Basaloid squamous cell carcinoma of the tongue: a case report

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Abstract: Basaloid squamous cell carcinoma (BSCC) is a rare distinct variant of squamous cell carcinoma. We report a case of basaloid squamous cell carcinoma of the tongue in a 76-year-old Japanese man. The initial clinical examinations revealed a 23 × 25 × 15 mm reddish ulcerated mass with an elastic hard texture at the left lateral border of the tongue. The histopathological findings revealed invasive growth of basaloid epithelial tumor cells that formed nests in the subepithelial layer to the muscle layer. Immunohistochemically, the tumor was positive for p63 protein and had a high Ki-67 labeling index of more than 70% in parts. The patient underwent chemotherapy involving super-selective intra-arterial administration of carboplatin and local irradiation, followed by a subtotal tongue resection. The patient has been followed for 48 months postoperatively without any evidence of disease. The super-selective intra-arterial chemotherapy is a feasible and important application in treating BSCC of the tongue showing aggressive biological behavior.

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Key words: basaloid squamous cell carcinoma, carboplatin, immunohistochemical examination, super-selective intra-arterial chemotherapy, tongue

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Introduction

Basaloid squamous cell carcinoma (BSCC) is a rare, highly aggressive malignant tumor and a distinctive histological variant of squamous cell carcinoma (SCC), which typically occurs in the base of the tongue, hypopharynx, supraglottic larynx or pyriform sinus (1). BSCC is usually diagnosed as an advanced stage carcinoma, since it reveals aggressive and deep infiltrative growth, as well as local and distant metastases even in the early stage. There are few prior reports regarding therapeutic strategies for BSCC (2). Here, we report a case of BSCC of the tongue, which was treated by chemoradiotherapy involving super-selective intra-arterial administration of carboplatin. The treatment modality was effective on the BSCC, which showed distinct histological change after the treatment.

Case report

A 76-year-old man had chief complaints of pain and

Fig. 1. Intraoral view of basaloid squamous cell carcinoma of the tongue in a 76-year-old man. The patient had an ulcerated mass protruding in the left lateral border of the tongue, measuring 25 mm in diameter. The central ulcer was surrounded by a white patch. The tumor border was not well defined.

Fig. 2. Gd-enhanced T1-weighted magnetic resonance imaging (MRI) of the lesion at admission. (a) axial and (b) coronal plane. MRIs revealed a tumor mass with an irregular margin, and high and heterogeneous signal intensity areas that extended toward the median line of the tongue (arrows). There were no cervical lymph node metastases.

swelling in the tongue. He had noticed a swelling at the left lateral border of the tongue 1 month prior to consulting a dental clinic. Since the swelling had been rapidly increasing in size, he was referred by the dental clinic to our hospital. The initial clinical examinations revealed a 23 × 25 × 15 mm reddish ulcerated mass with an elastic hard texture at the left lateral border of the tongue (Fig. 1). There were no abnormalities in other oral mucosa. No cervical lymphadenopathy was palpable. Physical examinations and laboratory data showed no abnormal findings except for a positive response to hepatitis B virus antigen.

Axial and coronal Gd-enhanced T1-weighted magnetic resonance imaging (MRI) showed a solid tumor mass extending toward the median line of the tongue from the submucosal area at the left lateral border of the tongue. The mass had an irregular margin and exhibited high and hetero-

geneous signal intensity areas at the central portion (Fig. 2). ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET) showed a high standardized uptake value with a maximum of 5.0 in the mass. There were no abnormal findings in any other regions and no clinical evidence of cervical or distant metastases. Laboratory data showed no abnormalities except for an increased serum cytokeratin 19 fragment level of 3.8 ng/ml (normal range: ≤3.5 ng/ml). The clinical stage was classified as T2N0M0.

The patient underwent a biopsy of the tongue mass. The histopathological findings revealed invasive growth of basaloid epithelial tumor cells forming nests in the subepithelial to the muscle layer (Fig. 3a). There were focal connections of the nests with the overlying small nests of well-differentiated SCC at an ulcer base (Fig. 3b). The basaloid tumor cells showed a high N/C ratio with round to ovoid nuclei with mitotic figures, and focal necrosis in the nests (c). Myxoid and hyalinized fibrous stroma in the nests (d).

Fig. 3. Histopathological findings of the biopsy specimen. HE stain, (a) × 4, (b, c) × 200, (d) × 400. Invasive growth of basaloid epithelial tumor cells forming nests in the subepithelial to the muscle layer (a). Focal connections with overlying SCC in ulcer base (b). The tumor cells showed a high N/C ratio with round to ovoid nuclei with mitotic figures, and focal necrosis in the nests (c). Myxoid and hyalinized fibrous stroma in the nests (d).

