

## Case Report

# Small cell carcinoma of the oral cavity (cheek mucosa): a case report with an immunohistochemical and molecular genetic analysis

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**Abstract:** Small cell carcinoma (SCC) of the oral cavity is extremely rare; only one case has been reported in the English Literature. The author herein reports the second case of SCC of the oral cavity. A 59-year-old man presented with oral tumor (5 cm) in the right cheek mucosa. A biopsy was taken. The HE histology was typical SCC consisting of small epithelial cells with hyperchromatic nuclei, molded nuclei, scant nucleocytoplasmic ratio, and negative nucleoli. Immunohistochemically, the tumor cells are positive for pancytokeratin (PCK) WSS, PCK MNF-116, cytokeratin (CK) 34BE12, CK5/6, CK14, vimentin, KIT (CD117), CD56, synaptophysin, p53 protein, and Ki67 antigen (Ki-67 labeling = 70%). The tumor cells are negative for PCK AE1/3, PSK CAM5.2, CK7, CK8, CK18, CK19, CK20, EMA, NSE, chromogranin, platelet-derived growth factor- $\alpha$  (PDGFRA), CD45, CD45RO, CD3, CD20, CD30, CD79a, and bcl-2. A retrospective genetic analysis using PCR-direct sequencing method in paraffin sections identified no mutations of *KIT* (exons 9, 11, 13 and 17) and *PDGFRA* (exons 12 and 18) genes. Various imaging modalities including CT and MRI and upper and lower gastrointestinal endoscopy did not identified no tumors other than the oral tumor. Thus, the oral tumor was thought primary. The oral tumor rapidly enlarged, and distant metastases to cervical lymph nodes, ribs and iliac bones emerged. The patient is now treated by cisplatin-based chemotherapy 16 months after the first manifestation.

**Keywords:** Oral cavity, cheek mucosa, small cell carcinoma, histopathology, immunohistochemistry, molecular biopsy of *KIT* and *PDGFRA*

## Introduction

Small cell carcinoma (SCC) of the head and neck region is very rare, but a few case series have been reported in the nasal cavity and paranasal sinuses [1-4]. In contrast, SCC of the oral cavity is extremely rare; only one case has been reported in the literature [5]. SCC of the lung is shown to express KIT and platelet-derived growth factor- $\alpha$  (PDGFRA), but has no mutations of these genes lung [6]. Several comprehensive studies of small cell carcinoma have been reported in the English literature [7-27]. However, there have been no reports of SCC of the oral cavity investigating protein expression and gene mutations of *KIT* and *platelet-derived growth factor receptor- $\alpha$*  (PDGFRA). The author reports herein a case of primary SCC of the oral cavity with an examination of protein expressions of KIT and PDGFRA

and gene status of *KIT* and *PDGFRA* genes. *KIT* and *PDGFRA* genes, both mapped to 4q12, encode receptor tyrosine kinase oncoproteins called KIT (CD117) and PDGFRA, respectively [28-33]. Both molecules are transmembranous oncoproteins, and play important roles in the carcinogenesis of several tumors such as gastrointestinal stromal tumor (GIST) [14-45].

## Case report

A 59-year-old man presented with oral tumor (5 cm) in the right cheek mucosa (**Figure 1A** and **1B**). A biopsy was taken. The HE histology was typical SCC consisting of small epithelial cells with hyperchromatic nuclei, molded nuclei, scant nucleocytoplasmic ratio, and negative nucleoli (**Figure 2A-C**).

An immunohistochemical analysis was performed by Dako Envision methods (Dako Corp,



**Figure 1.** Gross findings. A: The right cheek of the patient shows a swelling (tumor) (arrow). B: The oral cavity examination shows a tumor (arrow) in the right cheek.

Glostrup, Denmark), as previously reported [46-52]. Immunohistochemically, the tumor cells are positive for pancytokeratin (PCK) WSS (Figure 3A), PCK MNF-116, cytokeratin (CK) 34BE12, CK5/6, CK14, vimentin, KIT (CD117) (Figure 3B), CD56 (Figure 3C), synaptophysin (Figure 3D), p53 protein (Figure 3E), and Ki67 antigen (Ki-67 labeling = 70%) (Figure 3F). The tumor cells are negative for PCK AE1/3, PSK CAM5.2, CK7, CK8, CK18, CK19, CK20, EMA, NSE, chromogranin, PDGFRA, CD45, CD45RO, CD3, CD20, CD30, CD79a, and bcl-2.

