臨床報告

A Case of Lower Gingival Squamous Cell Carcinoma with Perineural Spread to the Cavernous Sinus and Orbit Caused by Mandibular Nerve Invasion

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下顎神経浸潤により海綿静脈洞・眼窩へ神経周囲進展したと考えられた下顎歯肉扁平上皮癌の1例

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要約：57歳の男性。左側下顎歯肉の咬合痛と左側舌のしびれを主訴として来院した。左側下顎歯肉癌診断下に、2012年、頸部郭清術、左側下顎半側切除術、金属プレートならびに外側大腿皮弁による再建術を施行した。術後5か月目に左眼複視が発現したため、MRI撮像したところ海綿静脈洞および眼窩への腫瘍進展が認められた。化学放射線療法を施行した。その後、脊髄に多発性に全身転移を来とし術後14か月目に呼吸不全で死亡した。腫瘍が下顎骨への浸潤傾向が強く下顎神経領域の知覚異常を伴う症例の場合、腫瘍が求心性（上行性）に浸潤していく可能性も考えられるため、術後の経過観察において脳神経に対する評価も重要であると考えられた。

Abstract : A 57-year-old male with lower gingival carcinoma visited our hospital with chief complaints of occlusal pain in the left lower gingiva and numbness on the left side of the tongue. In 2012, neck dissection, left hemimandibulectomy, reconstruction with metal plates and ALT flap were carried out. Five months after surgery, diplopia of the left eye appeared. A tumor invading the cavernous sinus and orbit was identified by MRI. Chemoradiotherapy was performed. The patient developed systemic metastasis mainly to the spinal cord and died of respiratory failure 14 months postoperatively. In cases of tumor invasion to the mandible causing dysesthesia in the mandibular nerve area, the possibility of afferent invasion should be considered. Hence, assessment of brain nerves is an important factor in postoperative follow-up.

Key words : lower gingival carcinoma (下顎歯肉癌), perineural spread (神経周囲進展), squamous cell carcinoma (扁平上皮癌), lingual nerve (舌神経)

[Received Apr. 14, 2015]

Introduction

Perineural spread is known as a significant course in the transmission of oral cancers¹⁻⁵⁾. Perineural spread is

a type of metastasis in which the primary lesion grows along the endoneurium or perineurium into the perineural cavity, and is a crucial factor in determining treatment policy for head and neck malignancy, such as

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whether to perform resection or not, to which region should radiation be delivered, etc⁶⁾. Its mechanism is characterized by tumors which have reached the perineural region spreading along the lines of the perineural cavity with less resistance⁷⁾. Perineural spread is commonly manifested with only asymptomatic or low specificity, and mild symptoms such as slight pain and hypaesthesia. Approximately 15% of cases have specific symptoms such as tumor infiltration to the neural area on the image^{6,8)}. Cases which spread to the central cavity tend to have poor prognosis compared with cases localized in the periphery. Also, symptomatic cases show a tendency of poor prognosis compared with asymptomatic ones^{9,10)}.

We would like to report a case of a lower gingival squamous cell carcinoma which appeared to have extended along the mandibular nerve into the cavernous sinus and orbit after primary treatment.

Case

Patient: 57-year-old male.

First visit: June 2012.

Chief complaints: Occlusal pain in left lower gingiva, numbness on the left side of the tongue.

Previous medical history: Pylorus excision at the age of 27 and two fracture repairs.

Current medical history: The patient experienced pain in the lower gingiva during occlusion and swallowing in April 2012. A detailed examination was performed and the patient was diagnosed with squamous cell carcinoma in May of the same year. The patient was referred to our center because he requested treatment at a hospital near a relative's house.

Present illness:

General condition: Body type was leptosomatic, and nutritional status was moderately poor. No outwardly visible abnormality was observed.

Facial appearance: Symmetrical. One lymph node exhibited partial swelling and oppressive pain occurred during palpitation of the left submandibular lymph node.