Fig. 4. Immunohistochemical findings of basaloid squamous cell carcinoma of the tongue. Immunoperoxidase stains for P63 protein (a), CAM5.2 (b), S-100 protein (c), Ki-67 (d), hematoxylin counterstain, $\times 200$. The tumor cells exhibited strong positivity for P63 (a) and CAM5.2 (b). S-100 protein showed focal positivity (c). The Ki-67 labeling index was higher than 70% in parts (d).

ovoid nuclei and exhibited a marked increase in mitotic figures. There was focal necrosis at the central portion of the nests (Fig. 3c). A myxoid and hyalinized fibrous stroma was present in the nests (Fig. 3d). There was no apparent evidence of permeation of the tumor into the blood and lymphatic vessels. The histopathological diagnosis of the biopsy specimen was a variant of SCC that was consistent with the WHO definition of BSCC (9).

Immunohistochemically, the basaloid tumor cells exhibited strong positive staining for *p63* gene products (P63) (Fig. 4a), CAM5.2 (Fig. 4b), AE1/AE3 and 34bE12. Epithelial membrane antigen and S-100 protein showed focal positivity (Fig. 4c). The Ki-67 labeling index was more than 70% in parts (Fig. 4d). Vimentin, CD56, chromogranin A, synaptophysin, neuron-specific enolase, α -smooth muscle actin, and melanoma-associated antigen (HMB45) were not positive in the tumor cells (Table 1).

The patient received chemotherapy involving super-selective intra-arterial administration of 400 mg of carboplatin (Paraplatin®) through the left tongue artery together with simultaneous external irradiation. The irradiation program consisted of a dose to the primary site that appeared clinically involved, which was administered at 1.5 Gy per fraction, two fractions daily for 10 days, for a total dose of 30 Gy. When the dosage reached about 10 Gy, the intra-arterial infusion chemotherapy was initiated. Angiographic images of the external carotid artery were obtained under fluoroscopic guidance in the main feeding artery of the tumor via the femoral artery using Seldinger's technique (Fig. 5a), and indigocarmine was infused to precisely identify the feeding vessels (Fig. 5b). Carboplatin was then infused slowly for 20 min via a continuous infusion pump. Two weeks after the chemoradiotherapy, MRI revealed regression of the tumor size (Fig. 6).

Table 1. Primary antibodies used in immunohistochemistry and results

antibody against	antibody type (clone)	dilution	pretreatment	distributor	results
cytokeratin 8	mouse IgG (CAM5.2)	1:1	trypsin	Becton	++
cytokeratin 1-8, 10,14 -16, 19	mouse IgG (AE1/AE3)	1:50	pepsin	Dako	++
cytokeratin 1, 5,10, 14	mouse IgG (34bE12)	1:100	heat	Dako	focal
vimentin	mouse IgG (V9)	1:50	none	Dako	–
α -smooth muscle actin	mouse IgG (31G7)	1:100	none	Dako	–
epithelial membrane antigen	mouse IgG (E29)	1:50	none	Dako	focal
p63 protein	mouse IgG (4A4)	1:100	heat	Dako	++
Ki-67	mouse IgG (MIB-1)	1:100	heat	Dako	++
S-100 protein	rabbit polyclonal	1:600	none	Dako	focal
neuron specific enolase	mouse IgG (VI-H14)	1:100	heat	Dako	–
CD56	mouse IgG (1B6)	1:50	heat	Novocastra	–
chromogranin A	mouse IgG (LK10H2)	1:100	heat	Dako	–
synaptophysin	mouse IgG (SY38)	1:20	heat	Dako	–
melanoma-associated antigen	mouse IgG (HMB45)	1:50	pepsin	Dako	–

Fig. 5. Appearance of the tongue at super-selective intra-arterial infusion chemotherapy. (a) Angiographic image of the main feeding artery of the tumor; (b) indigocarmine infusion for determination of the feeding vessels. The external carotid artery was obtained under fluoroscopic guidance via the femoral artery using Seldinger's technique (a), and indigocarmine was infused to precisely identify the feeding vessels (Fig. 4b).

Three weeks after the chemoradiotherapy, resection of the tumor and reconstruction with a skin graft were performed under general anesthesia. Surgical excision was performed with a wide margin to ensure complete removal. Histopathologically, the surgical specimen revealed invasive growth of the tumor cells forming small nests in the muscle layer without perineural or vascular spread (Fig. 7a). There was marked fibrosis with focal infiltration of lymphoplasmocytic cells in the muscle layer. The remaining tumor cells showed marked cellular pleomorphism with bizarre nucleus and marked degeneration with loss of the nucleus and eosinophilic large cytoplasm (Fig. 7b). In other areas, the tumor cells had almost been completely replaced by hyalinized stroma in the nests (Fig. 7c). Immunohistochemically, the remaining tumor cells were still P63-positive but showed a low Ki-67 labeling index of less than 5% (Fig. 7d). The postoperative course was uneventful, without local recurrence or metastasis for 48 months after the operation.