A molecular genetic analysis of *KIT* gene (exons 9, 11, 13, and 17) and *PDGFRA* (exons 12 and 18) gene were performed by the PCR direct sequencing method, as previously reported [4, 14-27, 34-40]. The exons of both genes were selected because they are frequent mutation sites [14-41]. The primers are shown in Table 1. In brief, genomic DNA was extracted from paraffin blocks with proteinase K digestion and phenol/chloroform extraction, and subjected to PCR for 40 cycles (94°C for one minute, 52°C for one minute, 72°C for one minute), using a thermal cycler (GeneAmp PCR system 9700, Applied Biosystems, ABI, CA). The annealing temperature was 53°C. PCR products were extracted, and subjected to a computed automatic DNA sequencer (ABI PRISM 3100 Genetic Analyzer, Applied Biosystems, ABI, CA).

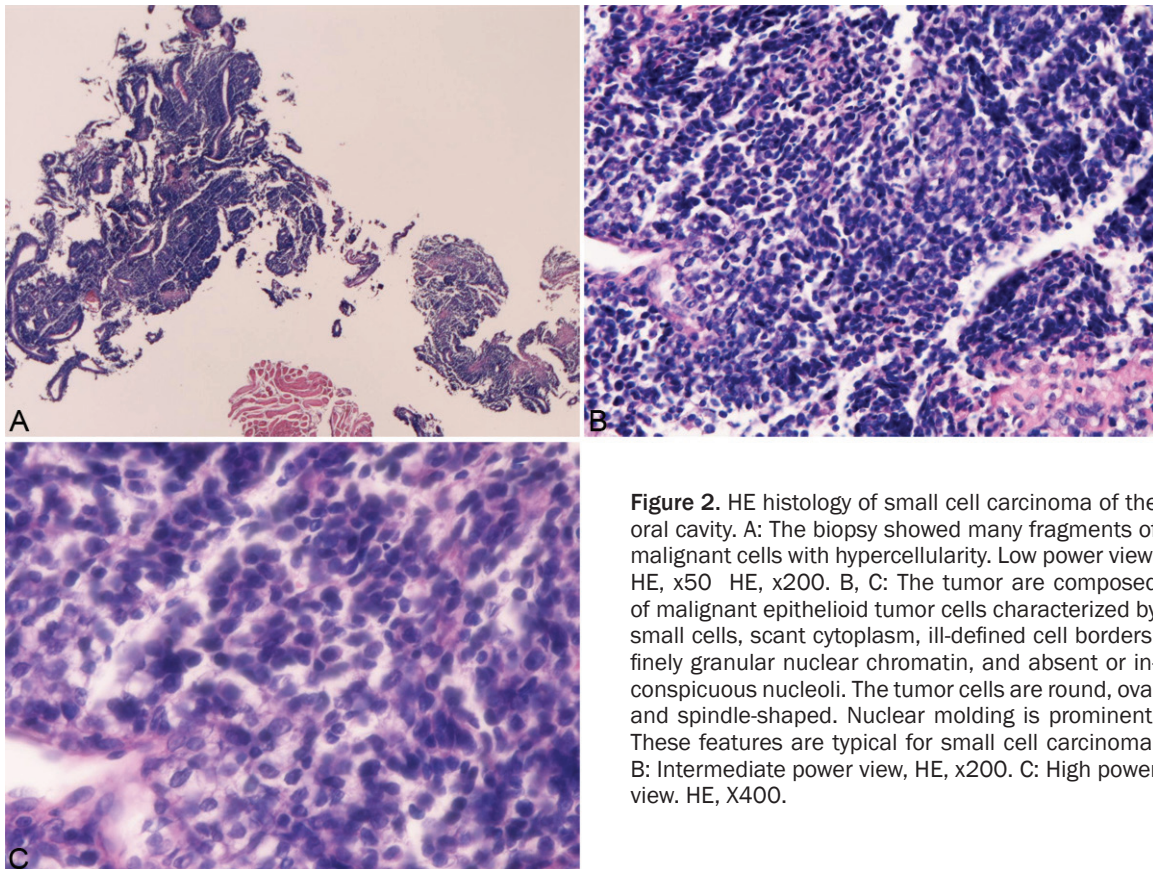
The retrospective genetic analysis using PCR-direct sequencing method in paraffin sections identified no mutations of *KIT* (exons 9, 11, 13 and 17) and *PDGFRA* (exons 12 and 18) genes.

