A p16 Positive M1 Oral Tongue Cancer Completely Responsive to the EXTREME Regimen: A Case Report

Hiroaki IIJIMA^{*1}, Koji EBISUMOTO^{*1}, Akihiro SAKAI^{*1}, Daisuke MAKI^{*1}, Takanobu TERAMURA^{*1}, Mayu YAMAUCHI^{*1}, Go OGURA^{*2}, Naoya NAKAMURA^{*2} and Kenji OKAMI^{*1}

> ^{*1}Department of Otolaryngology-Head and Neck Surgery, Tokai University School of Medicine ^{*2}Department of Pathology, Tokai University School of Medicine

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Methods: A 42-year-old woman presented to our clinic with tongue pain and dysarthria. She had a smoking history of 22 pack-years and no history of alcohol consumption. A deep ulcer at the left side of the tongue and induration across the whole tongue were observed. The bilateral cervical lymph nodes were palpable. A biopsy from the ulcer revealed squamous cell carcinoma. PET/CT showed sternal bone metastasis resulting in the final diagnosis of left-sided oral tongue cancer (cT4aN2cM1). Systemic chemotherapy treatment involving 6 courses of the EXTREME regimen followed by weekly cetuximab administration was indicated. Results: After the first two courses, diminished tongue pain and improved dysarthria were observed; complete response was obtained after 6 courses. Re-examination of the biopsy specimen showed that the tumor was pl6 positive. The pl6 protein is a surrogate marker for HPV, but in this case HPV in-situ hybridization was negative. Locoregional or distant failure were not observed during the 5-year follow-up period. Conclusions: The treatment regimen unexpectedly proved successful. It may be beneficial to examine pl6 expression in oral tongue cancer to identify patients that are more likely to benefit from the EXTREME treatment regimen.

Key words: Cetuximab, Distant metastasis, HPV, p16, Oral tongue cancer

INTRODUCTION

Human papilloma virus (HPV) involvement has been recently reported in head and neck carcinogenesis, particularly in the oropharynx. In addition, it has been reported that the prognosis of HPV-related oropharyngeal cancer is better than that the HPVunrelated one [1]. Based on these reports, HPV-related and unrelated cancers have been distinguished in the 8th edition TNM stage classification.

To date, more than 200 HPV types have been reported, 15 of which are high-risk types that can cause malignant tumors [2]. HPV type 16 accounts for 90% of HPV-related head and neck cancers and contrary to cervical cancer, presents with high type specificity [3, 4].

The relationship between oropharyngeal carcinoma and HPV infection has been well documented in head and neck cancer. A meta-analysis has shown that patients with HPV-positive oropharyngeal carcinoma are at significantly lower risks of death and recurrence than patients with HPV-negative oropharyngeal carcinoma [5, 6]. Overexpression of the cyclin-dependent kinase inhibitor p16 protein resulting from the inactivation of pRb protein involved in cell cycle suppression has been reported in HPV-related cancers. Therefore, p16 is widely used as a surrogate marker for HPVrelated cancers. Although the reported percentage frequency of p16 positive oropharyngeal carcinoma is 58.0% [7], that for oral cancers, including tongue cancer, is 9.5%-29.5% [8-10].

Moreover, a relationship between HPV infection and oral cancer has been reported [11]. However, reports on the involvement of HPV infection in oral tongue cancer, particularly concerning their relationship and characteristics, are limited. Although systemic chemotherapy is usually indicated for head and neck cancer with distant metastasis, the prognosis is poor.

Herein, we report the case of M1 oral tongue cancer successfully treated using the EXTREME regimen. Furthermore, we discuss the possible correlation between HPV infection and oral tongue cancer prognosis.

MATERIALS AND METHODS

Case Presentation

A 42-year-old woman presented with tongue pain and dysarthria persisted for 10 months. She had a smoking history of 22 pack-years and no history of alcohol consumption. A deep ulcer on the left side of the tongue (Fig. 1) and a wide deep induration spreading across the whole tongue were observed. In addition, the bilateral cervical lymph nodes were palpable. No other otolaryngological abnormality was noted.

A biopsy of the ulcer revealed squamous cell carcinoma. MRI showed a maximum tumor diameter of 85 mm and external tongue muscle invasion (Fig. 2). PET/CT showed marked accumulation of 18F-FDG in the primary lesion, bilateral cervical lymph nodes,

Hiroaki IIJIMA,Department of Otolaryngology-Head and Neck Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, 259-1193, Japan Tel: + 81-463-93-1121 Fax: +81-463-94-1611 E-mail: genzai9bo.syoraiyubo@gmail.com



Fig. 1 Pretreatment oral cavity appearance at initial visit.(a) Blue arrows show lesions a deep ulcer at the left side of the tongue, and (b) a wide deep induration spread across the whole tongue were observed.