Oral cavity: A pronounced neoplastic lesion with peripheral induration was observed in the left lower gingiva (equivalent to the left lower wisdom tooth). Lesion dimensions were 24 × 21 mm (Fig. 1). Tismus was not observed and the patient could eat normally.

CT findings: A 12 mm large lymph node was observed in the left submandibular lymph node but metastasis to

Fig. 1 Oral cavity at the initial visit
On the left lower gingiva, pronounced neoplastic lesion with peripheral induration was observed (arrow).

the cervical lymph node was not suspected due to the absence of significant swelling, irregular margin and heterogeneity. Lung metastasis was also not observed.

MRI findings: An invasive mass was observed from the left lower molar to the retromolar triangle. Partial inward invasion into the mylohyoid muscle was observed, downward invasion to the mandible was suspected, and upward invasion immediately beneath the mandibular foramen. However, oncogenic lesion to cavernous sinus and orbit was not preoperatively observed by axial section or coronal section of MR image (Fig. 2).

Clinical diagnosis at the initial visit: Lower gingival carcinoma (cT4aN0M0).

Treatment and course: From the results of cytological examination conducted at the initial visit in June 2012, a Class IV (squamous cell carcinoma) was diagnosed. In late June, a biopsy was performed and a pathological diagnosis of a well-differentiated type squamous cell carcinoma. In July 2012, surgery was performed under general anesthesia, with the procedures consisting of tracheostomy, neck dissection of the left omohyoid muscle (Level I, II, III), left hemimandibulectomy, reconstruction of the mandible with metal plates and an anterolateral thigh flap (Fig. 3). Pathological findings of the resected margin were negative at the time of surgery. Similarly, the central part of the resected margin of inferior alveolar nerve was also negative. Because the surgical margin was tumor free, adjuvant chemotherapy after surgery was not provided.

Histopathological findings: Examination of the tumor cells indicated an increase in the N/C ratio, densely stained nuclear chromatin and cellular atypia with nucle-

Fig. 2 Preoperative MRI image

- a-1, b-1: An invasive mass was observed from the left lower gingiva to the retromolar triangle, spreading into the posterior region of the retromolar triangle (arrow). Invasion from the alveolar of the molar through the adjacent retromolar triangle of the mandible is suggested. The mass reaches the ascending branch right below the mandibular foramen at the most.
- a-2, b-2: An oncogenic lesion reaching to the cavernous sinus and orbit is not preoperatively observed in the axial section or the coronal section according to MR imaging.

olar swelling and a strong tendency of cornification. Tumor cells also showed proliferation, forming an alveolus towards the deeper area; however, funicular invasion was partially observed as well. In addition, invasion of tumor cells into the periphery of the inferior alveolar nerve was observed (Fig. 4). Cytokeratin AE1/AE3 stained positive in perineural area. No signs of vascular invasion were observed but mild nerve invasion was indicated (Fig. 5). Metastasis to one lymph node in the IB region was observed in the cervical lymph node.

Pathological diagnosis: Squamous cell carcinoma (pT4aN1M0).

Postoperative course: Loss of appetite and vision in the left eye occurred from December 2012, five months

after surgery. In the same month, MR imaging showed an invasive mass in the left cavernous sinus and was diagnosed as a left intracranial metastasis (Fig. 6). In late December of 2012, a biopsy was performed on the nasal cavity by our otorhinologist and was pathologically diagnosed as squamous cell carcinoma. Chemoradiotherapy was performed on the left intracranial metastatic tumor from January 2013. Radiation dose was 60 Gy and chemotherapy with CDDP 80 mg/m² every three weeks was used in combination, for a total of three treatments. CT and MR images taken after radiation treatment indicated recurrence in the left oral floor. Consequently, radiation treatment at a dose of 42.5 Gy was performed on the recurrent tumor. The patient developed multiple

Fig. 3 Intraoperative image (a) and Excised sample (b)

- a: Image during the left hemimandibulectomy operation and reconstruction of the mandible with a metal plate.
 b: Excised sample image of the mandible and dissected tissue.