Various imaging modalities including CT and MRI and upper and lower gastrointestinal endoscopy did not identified no tumors other than the oral tumor. Thus, the oral tumor was thought primary. The oral tumor rapidly enlarged, and distant metastases to cervical lymph nodes, ribs and iliac bones emerged. The patient is now treated by cisplatin-based chemotherapy 16 months after the first manifestation.

## Discussion

The present case is the second case after Shenoy et al. [5] of oral SCC, and the first case with immunohistochemical examination of the oral SCC. The present case is the first case examining protein expression and gene mutational status of oral SCC. In the present study, the oral tumor is apparently SCC on HE sections. Some neuroendocrine antigens including CD56 and synaptophysin were positive. This finding supports the pathological diagnosis of SCC of the oral cavity in the current case. The positive p53 protein shows p53 gene mutation, and the high Ki-67 labeling (labeling index=70%) indicates high proliferative activity of tumor cells. The CK immunoprofile of the present SCC was PCK WSS+, PCK MNF-116+, CK34BE12+, CK5/6+, CK14+, PCK AE1/3-, PSK CAM5.2-, CK7-, CK8-, CK18-, CK19-, and CK20-. Immunoprofile of SCC of various organs is known to vary from case to case, and there are cases of SCC without expression of any CKs [53]. SCC somewhat resemble malignant lymphoma histologically. In the present tumor, the negative reaction of tumor cells to CD3, CD20, CD45, CD45RO, CD79a and bcl-2 implies that the present tumor is not malignant lymphoma. The reason for negative EMA and positive vimentin is unclear. However, vimentin is well known to be expressed in certain types of carcinoma, and EMA is well known to be negative in several carcinomas. The negative reaction of chromogranin and NSE in the current tumor does not imply that the current tumor has no neuroendocrine features [6, 14-27], because the current tumor showed positive CD56 and synaptophysin.

Small cell carcinoma is defined by only HE histology [54]. According to WHO criteria [54], it is defined as a malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear



**Figure 2.** HE histology of small cell carcinoma of the oral cavity. A: The biopsy showed many fragments of malignant cells with hypercellularity. Low power view. HE, x50. B, C: The tumor are composed of malignant epithelioid tumor cells characterized by small cells, scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli. The tumor cells are round, oval and spindle-shaped. Nuclear molding is prominent. These features are typical for small cell carcinoma. B: Intermediate power view, HE, x200. C: High power view. HE, x400.

