and stem cells of the squamous epithelium and could be helpful to differentiate NECs from SCCs and BSCCs, as staining is positive for SCCs and BSCCs, but negative for NECs [6] [23]. In our case, tumor cells of the squamous cell differentiated area and a few basaloid nests were positive for 34 β E12 and p63, but negative for the neuroendocrine markers. Immunohistochemical analysis of NECs is usually positive for at least one neuroendocrine marker (chromogranin, synaptophysin, or CD56) [2] [3] [6] [7] [23]. In our case, nests of atypical small cells were positive all of neuroendocrine markers (chromogranin A, synaptophysin, or CD56), while negative for high molecular weight cytokeratin 34 β E12 and p63. Therefore, the final diagnosis of the present case, according to the histological and immunohistochemical features, was primary NEC combined with SCC. Adenosquamous carcinoma was excluded due to the lack of CEA immunoreactivity [24]. The possibility that the current tumor was a metastatic NEC was not favored, as an extensive clinical investigation failed to detect a primary tumor site.

In addition, recently, El-Mofty *et al.* [25] reported that human papillomavirus (HPV)-related oropharyngeal SCC had unique microscopic features due to the lack of keratinization and the presence of tumor cells containing bizarre nuclei

Table 2. Summary of clinicopathological features of the reported cases of primary neuroendocrine tumor of the oral cavity.

No.	Age/sex	Site	Smoking history	Histology	Cell size of NEC	IHC of NEC	IHC of SCC	Follow-up	Reference
1	63/M	Retromolar	NA	NEC	Small	NA	-	DOD at 24 mths	Benning, <i>et al.</i> 1990 [11]
2	76/M	Tongue	Yes	NEC	Small	+Keratin, EMA, CEA, NSE	-	DUC at 2 mths	Yoshida, <i>et al.</i> 1995 [12]
3	46/F	Mandible	NA	TC	-	+CGA, NSE	-	NED at 24 mths	Coleman, <i>et al.</i> 1996 [13]
4	49/M	Floor of mouth	Yes	NEC	Medium to large	+CGA, SYP, CT, LMW-CK	-	DOD at 10 days	Baker, <i>et al.</i> 1999 [14]
5	59/M	Gingiva	NA	NEC and SCC	Large	+CGA, CD56	+CAM5.2	NA	Oku, <i>et al.</i> 2002 [8]
6	68/M	Gingiva	NA	AC	-	+CGA, SYP, NSE, CAM5.2, AE1/AE3	-	NA	Abiko, <i>et al.</i> 2004 [15]
7	79/M	Tongue	NA	NEC	Large	+CD56, NSE, p16, p53, p63, 34 β E12, CK5/6, CK19	-	NED at 18 mths	Kusafuka, <i>et al.</i> 2009 [16]
8	62/F	Gingiva	NA	NEC and SCC	Small	+CGA, SYP, CD56, NSE, K7, K19	+K5, K14, K15, K17, p63	NED at 23 mths	Mochizuki, <i>et al.</i> 2010 [7]
9	34/F	Retromolar	NA	NEC	Large	+CGA, CD56, CD57, S100P, Keratin, EMA	-	AWD at 9 mths	Krishnamurthy, <i>et al.</i> 2011 [17]
10	46/F	Retromolar	NA	TC	-	+CGA, SYP, NSE, AE1/AE3, CK7, p63, S100, Vimentin, CD57	-	NED at 11 mths	Yang, <i>et al.</i> 2011 [18]
11	57/M	Uvula	NA	AC	-	+SYP, EMA, AE1/AE2	-	DOD at 9 mths	Goldman, <i>et al.</i> 2012 [19]
12	25/F	Gingiva	NA	NEC	Medium to large	+SYP, NSE, S100	-	NED at 13 mths	Wu, <i>et al.</i> 2014 [3]
13	38/F	Buccal mucosa	NA	NEC	Small	+SYP, EMA, AE1/AE3	-	NED at 8 mths	Wu, <i>et al.</i> 2014 [3]
14	73/M	Gingiva	Yes	NEC	Small	+CGA, SYP, NSE, AE1/AE3	-	NED at 14 mths	Zeng, <i>et al.</i> 2015 [4]
15	65/M	Floor of mouth	NA	AC and SCC	-	+SYP, CD56	+34 β E12, p63	AWRR at 6 mths	Yamagata, <i>et al.</i> 2016 [6]
16	59/M	Soft palate	Yes	NEC and SCC	Small	+CGA, SYP, CD56, p16	+34 β E12, p63, p16	NED at 30 mths	Our case

M, Male; *F*, Female; *NA*, Not available; *TC*, Typical carcinoid; *AC*, Atypical carcinoid; *NEC*, Neuroendocrine carcinoma; *SCC*, Squamous cell carcinoma; *IHC*, immunohistochemistry; *EMA*, Epithelial membrane antigen; *CEA*, Carcinoembryonic antigen; *NSE*, Neuron specific enolase; *CGA*, Chromogranin A; *SYP*, Synaptophysin; *CK*, Cytokeratin; *LMW*, Low molecular weight; *CT*, Calcitonin; *K*, Keratin; *DOD*, Died of disease; *DUC*, Died of unrelated cause; *NED*, No evidence of disease; *AWD*, Alive with disease; *AWRR*, Alive with recurrent relapses; *mths*, months.

with extensive mitotic activities. In the present case, the histomorphology of the SCC part was similar to that describe by El-Mofty *et al.* [25]. The NEC part of our case was comprised of small round to oval atypical cells with high mitotic activities, hyperchromatic molded nuclei, and a high nuclear-to-cytoplasmic ratio. Furthermore, in our case, the tumorcells of both components were diffuse and strongly positive for p16. Immunohistochemistry of this marker is considered to be a reliable surrogate marker of high-risk HPV infection when considering with the appropriate morphologies in oropharyngeal carcinomas [26]. Therefore, in our case, there was a possibility of HPV infection in both NEC and SCC components.

The prognosis of NEC of the oral cavity remains obscure. Variations in the location, size, extension, and differentiation of the primary tumor influence the prognosis [27]. For laryngeal NECs, the 5-year survival rates of the well, moderately, and poorly differentiated types are approximately 80%, 50%, and 15%, respectively [10]. In our case, there was no evidence of disease at 30 months after surgery.

To the best of our knowledge, the present case is the first of a composite tumor consisting of NEC and SCC of the soft palate. Further studies are needed to elucidate the histogenesis, precise treatment, and prognosis of oral NEC. Hence, more cases and future studies are needed to clarify the pathophysiology of NEC combined with SCC.

5. Conclusion

In summary, we have presented a rare case of primary NEC combined with SCC of the soft palate. The final diagnosis was concluded through the combination of morphological and immunohistochemical results. More cases of this composite tumor in the oral region are required to clarify their pathophysiology.

Declarations

The study protocol was approved by the Ethics Committee of Kyushu Dental University Hospital and written informed consent was obtained from the patient.

Competing Interests

The authors declare no conflicts of interest.

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