Fig. 4 H-E staining

- a, b, c, d: Typical histopathological image of squamous cell carcinoma is shown (a; ×4, b; ×10).
 Invasion of tumor cells (→ A) into the periphery of the inferior alveolar nerve (→ B) was observed. → C: A branch of the inferior alveolar nerve.

systemic metastases to the spinal cord and died of respiratory failure for (14 months postoperatively) in September 2013.

Discussion

Perineural spread is a type of metastasis in which the primary lesion grows along the endoneurium or perineu-

Fig. 5 H-E staining (a) and Immunohistochemical staining (AE1/AE3) (b)
A: Carcinoma, B: Nerve. Cytokeratin AE1/AE3 stains positive in the perineurium. Mild perineurium invasion was observed (neu 1).

Fig. 6 MRI showing endocranial metastasis

An invasive mass was observed in the left cavernous sinus, surrounding the carotid artery, and invading the left sphenoidal sinus. In the anterior, spread to the orbital apex area through the superior orbital fissure was observed (a) (arrow). In the lower anterior, spread to the pterygopalatine fossa through the expanded foramen rotundum and to the infraorbital neural tube through the inferior orbital fissure was also observed (b) (arrow).

rium into the perineurium cavity. For lower gingival carcinoma, it is an important factor in determining the course of treatment, such as the necessity for excision or radiation therapy⁶⁾. While its mechanism remains unclear, in cases of tumor invasion to the mandible, tumors that reach around the nerve are understood to spread along the perineurium cavity with less resistance⁷⁾. Especially, when a tumor invades the mandibular canal, invasion is considered to occur along the vascular bundle of nerves in the mesiodistal direction^{1, 11, 12)}. In the margin of excised samples from 15 squamous cell carcinoma cases with mandibular invasion, Southam et al.¹³⁾ observed invasion into the vascular bundle of the inferior alveolar nerve in 4 cases. The importance of a mesiodistal histo-

logical examination of the mandibular vascular bundle was reported.

In this case, dysesthesia of the left lingual nerve area was observed. CT and MR image findings showed tumors spreading into the peripheral soft tissue, including the periphery of the mandibular canal and the medial pterygoid muscle. A mesiodistal and buccolingually sufficient safety margin was taken into account in the hemimandibulectomy. No tumor cells in the excision margin were observed in the histopathological findings of the excised section. However, when histopathological examination at the periphery of the mandibular canal was performed, tumor spread into the inferior alveolar nerve was observed. Since the central part of the resected

margin of inferior alveolar nerve tested negative during pathological diagnosis during surgery, postoperative treatment was not performed. Nevertheless, in consideration of preoperative neurological symptoms such as numbness of the tongue, nerve infiltration was suspected by preoperative MRI, and perineural spreading on the surgical specimen, prompt postoperative treatment should have been carried out.

The pathway of spread into the intracranial area is understood as follows; a lower gingival carcinoma spreading to the inferior alveolar nerve grows upward along the mandibular nerve, then from the foramen ovale to the cavernous sinus and orbit, resulting in eye symptoms such as reduced vision.

Curtin et al.¹⁴⁾ stated that because the pterygopalatine fossa is an important course in the spread of malignant tumors occurring in the palate, paranasal sinus and face that spread along the trigeminal nerve. CT findings indicating obliteration of fat in the pterygopalatine fossa are important as an indication of nerve invasion. Likewise in Japan, a case of brain metastasis from an oral squamous cell carcinoma receiving surgery and radical treatment has been reported¹⁵⁾. Although the course of cancer growth is not described, the possibility of perineural spread similar to this case cannot be ruled out.