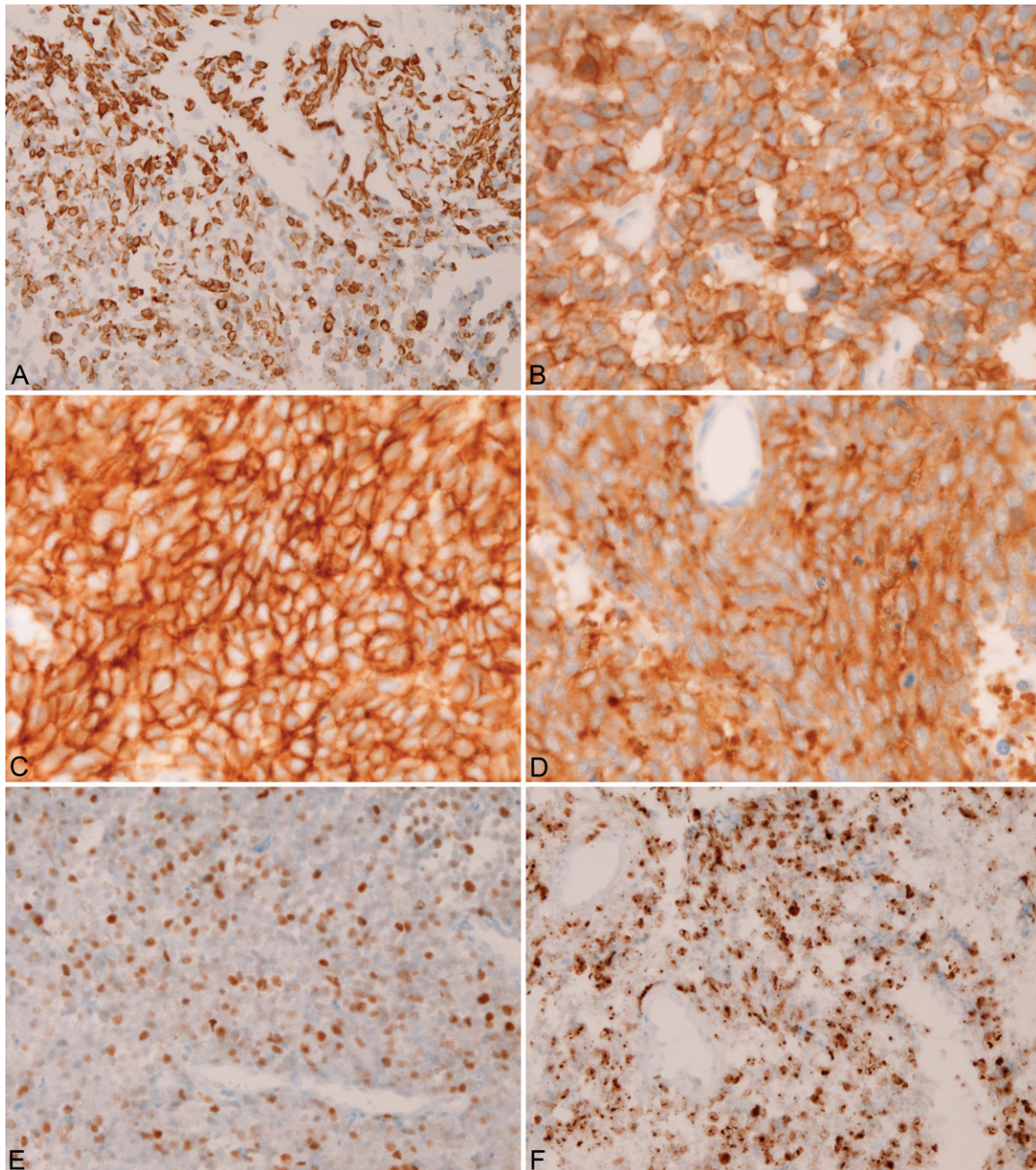
chromatin, and absent or inconspicuous nucleoli. The tumor cells are round, oval and spindle-shaped. Nuclear molding is prominent. Necrosis is typically extensive and mitotic count is high [54]. More than 90 % of small cell carcinoma has neuroendocrine features [54]. The present cases fulfill the criteria of small cell carcinoma. The present case of oral SCC had neuroendocrine features. Thus, the present cases are small cell carcinomas in strict criteria.

The current oral tumor rapidly enlarged, and distant metastases to cervical lymph nodes, ribs and iliac bones emerged. The patient is now treated by cisplatin-based chemotherapy 16 months after the first manifestation. This findings implies that oral SCC has poor prognosis.

The pathogenesis of the current SCC of the oral cavity is unclear. It has been considered that SCC may arise from totipotential stem cell present in the mucosal epithelium [41]. In the present case, the oral SCC may arise from such totipotential stem cells.

The novel findings in the present oral SCC are that immunoreactive KIT was positive, but immunoreactive PDGFRA was absent. In SCC of other organs, both KIT and PDGFRA tend to be positive [4, 6, 14-27]. The present is the first report of oral SCC that examined KIT and PDGFRA proteins and *KIT* and *PDGFRA* genes. KIT and PDGFRA proteins and *KIT* and *PDGFRA* genes have rarely been investigated in extrapulmonary small cell carcinoma [4, 14-27], while several comprehensive reports are present in small cell lung carcinoma. KIT has been reported to be expressed in 30-80% of the small cell lung carcinoma [6, 42, 43]. The present case shows that oral SCC also expresses KIT protein. Only one study of PDGFRA protein has been reported in small cell lung carcinoma [6], but many studies showed that of positive protein expression of KIT and PDGFRA in SCC of other organs have been reported [14-27]. The present case of oral SCC did not show PDGFRA expression, suggesting that the present oral SCC does not express this oncoprotein.