Fig. 2 Pretreatment MRI analysis of the tumor. (a) Axial and (b) Coronal views of the T2 weighed image. Red arrows show a tumor with maximum diameter of 85 mm on the left edge of the tongue. The lower part of the tumor invaded the external tongue muscle and it was considered stage T4a (Yellow arrows).



Fig. 3 Pretreatment ¹⁸F-FDG PET/CT scan for tumor staging. (a) Coronal and (b) axial views. Arrowhead show marked accumulation of ¹⁸F-FDG in the primary lesion and bilateral cervical lymph nodes (N2b), and arrows show the evident sternal metastasis (M1).



Fig. 4 Posttreatment oral images after 6 courses of the EXTREME regimen show that (a) the tumor disappeared macroscopically and (b) sternal metastasis could not be detected on the PET/CT scan. Complete response was achieved.



Fig. 5 Immunohistopathological analysis of the pretreated tumor biopsy specimen using.
(a) Hematoxylin and eosin staining (original magnification × 20) which demonstrated and (b) Immunohistochemistry staining for p16 (original magnification × 20) which demonstrated widespread expression of p16.

and in the sternum, suggesting bone metastasis (Fig. 3). The patient was diagnosed with left-sided oral tongue cancer (cT4aN2cM1).

A tumor board meeting indicated systemic chemotherapy with the EXTREME regimen, followed by weekly cetuximab (Cmab) administration. The EXTREME regimen comprised cisplatin (100 mg/m², day 1), 5-fluorouracil (5-FU, 1000 mg/m², days 1-4), and Cmab (400 mg/m² as loading dose, followed by 250 mg/m² once weekly), which were administered tri-weekly. After two courses of treatment, a reduction in pain and dysphagia was observed. After six courses of treatment, the tumor disappeared macroscopically, and follow-up imaging showed that the sternal metastasis also disappeared, thus achieving complete response (Fig. 4). After completion of the 6-course EXTREME regimen, Cmab was administered once weekly for 3 years. Maintenance of Cmab administration was ceased based on the patient's decision. No locoregional or distant failure was observed during the 5-year follow-up period.

Owing to the unexpectedly successful treatment course, we performed immunohistochemistry analysis of the biopsy specimen and showed that the tumor was p16 positive (Fig. 5). Although the results of the immunohistochemistry analysis suggested a possible relationship between HPV infection and carcinogenesis of oral tongue cancer, in-situ hybridization (ISH) showed that the biopsy specimen was negative for HPV probes specific for high-risk (HPV 16, 18, 31, 33, 51) and lowrisk (HPV 6, 11) HPV types.

DISCUSSION

Chemotherapy is chiefly indicated for the treatment of head and neck cancer with distant metastasis; however, the prognosis is poor. Such cases have long been treated with cisplatin alone. More recently, combination treatment with 5-FU and cisplatin (FP) showed excellent response rates with no proven survival benefit. In 2008, Vermorken *et al.* reported a better survival benefit for the EXTREME regimen compared with the FP regimen. According to the ver. 2 of 2018 National Comprehensive Cancer Network guidelines, the EXTREME regimen is a standard therapy for the recurrent and metastatic head and neck cancers. In this case, treatment with the EXTREME regimen was indicated because local treatment is contraindicated in stage M1 cancers. Despite the poor long-term prognosis for cancers with distant metastases that initially respond positively to treatment, a rapid complete response and long-term survival was observed in our patient. Therefore, we wanted to understand the mechanism behind this extraordinary response.

In a previous study involving patients with pl6 positive oropharyngeal carcinoma, the patient group that received additional Cmab appeared to have favorable prognosis [12, 13], and also pl6 and/or HPV status are prognostic factors for treatment of the EXTREME regimen [14]. The EXTREME regimen was highly effective for our pl6 positive oral tongue cancer patient. Although no study has directly examined the additional effect of Cmab on pl6 positive oral cancer, it might be more effective.

In the present case, ISH revealed that the tumor specimen was HPV negative. Although p16 is considered as a surrogate marker of HPV in oropharyngeal cancer, it is not a specific marker of HPV status in non-oropharyngeal squamous cell carcinoma (SCC) [15]. Moreover, SCC of the oral cavity often overexpresses p16, but it is rarely driven by HPV [10]. Thus, HPV-independent p16 overexpression mechanisms could be involved in oral cavity carcinogenesis or virus types other than the high-risk types we adopted for ISH analysis could be involved.

In the present case, patient response to the EXTREME treatment regimen suggested that chemotherapy might be more effective in the treatment of p16-positive oral tongue cancer as opposed to p16-negative oral cancer. Therefore, it may be beneficial to examine p16 expression in oral tongue cancer to identify patients that are more likely to benefit from the EXTREME treatment regimen. In addition, this suggests a possible benefit of Cmab for HPV-related head and neck cancer with distant metastasis.

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