Discussion

BSCC was first reported as a high-grade histological variant of SCC in the oral cavity, larynx and hypopharynx, and also in esophagus (1, 3). In a previous study, the base of

the tongue was the preferred site for oral BSCC, the patient's mean age was 61 years old, and most cases (62%) were found at advanced stage III or IV (2). It is generally accepted that BSCCs in the head and neck region tend to have an aggressive clinical course compared with stage-matched conventional SCCs, which have frequent local recurrences and regional and distant metastases (1, 4-5).

Regional super-selective intra-arterial infusion chemotherapy is potentially advantageous over other therapies because higher concentrations of effective chemotherapeutic agents can be delivered directly to the tumor site, and systemic toxic reactions can be minimized owing to the site selectivity. Chemotherapy is effective for oral SCC, and a cisplatin analogue of carboplatin is regarded as one of the most active chemotherapeutic agents (6). However, the recommended treatment protocol for BSCC has been reported to be radical surgery followed by radiotherapy and/or systemic chemotherapy (1, 4-5, 7-8). Ide *et al.* reported that a surgical resection following the chemotherapy of carboplatin and local irradiation (20 Gy) had led to good prognosis in a case of BSCC in the floor of the mouth (2). In the present case, preoperative radiotherapy and super-selective intra-arterial infusion chemotherapy with carboplatin were very effective against the primary lesion.

Fig. 6. Gd-enhanced T1-weighted magnetic resonance imaging (MRI) of the lesion at 2 weeks after the chemoradiotherapy. (a) axial and (b) coronal plane. MRI revealed regression of the tumor size (arrows) by the chemoradiotherapy.

Fig. 7. Histological and immunohistochemical findings of the surgically resected specimen. HE stain (a-c) and immunoperoxidase stain for Ki-67 (d), (a) $\times 2$, (b-d) $\times 200$. Invasive growth of the tumor nests in the muscle layer with marked fibrosis (a). The remaining tumor cells showed marked cellular pleomorphism with bizarre nucleus and loss of the nucleus with eosinophilic large cytoplasm (b). The tumor cells were almost totally replaced by hyalinized stroma in the nests (c). The remaining tumor cells showed a low Ki-67 labeling index (d).

Furthermore, no systemic toxicity was observed, and the only local toxicity encountered was a relatively mild mucositis. Tumor resection of BSCC should be as wide as possible, relative to conventional SCC, and associated with subsequent reconstruction.

The histopathological differential diagnoses of BSCC should include neuroendocrine tumors, adenosquamous carcinoma (ASC), and adenoid cystic carcinoma (ACC). Immunohistochemical examination is essential to distinguish BSCC from these lesions in addition to histomorphological examination (9-10). Unlike neuroendocrine tumors, BSCCs never express neuroendocrine markers such as chromogranin A, synaptophysin and NSE. ASCs can be distinguished from BSCCs by their morphological features, since ASCs have a prominent squamous cell component with scarce basaloid cells and the presence of glandular differentiation. P63 is a useful immunohistochemical marker for distinguishing ACCs from BSCCs (11). Specifically, P63 shows diffuse nuclear staining in BSCCs, but is only detected in peripheral

cells in the basal and/or myoepithelial compartments in ACCs (11). The present case showed focal positivity for S-100 protein, which is more frequently positive in ACC than in BSCC (4). The utilities of S-100 protein and α SMA for this distinction seem to be limited, since some cases show a large portion of positive cells while other cases are negative (4). The labeling index for the proliferation marker Ki-67 was reported to be more than 50% in BSCCs and lower in ACCs (7), and can easily separate these two entities. Furthermore, this index may clearly reflect the different biological behaviors as highly aggressive for BSCCs and slowly progressive for ACCs (7).

After the chemoradiotherapy, the number of tumor cells was reduced and the remaining tumor cells showed marked pleomorphism regarded as a degenerative cellular atypia with low proliferation ability (Fig. 7). In present case, the tumor cells were replaced with hyalinized stroma in the nests, whereas multinucleated foreign body giant cells are often associated with degenerated carcinoma foci in ordinary

SCC. These findings may reflect the rapid effects of the regional super-selective intra-arterial infusion chemotherapy.

It is important to recognize that BSCC is a distinctive carcinoma with a more aggressive biological behavior compared with that of conventional SCC, and that further follow-up for distant metastases is required because such metastases occur in more than half of BSCC patients (8). The recommended follow-up intervals and investigative tools such as chest computed tomography (CT) and FDG-PET for patients with BSCC are still unclear. The follow-up interval is every 3 months in the protocol for SCC in our hospital, with investigations of the excised tumor site as well as other head and neck regions by CT or MRI.

In conclusion, for effective treatment of BSCC, it is important to achieve a precise and rapid diagnosis, since BSCC is a biologically high-grade tumor with a propensity for regional as well as systemic lymph node metastases. Once the diagnosis of BSCC has been confirmed, patients should receive preoperative chemoradiotherapy based on the tumor size and regional lymph node metastases. Indeed, a previously reported procedure was found to decrease locoregional recurrence and may improve the patient survival rate (5). It is highly appropriate to state that further accumulation of investigations into oral BSCC cases is necessary to establish a standard treatment.

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