**Figure 3.** Immunohistochemical findings of the tumor cells. The tumor cells are positive for pancytokeratin WSS (A), KIT (CD117) (B), CD56 (C), synaptophysin (D), p53 (E) and Ki67 (labeling index=70%) (F). The expression of KIT is membranous. A, E, F: x200. B, C, D: x400.

The present cases did not identify mutations of *KIT* and *PDGFR* genes. Most reports of small cell lung carcinoma have shown no mutations in *KIT* genes [6, 42], except for Boldrini et al. [43] who found five mutations in 60 small cell lung carcinomas. On the other hand, Terada [6] and Sihto et al. [42] identified no *KIT* mutations in many cases of small cell lung carcinomas.

More studies of *KIT* mutations remain to be performed in the SCC. With regard to *PDGFR* mutations, Terada [43] and Sihto et al. [42] found no mutations in many cases of small cell lung carcinomas. Sihto et al. [42] insisted that *KIT* expression in small cell lung carcinoma is due not to *KIT* gene mutations but to *KIT* gene amplification. With regard to extrapulmonary

**Table 1.** Primer sequence

Forward	Reverse
<i>KIT</i> exon 9	
5'-TCC TAG AGT AAG CCA GGG CTT-3'	5'-TGG TAG ACA GAG CCT AAA CAT CC-3'
<i>KIT</i> exon11	
5'-GAT CTA TTT TTC CCT TTC TC-3'	5'-AGC CCC TGT TTC ATA CTG AC-3'
<i>KIT</i> exon 13	
5'-GCT TGA CAT CAG TTT GCC AG -3'	5'-AAA GGC AGC TTG GAC ACG GCT TTA-3'
<i>KIT</i> exon 17	
5'-CTC CTC CAA CCT AAT AGT GT-3'	5'-GTC AAG CAG AGA ATG GGT AC-3'
<i>PDGFRA</i> exon12	
5'-TTG GAT ATT CAC CAG TTA CCT GTC-3'	5'-CAA GGG AAA AGC TCT TGG-3'
<i>PDGFRA</i> exon 18	
5'-ACC ATG GAT CAG CCA GTC TT-3'	5'-TGA AGG AGG ATG AGC CTG ACC-3'

SCC, Terada [6, 14-27] showed that there are no mutations of *KIT* and *PDGFRA* in the extra-pulmonary SCC.

Among many *KIT*-positive tumors, GIST is representative [10-15]. It is thought that GIST arises from interstitial cell of Cajal, a pacemaker neuronal cell that normally expresses *KIT* protein [28-36]. In contrast, SCC is an undifferentiated carcinoma with neuroendocrine phenotypes. The original cell of SCC is unknown. Recently, Blumming et al. [44] found that GIST expresses synaptic vesicle proteins, and suggested that GIST has endocrine features. Therefore, it is suggested that there may be an association between GIST and SCC in that the both entities have neuroendocrine features.

Several studies of GIST have revealed that there are minute subclinical microGISTs or "GIST tumorlets" in the gastrointestinal tract [55, 56]. The incidence of these is about 20%, and these are considered as GIST precursors. Frequent *KIT* mutations (about 46%) and occasional *PDGFRA* mutations (about 4%) are present in these "GIST tumorlets" [55, 56]. However, these "GIST tumorlets" do not always develop into clinical GIST. Other genetic events are necessary for the development of clinical GIST. In contrast, little is known about the precursor lesions in SCC.

Recently, the phosphorylation (activation) status of *KIT* and *PDGFRA* has been studied [57, 58]. This is particularly important in *KIT* mutation-negative tumors as in the present case. *KIT* kinase activation and downstream signaling proteins leading to tumorigenesis have

been studied, but little is known as yet. Protein kinase C- $\theta$  and PI3-kinase/AKT are activated in imatinib-resistant GIST [57, 58], and analyses of these *KIT* signaling molecules may be important in the treatment of GIST. Such studies are not performed in SCC. In the present case, the author could not investigate these molecules, because no rel-

evant antibodies were available. *KIT* tyrosine kinase activity and *KIT* signaling abnormalities in SCC remain to be elucidated.

In summary, the author reported the second case of oral SCC. An extensive immunohistochemical study was performed. The oral SCC expressed *KIT* protein, but not *PDGFRA* protein. No *KIT* and *PDGFRA* mutations were recognized.

#### Conflict of interest statement

The author has no conflict of interest.

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This work was approved by Ethics Committee of our hospital.

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