Treatment of the primary lesion is the most important factor in determining prognosis. Specifically, for cases with strong progression of invasion, treatment must consider the possibility of nerve invasion and spread into the central section¹⁶⁾. As with this case, peripheral spread to the inferior alveolar nerve and dysesthesia of the lingual nerve area are indications of strong invasive tendency. Therefore, it is also very important to predict the excision range extending into the center of the nerve bundle, as well as the assessment of the cerebral nerves during follow-up after treatment while understanding the pre- and post-operative chemoradiation treatment.

Conclusion

We have experienced a case of a 57 year-old male patient with lower gingival squamous cell carcinoma that

spread into the cavernous sinus and orbit along the mandibular nerve after primary treatment, and have reported the progression and treatment of the patient.

Reference

- 1) Shibahara, T., Noma, Y., Arai, K., et al.: Histopathological investigation of mandibular invasion by gingival carcinoma according to procedure for mandibular resection (in Japanese). *Jpn J Oral Maxillofac Surg*, 48 : 129-134, 2002.
- 2) Vikram, B., Chu, F.C.H.: Radiation therapy for metastasis to the base of the skull. *Radiology*, 130 : 465-468, 1979.
- 3) Ballantyne, A.J., McCarten, A.B., Ibanez, M.L.: The extension of cancer of the head and neck through peripheral nerves. *Am J Surg*, 106 : 651-667, 1963.
- 4) Trobe, J.D., Hood, C.I., Parsons, J.T., et al.: Intracranial spread of squamous carcinoma along the trigeminal nerve. *Arch Ophthalmol*, 100 : 608-611, 1982.
- 5) Fujita, M., Hirokawa, Y., Naito, K., et al.: Recurrent lower gingival squamous cell carcinoma spreading along the pathway of the inferior alveolar nerve. *Oral Surg Oral Med Oral Pathol*, 80 : 369-375, 1995.
- 6) Ojiri, H.: Perineural spread in head and neck malignancies. *Rad Med*, 24 : 1-8, 2006.
- 7) Ibrahim, M., Parmar, H., Gandhi, D., et al.: Imaging nuances of perineural spread of head and neck malignancies. *J Neuroophthalmol*, 27 : 129-137, 2007.
- 8) Williams, L.S.: Advanced concept in the imaging of perineural spread of tumor to the trigeminal nerve. *Top Magn Reson Imaging*, 10 : 376-383, 1999.
- 9) Galloway, T.J., Morris, C.G., Mancuso, A.A., et al.: Impact of radiographic findings on prognosis for skin carcinoma with clinical perineural invasion. *Cancer*, 103 : 1254-1257, 2005.
- 10) Mendenhall, W.M., Amdur, R.J., Williams, L.S., et al.: Carcinoma of the skin of the head and neck with perineural invasion. *Head Neck*, 24 : 78-83, 2002.
- 11) Totsuka, Y., Usui, Y., Notani, K., et al.: A clinic-pathological study of the oral carcinoma involving the mandible-Surgical margin of the mandible (in Japanese). *Jpn J Oral Maxillofac Surg*, 29 : 811-819, 1983.
- 12) Byars, L.T.: Extent of mandibular resection required for treatment of oral cancer. *Arch Surg*, 70 : 914-922, 1995.
- 13) Southam, J.C.: The extension of squamous carcinoma along the inferior dental neurovascular bundle. *Br J Oral Surg*, 7 : 137-145, 1970.
- 14) Curtin, H.D., Williams, R., Johnson, J.: CT of perineural tumor extension: Pterygopalatine fossa. *Am J Roentgenol*, 144 : 163-169, 1985.
- 15) Inoue, T., Nakazawa, T., Kyoshima, K., et al.: Central nervous system metastasis from lingual carcinoma: report of a case. *Neurological Surg*, 21 : 833-836, 1993.
- 16) Kinoshita, K., Nishida, M., Yasuda, S., et al.: Intracranial development of lower gingival squamous cell carcinoma caused by lingual nerve invasion (in Japanese). *J Jpn Soc Oral Tumor*, 18 : 17-23, 2006.